EMJ EUROPEAN MEDICAL JOURNAL

UROLOGY

ISSN 2053-4213 — May 2014 • emjreviews.com

INSIDE

Review of

EAU 2014

Stockholm, Sweden

CONTENTS

UROLOGY

Editorial Board

Urology

Welcome

Welcome to the second edition of the *European Medical Journal – Urology.* Building on our strengths from last year, this journal features more peer-reviewed articles written by revered urologists, more coverage of the European Association of Urology (EAU) Congress, and more illumining developments within the field.

The 29th Annual EAU Congress was held in the beautiful city of Stockholm, Sweden, from the 11th-15th April. Prostate cancer was the main topic discussed this year at the Congress as there are over 340,000 new cases diagnosed each year in Europe alone. In our 'Congress Review' section we describe a new study which has suggested that radical prostatectomy alongside hormonal treatment could increase survival rates among men with advanced prostate cancer. As a result of these new findings, the treatment guidelines for prostate cancer may need to be rewritten.

One of the many aims of the EAU Congress is to discuss and review innovative techniques and scientific advancements within the field, as well as its subspecialties. Therefore, listening and understanding patient needs and concerns, as well as developing new technologies to benefit them, is of the highest importance to the urologist. As Prof Michele Pavone-Macaluso, Department of Urology, University of Palermo, Sicily, Italy, said: "The future challenges in urology remain the fusion of technological advances and the fundamental relationship with the patient."

To address this challenge, two revolutionary devices were presented at the meeting – the da Vinci Xi® Surgical System and a personalised 3D printed kidney model, both of which hope to improve surgical procedures. The da Vinci system, a '*Giant Leap Forward for Robotic Surgery*' has the potential to replace large abdominal surgeries as it allows for a minimally invasive approach. A 3D to-scale model of cancer-infested kidneys can now be printed, which will give an insight into the disease morphology. This new technology will allow surgeons to practice treating difficult cases before operating.

Prof Louis Denis, Director of Clinical Research and Development, Pfizer Oncology, USA, suggested: "With the ageing population and the increasing emphasis on quality of life, it will become more challenging to combine holistic personalised care with optimal medical treatment."

It has been suggested that nocturia is a condition which should be taken seriously by all physicians, as it can have a huge negative impact on a patient's quality of life. In Prof Christopher Chapple's paper, '*Health and Wellbeing Impact and Treatment of Nocturia – A Review of the Literature*', he discusses the impact of nocturia as well as contemporary therapeutic approaches, focusing on the role of antidiuretic pharmacotherapy.

We have several peer-reviewed articles in this edition which have received much positive attention. Our hope is that this journal proves to be not only informative - providing interesting articles - but also insightful - providing the most recent developments within the field.

Spencer Gore

Director, European Medical Journal

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

Front cover and contents photograph: Kalin Eftimov/shutterstock.com

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European Medical Journal
Urology
May 2014

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Foreword

Dr Ali Serdar Gözen

Department of Urology,
University of Heidelberg, Germany.

Dear Colleagues,

It is a great pleasure for me to introduce the 2014 issue of the *European Medical Journal – Urology*. The main highlight of this edition is the coverage of the 29th Annual European Association of Urology (EAU) Congress which was held in the beautiful city of Stockholm, Sweden from 11th-15th April 2014.

There has been much advancement within the field of urology this past year, which is why the EAU Congress once again attracted a wide range of experts and participants in the field. The scientific programme offered complete coverage of this field, including innovative approaches in urological cancers, glycosaminoglycan-replenishment therapy, and the complexity of overactive bladder.

> "I invite you to relive the memorable congress highlights and read the stimulating range of news articles through the turning of each page."

In addition to the EAU coverage, this journal also contains very interesting and high quality peer reviewed articles from basic science to robotic surgery. A wide range of topics are covered in this edition, such as advances in percutaneous nephrolithotomy, the evolution of laparoscopic surgery and new applied technologies, as well as recent therapies in bladder cancer. I invite you all to submit your work to *European Medical Journal - Urology* for next year's issue.

The equally stimulating 'What's New' section is also a highlight of the journal where interesting, ground-breaking short stories from around the world are conveyed in an easy to read format.

This open access journal is an informative resource for busy healthcare professionals with a particular interest in urology to stay abreast with the latest clinical news. I invite you to relive the memorable Congress highlights and read the stimulating range of news articles through the turning of each page. I would also invite you to visit the rest of the website to view very interesting and useful past publications and see regularly updated news stories.

I hope you all enjoy reading the articles and the Congress coverage in this journal, and I wish you all the very best with your future ventures into this exciting field.

Kind regards,

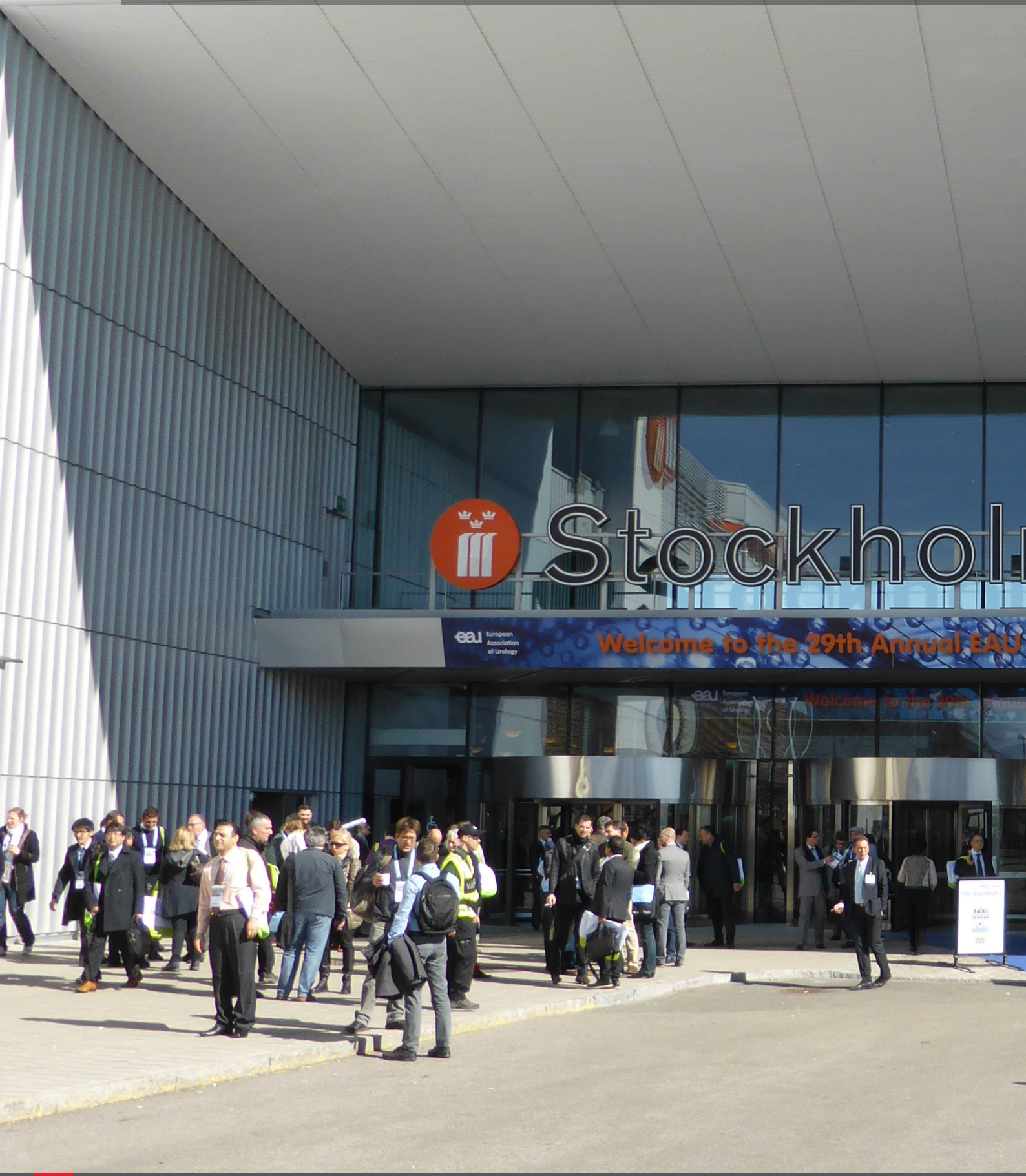
Ali Serdar Gozen

Department of Urology, Sozial Leistungsstark Kommunal (SLK)-Klinikum Heilbronn, University of Heidelberg, Heilbronn, Germany.

EAU ANNUAL CONGRESS 2014

STOCKHOLMSMÄSSAN, STOCKHOLM, SWEDEN

11TH - 15TH APRIL 2014



Welcome to the *European Medical Journal* review of the European Association of Urology Congress 2014

EMJ EUROPEAN MEDICAL JOURNAL

EAU ANNUAL CONGRESS 2014

STOCKHOLMSMÄSSAN, STOCKHOLM, SWEDEN
11TH - 15TH APRIL 2014

Welcome to the *European Medical Journal* review of the European Association of Urology Congress 2014

The 29th Annual European Association of Urology (EAU) Congress was held from the 11th-15th April 2014 in the picturesque city of Stockholm, Sweden. Comprising of 14 islands connected by 57 bridges, packed with spectacular architecture, rich foliage, fresh Scandinavian air, and the close propinquity to open water, Stockholm was the perfect location for this prestigious meeting.

Cementing its status as the platform for the international urological community, the EAU Congress continues to disseminate the latest and the most relevant knowledge from world-renowned medical experts. Clinical and research findings were presented through lectures, debates, live surgeries, presentations, and courses. Prof Per-Anders Abrahamsson, EAU Secretary General, mentioned: "The annual EAU Congress not only gathers the best minds for a critical assessment of clinical practices, but is also complemented by satellite symposia of specialists and the EAU Exhibition showcasing the newest technology in medical therapies, equipment, and the pharmaceutical industries."

The Congress attracted more than 14,000 delegates and exhibitors from over 100 countries. This year there was a record-breaking number of abstracts and posters submitted, with Italy, Germany, and the United Kingdom taking the top three spots.

One of the main Congress highlights that will resonate in the memory of the delegates was the opening ceremony, which took a musical turn in the successive performance by the soprano trio Divine, Stockholm Sinfonietta, and male student choir Stockholms Studentsångare.

> "The annual EAU Congress not only gathers the best minds for a critical assessment of clinical practices, but is also complemented by satellite symposia of specialists and the EAU Exhibition."
>
> *Prof Per-Anders Abrahammson, EAU Secretary General*

At the opening ceremony, the EAU Congress recognised members that contribute greatly to urological advancements through the presentation of prestigious awards. The main awards given were the Willy Gregoir Medal 2014 - the EAU's highest honour bestowed to a member for their contribution to Urology in Europe; the Frans Debruyne Lifetime Achievement Award - given to a member for their longstanding contribution to the activities and development of the EAU; the EAU Crystal Matula Award 2014 - given to a young promising European urologist; and the EAU Prostate Cancer Research Award 2014.

The topic most extensively covered, and considered the most studied, is the management of localised prostate cancer. The advances in robotic surgery, radical treatments to improve prostate cancer survival, the link that blood groups may influence prostate cancer recurrence, and the latest data regarding the feasibility of active surveillance were all discussed in-depth. Emphasis was also greatly placed on the recent advances in bladder cancer, surgical treatments for kidney tumours, and further information on kidney transplantation. Sessions dedicated to paediatric urology were also presented.

There was collaboration between European and international experts in the joint sessions on 'Urology Beyond Europe'. Reports from the EAU-World Chinese Joint Session, Joint Session of the EAU, and the Société Internationale d'Urologie were discussed to understand the different perspectives and challenges faced from various countries in the screening of prostate cancer.

Stem cells: a possible new tool to preserve erectile function

ERECTILE function is a key priority for preservation in patients who have had a radical prostatectomy, with stem cell injections showing promise as a regenerative medicine.

The advent of the robot-assisted laparoscopic radical prostatectomy has reduced collateral damage to penile nerves during surgery; notable are the successes in preserving the periprostatic neurovascular bundle; however, the continual updating of nerve sparing techniques has not yet succeeded in preventing involuntary damage to the cavernous nerves as a result of coagulation, stretching, and in some cases even transection. These errors cause neuropraxia, axonotmesis, and/or neurotmesis. Consequently, the degree of damage (or nerve sparing) directly correlates with the rate and time to recovery of erectile function after radical pelvic surgery.

"We still observe a high percentage of men who develop, either-or-not temporarily, erectile dysfunction. While only a small percentage of men regain erectile function as good as baseline (pre-operatively). The portion of men who do regain erectile dysfunction,.. will never reach baseline, or are not able to have pharmacologically unassisted intercourse is still a large majority of patients," explained Dr Maarten Albersen, Scientific Chairman at European Society for Sexual Medicine and Research Fellow, University Hospitals Leuven, Belgium.

Where therapies focus on preserving sexual function, regenerative medicine - grafting bio-engineered genes, cells, or tissues in place of the atrophied tissues - has been employed in many different contexts.

Gene therapy is used to stimulate endogenous tissues into nerve regeneration by restoring expression patterns *in situ*. For areas that have been more gravely damaged, whole tissues can be grown *in vitro* using the patient's own cells and matrix scaffolding.

Stem cell injection also shows promising preclinical data. It is recognised that stem cells migrate towards injured neuronal cell bodies, contributing to regeneration in a manner not fully understood but with potential as a therapeutic option for treating cavernous nerve injury.

Since denervation can occur as a result of injection, due to the Wallerian degeneration inflammatory cascade, it is now important to consider transplantation routes other than the standard intracavernous injection.

To date, other routes have not shown evidence of generating superior outcomes and therefore it is vital to focus on increasing understanding of efficacy and safety issues surrounding intrapenile stem cell injection.

Phase I and II clinical trials on intracavernous injection of stem cells are being initiated by several groups at present.

Pelvic floor muscle exercises:
the solution to premature ejaculation

PREMATURE ejaculation (PE), a common sexual disorder that blights the sex lives of many men worldwide, may be solved through pelvic floor muscle (PFM) exercises.

Defined by the International Society of Sexual Medicine as "ejaculation within a minute", PE is the most common male sexual disorder and is known to cause significant stress in relationships. The condition affects many men at some point in their lives, while others suffer lifelong problems with PE.

However, working out the PFM has been shown to cause significant improvement in patients. Already a hit with male incontinence, and recommended following surgery including prostate cancer operations, PFM exercises look to take centre stage for PE treatment.

With little positive response to a range of current treatments, all with varying effectiveness, PE sufferers need a fool-proof way to fix their problem. The answer seems to lie in the one part of the body causing them the most angst.

In a study led by Dr Antonio Pastore, Sapienza University of Rome, Italy, 40 men (aged between 19-46 years of age) suffering from PE who had had little success with other treatments had their pelvic floors exercised over a 12-week period. The men's time-to-orgasm was also analysed throughout this period.

The results were impressive; the average ejaculation time for subjects at the start of the trial was 31.7 seconds, and by the end this had increased by more than 4-fold to 146.2 seconds. 82.5% (N=33/40) of the subjects experienced significant improvements after 12 weeks, with only 12.5% (N=5/40) making negligible progress.

"This is a small study, so the effects need to be verified in a bigger trial. Nevertheless, the results are very positive," said Dr Pastore. "Previously, the men in the trial had tried a variety of treatments, including creams, behavioural therapy, SSRIs, and psychological treatments, with little success."

Dr Pastore added: "This technique seems to offer significant benefits over many existing techniques, including cost-savings and lack of side-effects. Although the exact exercises are still to be standardised, the results obtained in our patients with lifelong PE suggest that it may be considered as a therapeutic option for patients with PE."

Prof Carlo Bettocchi, Chief of the Centre of Urological Andrology, Polyclinic Hospital, University of Bari, Italy said: "This method [is] particularly welcome because it is the sufferers themselves who overcome the problem through their own efforts, which will have additional psychological benefits."

Lumenis Pulse™: making urological procedures easier

UNRIVALLED power, speed, safety, and versatility have been promised with the introduction of the Lumenis Pulse™ 120H Holmium laser platform (120 W, 80 Hz, and 6 J), designed as a superior product - enabling optimal clinical results and a stronger return on investment - for physicians performing urological procedures.

"Our new superior platform, along with a new set of supplemental tools such as fibres, morcellator, training programmes, and simulator, offers comprehensive solutions in enucleation, vaporisation of the prostate, stone flexible ureteroscopy, and percutaneous nephrolithotomy (PCNL). We strongly believe that with this new set of tools we have the right answers for reducing procedure time, while enhancing procedures' safety and efficacy to address the needs of all the major stakeholders in the healthcare industry: patients, physicians, providers, and insurers," said Ms Tzipi Ozer-Armon, CEO of Lumenis, Yokneam, Israel.

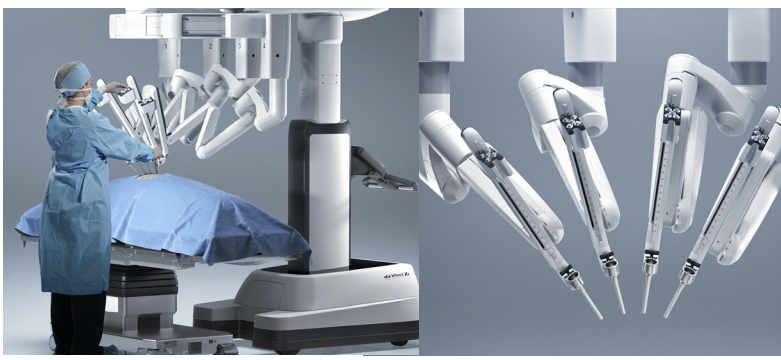
Expectations are high following positive feedback on several of the laser's capabilities. "The Lumenis Pulse™ 120H will make Holmium Laser Enucleation of the Prostate (HoLEP) procedures more precise, faster, and efficient," said Mr Tev Aho, Consultant Urologist, Cambridge University NHS Trust, UK. "When using the product, I found that no matter how fast I went with the enucleation, the haemostasis was excellent, the view was very good, and it allowed me to significantly reduce procedure time."

Mr Christof Kastner, Consultant Urologist, Cambridge University NHS Trust, said: "For vaporisation of the prostate, the Lumenis Pulse™ 120H stands apart from other available technologies and is clearly superior to KTP (Greenlight® Laser) or transurethral resection of the prostates (TURP's).

"Bleeding is minimal, tissue is easier to remove and, as we have experienced, patients can have their catheter removed almost immediately and go home the same day."

On stone dusting for flexible ureteroscopy and PCNL, Dr Mahesh Desai, Medical Director, Muljibhai Patel Urological Hospital, Nadiad, India, said: "The combination of suction with high energy laser to break the stones is innovative and very attractive.

"The laser would be faster in breaking the stone to powder than any other alternative. When using the embedded suction it definitely reduces the procedure duration and provides superior solution compared to what is currently available on the market, based on my personal experience, yet it requires a comparative study to prove it scientifically."



A giant leap forward for robotic surgery

A FRONTIER in the field of robotic-assisted minimally invasive surgery has been unveiled by Intuitive Surgical, Inc. The introduction of its new *da Vinci Xi®* System has now received Food and Drug Association (FDA) approval.

The *da Vinci* System features wristed instruments, 3D-HD visualisation, intuitive motion, and an ergonomic design. This surgical platform lends greater precision to the surgeon's hand movement from wristed instruments, allowing improved skilfulness, and accuracy. This new technology has the potential to encourage adoption and expansion of minimally invasive approaches, which might possibly replace the need for large incision abdominal surgeries.

This new surgical system caters to the needs of the surgeon through its greater range of motion and longer and thinner instrument shafts, which are designed to give superior operative reach. Other improvements include new overhead instrument arm architecture, a new endoscope digital architecture, and the ability to attach the endoscope to any arm.

"Our goal is to develop technology that enhances surgical performance," said Dr Gary Guthart, President and CEO, Intuitive Surgical, California, USA. "The *da Vinci Xi®* System's new overhead architecture means that multi-quadrant surgery can be performed without repositioning the system, an innovation long sought by surgeons who perform complex procedures. We strive to provide the most advanced, least invasive option for surgery, and we are working hard to make minimally invasive surgery the standard of care."

The technology has been made to ensure the compatibility with future technologies, e.g. *Firefly™* Fluorescence Imaging System. Although not currently available, this imaging device will be combinable with the *da Vinci Xi®* System, enabling the use of real-time visualisation to allow assessment of vessels, bile ducts, and tissue perfusion.

The *da Vinci Xi®* System has the ability to evolve with current and future technologies due to its adaptable design. There is also a low-cost version called the *da Vinci Si-e™* System, which can perform more common/lower risk procedures.

Personalised, 3D-printed, 'practice', cancer-ridden kidneys

PERSONALISED three-dimensional (3D) models of to-scale, cancer-riddled kidneys are being printed for insight into the disease morphology. The production of these models gives surgeons the perfect opportunity to practice difficult cases beforehand.

Statistically, kidney cancer is the eighth most common cancer, representing 3% of all cancers in Europe.

Computer tomography (CT) was utilised to produce a 3D scan of the kidney; the information gathered was then entered into a 3D printer to produce an exact model replica of the kidney prior to surgery.

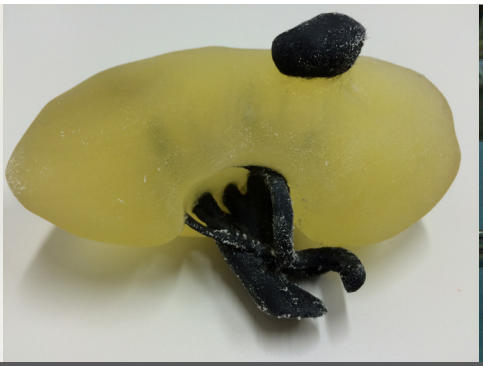
This model helped to identify the margins of kidney tumours and, due to the transparency of the resin material it is composed of, the exact positions of blood vessels were visualised. The surgeons then simulated the surgery on the kidney model's tumours, with the actual surgery performed later using robotic-assisted partial nephrectomy. A total of ten 3D models have been produced so far to assist in operations.

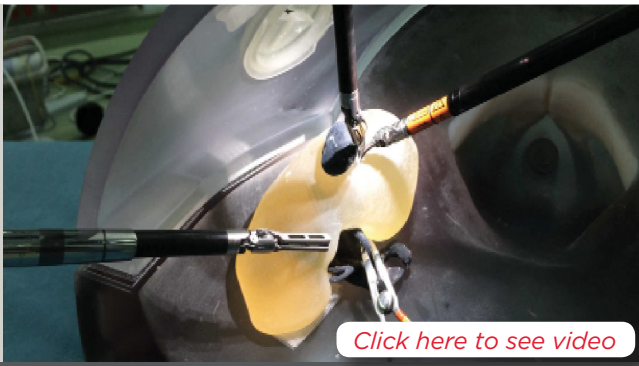
"The use of this 'hands-on' model system gave us a 3D anatomical understanding of the kidney and the tumour. This enabled the surgeon to work on a smaller area. This is important, as it means that the area where the blood supply is interrupted during surgery can be reduced, in fact we found that the shortest interruption time was only 8 minutes, compared to a normal average of 22 minutes.

> "The fact that we knew the exact location of the blood vessels helped us greatly."
>
> *Dr Yoshiyuki Shiga, Yamato Hospital, Tokyo, Japan*

"We also found that where we had to remove part of the kidney, the fact that we knew the exact location of the blood vessels helped us greatly," said Dr Yoshiyuki Shiga, lead researcher and Director, Tokyo Nephro Urology Center Yamato Hospital, Tokyo, Japan.

Dr Shiga added: "At the moment this is still an expensive technique, adding between $500 and $1,500 to the cost of surgery, but we hope that if it is more widely used then costs will fall."





Nightmare of nocturia hits patient activity levels

NOCTURIA (waking to void one or more times a night followed by sleep) has a strong adverse impact on a patient's utility, work productivity, and health-related quality of life (HRQL), with these activity levels falling further with increasing nocturia severity.

Data from a survey involving physicians and their urology patients (N=8,738) in Europe and the USA illustrated a link between a patient's activity levels and the number of voids experienced during night-time. Data showed that nocturia severity – defined by the number of hours in the first sleep period (FUSP) – inversely correlated with activity levels, how refreshed the patient felt the next day, the average number of daily naps taken, and their HRQL.

Loss of sleep as a result of a frequent need to urinate is one of the biggest problems faced by nocturia patients, with a disruption of restorative slow wave sleep in the first 4 hours having the biggest impact on a patient's sleep.

Subjects who achieved more than 4 hours of undisturbed sleep before getting up to urinate showed the greatest improvement in symptom bother, HRQL, activity levels, health status, and comparative refreshment the next day compared to those having up to 4 hours of undisturbed sleep.

The correlation between nocturia severity and patient activity levels was backed up by further results; subjects that woke to void 2 or more times a night were much more negatively impacted on HRQL, utility, and work productivity levels compared to subjects who voided once or not at all each night.

> "Nocturia is common and bothersome, but it is often under-recognised as a separate condition, and its burden underestimated."
>
> *Prof Donald Bliwise, Professor of Neurology, Emory University School of Medicine, Atlanta, USA*

Nocturia currently affects a staggering 77% of men and women aged 60-80, highlighting the urgent need to understand and treat the condition accordingly. Disturbed sleep is reported to be the worst symptom by sufferers, with one-third of patients suffering insomnia as a result of an inability to fall asleep post urination.

Prof Donald Bliwise, Professor of Neurology, Emory University School of Medicine, Atlanta, USA said: "Nocturia is common and bothersome, but it is often under-recognised as a separate condition, and its burden underestimated.

"These new data highlight the need for physicians to take nocturia seriously, given how profound its impact can be on a patient's quality of life. For people that suspect they have nocturia, they should visit their doctor to discuss treatment options."

Radial therapy for prostate cancer patients

SURVIVAL rates among men with advanced prostate cancer may increase if the treatment received, such as radical prostatectomy and hormonal treatment, specifically targets the prostate. In light of these findings, the standard treatment of advanced prostate cancer will need to be revised.

"We found that men with advanced prostate cancer have significantly improved survival after radical therapy plus hormonal treatment compared to hormonal treatment alone. We performed sensitivity tests to check that these results were unlikely to be due to abnormalities or deficiencies in the dataset, so we are confident in these results. This means we need to test these findings in a controlled study," said Dr Prasanna Sooriakumaran, Senior Clinical Researcher, University of Oxford, Oxford, UK, and Assistant Professor, Karolinska Institutet, Solna, Stockholm, Sweden.

Prostate cancer remains the second leading cause of cancer deaths among Western men, with over 40,000 men diagnosed with prostate cancer every year. The incidence of this cancer is high: 1 in 8 men will develop prostate cancer. The current standard treatment of advanced prostate cancer is androgen deprivation therapy (ADT), which promotes the reduction of cancer-stimulating androgen hormones, such as testosterone. The average survival rate under this therapy is approximately 5 years.

Records from the National Prostate Cancer Registry of Sweden, which contains most of all the prostate cancer cases (over 109,000 men) in Sweden during 1996 – 2010, were analysed. Two groups of 699 men were selected based on whether they had been offered ADT as first treatment or if they had been treated with radical prostatectomy/radiotherapy followed by ADT.

The results revealed that nearly 2.5-times the number of deaths occurred in the first group compared to those that underwent the invasive procedures and subsequent hormonal therapy. A follow-up investigation 14 years later revealed that there were 231 men that died from prostate cancer from the first group, in comparison to just 93 deaths in the second group.

According to Prof Peter Wiklund, team leader and Professor of Urology, Department of Molecular Medicine and Surgery, Karolinska Institutet, further investigations will be carried out to support this research.

> "We found that men with advanced prostate cancer have significantly improved survival after radical therapy plus hormonal treatment compared to hormonal treatment alone."
>
> *Dr Prasanna Sooriakumaran, University of Oxford, Oxford, UK*

Golden rubric of renal transplantation ruling out the role of urologist

RENAL transplantation (RTx) cannot be carried out by a single surgeon or urologist any longer; it is now considered a multidisciplinary field. In the past, the inception of centres for RTx was left in the hands of the urologist, and while their presence is still considered critical to the success of an operation, the advent of techniques requires specialists in radiology, immunology, as well as genetics, and other areas.

Seemingly indispensable are the urologists' expertise: (1) pre-transplant for urological evaluation, preparing transplant recipients, and problem solving, and (2) post-transplant to manage either living donor or cadaver nephrectomy.

Pre-transplantation complications addressed by a urologist can include 'search and treatment' for malignancy - a serious issue in RTx - and one of the 'three golden rules' or urological prerequisites. RTx patients face a 15-fold increased risk of kidney cancer alongside a significantly elevated risk of other malignancies. For recipients who were previously cancer sufferers, this also affects the timeline for surgery, with some types requiring more than a 5-year wait after remission/ successful tumour treatment before RTx.

It is during surgery however, that the role of the urologist becomes unclear. The proficient urologist, with their in-depth knowledge of renal anatomy and perseveration should be capable of performing open and laparascopic live-donor nephrectomy, cadaveric renal harvesting, transplantation, and addressing post-surgical complications.

However, the complexity of laparoscopy for live donor nephrectomy necessitates that its practitioner has superior laparascopic skills in order to recover a well-preserved kidney with minimum ischaemic time, lengthy blood vessels, and a strong vascular supply to the ureter. Therefore, in much of the USA and Europe, the challenge, and subsequent gratification from successful RTx, falls with general surgeons. Though this is not always the case, mastery of new advances in subspecialties of urology is therefore a new priority for these doctors.

"At our hospital, all donor nephrectomies (and RTx) are now performed by a urologist through a pure laparoscopic approach and suprapubic extraction of the kidney with excellent functional and cosmetic results. In experienced hands, multiple renal arteries or veins are not absolute contraindications, and laparoscopic right kidney nephrectomy is as safe as left kidney in terms of complications and graft survival," pronounced Prof Maroun Moukarzel, Chief, Department of Urology, Hotel Dieu de France, University Hospital, Saint Joseph University, Beirut, Lebanon.

Blood group influences chance of prostate cancer recurrence

ABO blood groups may have an impact on prostate cancer recurrence after surgery. This is not the first time that the variation blood grouping system has influenced the development of prostate cancer, but this relationship after surgery has not been previously investigated.

"This is the first time that anyone has shown that prostate cancer recurrence can vary with blood group. Of course we need bigger studies to confirm the effect and also to see what practical application the finding might have. For example, we know that there are wide racial and geographical variations in the distribution of the ABO blood groups, and we need to be sure that this effect is significant in other groups," said Dr Yoshio Ohno, study author and lead researcher, Tokyo Medical University, Tokyo, Japan.

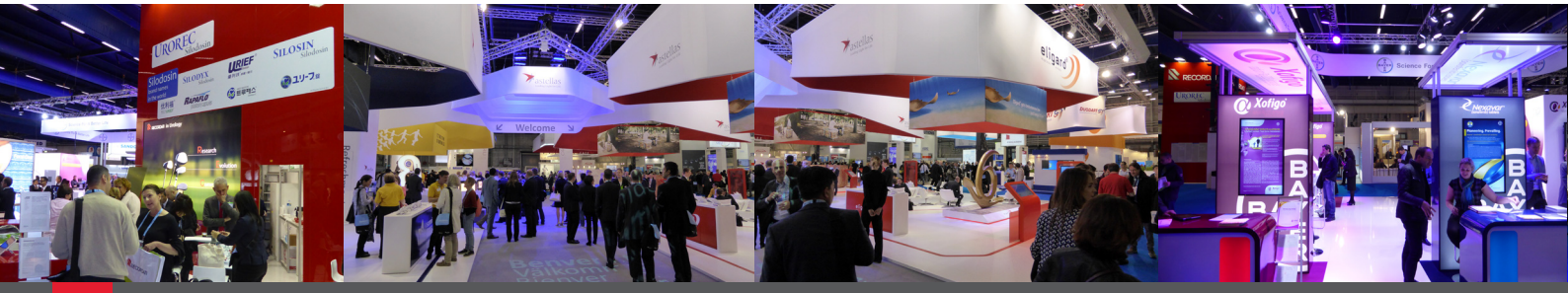
555 patients took part in a study between 2004 and 2010, which revealed that men with blood group O are 35% less likely to suffer prostate cancer recurrence following a radical prostatectomy, in comparison with a patient with blood group A. A retrospective analysis of blood group frequencies in the UK has shown that the most common blood group is O (44%) followed by A (42%).

Statistically, even after a radical prostatectomy, 30% of patients experienced an increase of prostate-specific antigen during long-term follow-up appointments.

"As yet, we don't know why the risks vary with blood group, but this work may guide us towards new avenues of molecular research on prostate cancer progression. We need to consider what these results mean in practical, clinical terms. For example, should we be counselling people with certain blood groups that they have a greater or lesser chance of recurrence, and should these risk factors be built into decisions on treatment?" Dr Ohno added.

"This is the first time that anyone has shown that prostate cancer recurrence can vary with blood group. Of course we need bigger studies to confirm the effect and also to see what practical application the finding might have."

Dr Yoshio Ohno,
Tokyo Medical University,
Tokyo, Japan



Non-attendance for prostate cancer monitoring casting uncertainty on 'active surveillance'

> "Some men might have real concerns about the risk of there being a more severe cancer. Or it may be to do with the risk of incontinence or impotence after treatment."
>
> *Dr Lukas Hefermehl, Kantonsspital Baden, Baden, Switzerland*

LACK of appointment attendance for prostate cancer patients in the long-term monitoring of the slow progressive disease is casting a shadow on the safety of the active surveillance programme. New data have shown that one-quarter of men are not in full compliance with the programme, resulting in the possibility of succumbing to the disease.

Putting low-risk prostate cancer patients on active surveillance, involving regular checks to monitor potential cancer progression, prevents the need for extensive radiotherapy or invasive surgery, which can produce negative effects such as incontinence and impotence.

To investigate this theory further, 157 patients were put on active surveillance in a 13-year study, completed in a regular-sized hospital to simulate real-life prostate cancer follow-up. 28% of the patient population were found to require treatment at the end of the study, upon which almost all were cured. Conversely, 27% of patients did not attend subsequent appointments – the defining element of active surveillance - nor did they reply to follow-up letters requesting compliance to the programme.

"We don't know exactly what the reasons are. It may be that once the patient was told that this cancer is probably 'not immediately threatening', he might downplay the importance of another test.

"On the other hand some men might have real concerns about the risk of there being a more severe cancer. Or it may be to do with the risk of incontinence or impotence after treatment, the idea of having cancer, a sense that nothing will really happen to them or it may be due to another reason which we just don't know about," said lead researcher, Dr Lukas Hefermehl, Kantonsspital Baden, Baden, Switzerland.

Virginal tissue gives birth to new endourological strategy

INCIDENCE of anastomotic stricture (AS) is significantly greater among those who undergo surgical versus laparoscopic radical prostatectomy (RP).

The heterogeneity of the recurrent AS patient population is reflected by a diverse range of treatment options for it. While there is no single established endourological treatment strategy, therapies range from implantation of urethral stents to dilatation, and electrocoagulation. There is however, a general consensus that, for first attempts, endoscopy is favoured over surgery.

The success rate of these techniques ranges from >80% for dilatation to between 50-90% for stents; the latter is looked upon by Dr Roland Dahlem, Chief Medical Officer, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Denmark and colleagues as 'obsolete' due to stent-associated complications, including encrustation, migration, and/or infection.

"In our department, we perform three times an endoscopic treatment and then an open reconstruction by transperineal reanastomosis. In patients after irradiation, we initially prefer, after endoscopic treatment failure, a urinary diversion," remarked Dr Dahlem.

Owing to their own algorithm, Dr Dahlem and colleagues advocate cold knife incision – known to have a success rate similar to dilatation - in an inverse Y-shaped manner. The technique has a success rate of 87% reported for a primary attempt of direct visual internal urethrotomy.

> "The big advantage is surgery in virginal tissue. The approach allows mobilisation and resection of scarred tissue in distal and proximal direction, and suturing of the anastomosis under direct vision."
>
> *Dr Roland Dahlem, Chief Medical Officer, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Denmark*

Yet the team have also devised their own transperineal approach, with a success rate of 93.3% and follow-up required 24.2 months later.

"The big advantage is surgery in virginal tissue. The approach allows mobilisation and resection of scarred tissue in distal and proximal direction, and suturing of the anastomosis under direct vision," described Dr Dahlem.

Recurrent AS is a troublesome complication of RP which can occur as a result of several factors from excessive blood loss during surgery, to the timing of the RP, or extravasation at the site of anastomosis.

In related studies, patients required an artificial sphincter system (AUS) to safely treat concomitant urinary incontinence – most of whom were willing to accept the necessity of AUS against the side-effects of AS - and this has therefore been seen as a positive outcome in need of further refinement.

Urological tumour treatment looks to transplant techniques for revival

WOUND infections, massive perioperative haemorrhage, and preventable technique-related accidents are the result of a stagnant system of treatment for urological tumours, leading specialists to look to the innovative field of transplantation for its reform.

The potential to cause life-threatening complications to their patients while attempting to remove renal cell carcinoma (RCC) is a challenge faced by many surgeons. Reports show that close to half of all surgical mishaps are avoidable events caused by the difficulty of aiming to achieve total surgical removal of urogenital tumour load.

The very rigid disposition of the surgical field is the main reason the heavily flawed procedures continue to be used. The selection of a technique depends on surrounding structures, the level and degree of constriction, and the presence and extent of collateral circulation in response to occlusion.

Something that can be done to overcome the significant rates of morbidity and mortality associated with tumour thrombectomy is to identify potential complications and employ preventive surgical protocols.

It is therefore important that surgical care is treated as a subspecialty and subject to continuous innovation. Still, while safety remains a big issue, there are also aims to treat tumours transabdominally without using extracorporeal circulation.

Transplantation techniques are key in this area and have been applied to urological tumours for some time. Procedures include using specific self-retaining retractors, which enhance accessibility and visibility in the upper abdominal quadrants, implementation of the trirradiate Chevron incision, vascular manoeuvres, and complete liver mobilisation plus en masse mobilisation of the pancreas and spleen.

In their own study, lead author Dr Javier González, Servicio de Urología, Hospital Central de la Cruz Roja San José y Santa Adela, Madrid, Spain and colleagues treated 68 RCC patients with level 3 and 4 tumours. All patients underwent complete tumour resection, no patient experienced intraoperative tumour embolism, and just three died in the immediate postoperative period.

Referring to other US centres reporting volumes of three cases of tumour thrombectomy per year, Dr González had noted that: "A number of other centres have employed surgical techniques derived from experience with transplantation surgery for the management of RCC with tumour thrombus. Uniformly, these centres have reported good surgical outcomes with relatively low rates of Clavien Grade 3-4 complications."

He concluded: "These experiences support the application of transplantation techniques in the management of RCC with tumour thrombus."

Improved survival in chemotherapy-naïve metastatic prostate cancer patients

XTANDI™ (Enzalutamide), an androgen receptor-signalling inhibitor, has yielded promising results in a Phase III PREVAIL trial. Xtandi™ is used for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in chemotherapy-naïve adult men.

"Oncology is a growing area of focus for Astellas, and we are committed to developing and bringing to market medicines which meet current unmet medical needs," said Dr Ayad Abdulahad, Senior Vice President, Medical Affairs and Health Economics, Astellas Pharma Europe Ltd., London, UK. "We will continue to work with our partner, Medivation, to seek the necessary European regulatory approval for Xtandi™ that will allow for its use amongst patients who have not received chemotherapy for their advanced prostate cancer."

In Europe, prostate cancer remains the most common cancer in men and approximately 40% of men progress onto metastatic disease. A high proportion of this population will not respond to androgen deprivation treatment, which is then referred to as CRPC.

The potential treatment for CRPC is Xtandi™, which targets all three steps of the androgen receptors (AR) i.e. blocks androgen binding, hinders nuclear translocation, and weakens DNA binding. This international randomised, double-blind, placebo-controlled PREVAIL trial included more than 1,700 participants in the evaluation of the drug taken once a day at a dosage of 160 mg. The endpoints for the investigation include the overall survival and radiographic progression-free survival.

"We will continue to work with our partner, Medivation, to seek the necessary European regulatory approval for Xtandi™ that will allow for its use amongst patients who have not received chemotherapy for their advanced prostate cancer."

Dr Ayad Abdulahad, Senior Vice President, Medical Affairs and Health Economics, Astellas Pharma Europe Ltd., London, UK

The results showed that Xtandi™ treatment caused a 29% reduction in risk of death and 81% reduction in risk of radiographic progression or death, thus significantly improving overall survival benefit compared with the placebo. The drug was also well tolerated by patients, reaching all secondary endpoints.

Robotic technology in paediatric urology: who is really cracking the whip?

ROBOTIC technologies used to assist in movement transfer during laparoscopy, address shortfalls of their manual predecessors, but also challenge users with their restraints in both learning and applying the technique to paediatrics.

Laparascopic surgery, now a preferential treatment, is currently limited by the immaturity of first generation equipment, in addition to the requirement that surgeons learn how to use these techniques with each new development. There is an added layer of intricacy in paediatric urological surgery too, which requires adapting to different a scale of body.

The Da Vinci System is a favoured tool, which assists in complex robotic-assisted surgery (RAS), but is not a traditional robot as it facilitates – magnifying and adding seven degrees of freedom for precision - rather than automates these procedures.

In surgery with the Da Vinci System, the physician benefits from access to an ergonomically-optimised console away from the operating table, where he is able to use hand and foot controls to operate the 'robot' and accompanying three-dimensional (3D) viewing cameras. For prolonged surgery, a less fatigued surgeon with less musculoskeletal stress is able to treat patients who will benefit from reduced blood loss and trauma, post-operative morbidity, and faster recovery due to RAS.

Studies are therefore being carried out to determine where the adoption of RAS in paediatric urology stands. Encouragingly, the results have showed that the learning curve for performing RAS pyeloplasty has decreased over time in correlation with surgical experience gained.

"RAS is increasingly being adopted within paediatric urology by not just increased numbers of common cases like nephrectomy and pyeloplasty but by the addition of new procedures like bladder reconstructive surgery where even traditional laparoscopy lagged behind," explained Mr Ramnath Subramaniam, Consultant Paediatric Urologist, Leeds Teaching Hospital NHS Trust, Leeds, UK.

RAS systems are being developed worldwide with the aim of reducing costs and increasing successes.

"It is possible that robotic surgery may prove to be cost-effective," added Mr Subramaniam.

There are also future applications for the Da Vinci System as a platform for 'stealth surgeries' such as laparoendoscopic single-site surgery, which leaves no evidence of incision, and are therefore ideal for reducing cosmetic and psychosocial effects in growing children. No major advantage has been demonstrated as yet.

EAU ANNUAL CONGRESS 2014

STOCKHOLMSMÄSSAN, STOCKHOLM, SWEDEN

11TH - 15TH APRIL 2014

EAU 2014 AWARDS

Surrounded by the world's leading experts in Urology, special awards and prizes were bestowed to exceptional dignitaries at the EAU Opening Ceremony, for the recognition of their cutting-edge achievements within the field of clinical research and practice. The chosen individuals have embodied the ideals of patience, perseverance, and dedication since their exemplary work has pushed the boundaries of urological developments. The award ceremony also serves as a reflection as to how much progress has been made and gives hope for the future through therapeutic evolution.

NEW EAU HONORARY MEMBERS

Prof Robert Flanigan, USA

Dr Seiji Naito, Japan

Prof Joachim Thüroff, Germany

MAIN AWARDS

EAU Willy Gregoir Medal 2014

For a significant contribution to the development of the urological specialty in Europe.

Prof Michele Pavone-Macaluso, Palermo, Italy

EAU Frans Debruyne Life Time Achievement Award 2014

For a longstanding and important contribution to the activities and development of the EAU.

Prof Dr Louis Denis, Antwerp, Belgium

EAU Hans Marberger Award 2014

For the best European paper published on Minimally Invasive Surgery in Urology.
Supported by an unrestricted educational grant from KARL STORZ GMBH & CO.KG.

Dr Christopher Netsch, Hamburg, Germany

Complications and Early Postoperative Outcome in 1080 Patients after Thulium Vapoenucleation of the Prostate: Results at a Single Institution.

EAU Crystal Matula Award 2014

For a young promising European urologist.
Supported by an unrestricted educational grant from LABORIE.

Dr Shahrokh F. Shariat, Vienna, Austria

EAU Innovators in Urology Award 2014

For inventions and clinical contributions which have had a major impact on influencing the treatment and/or diagnosis of a urological disease.

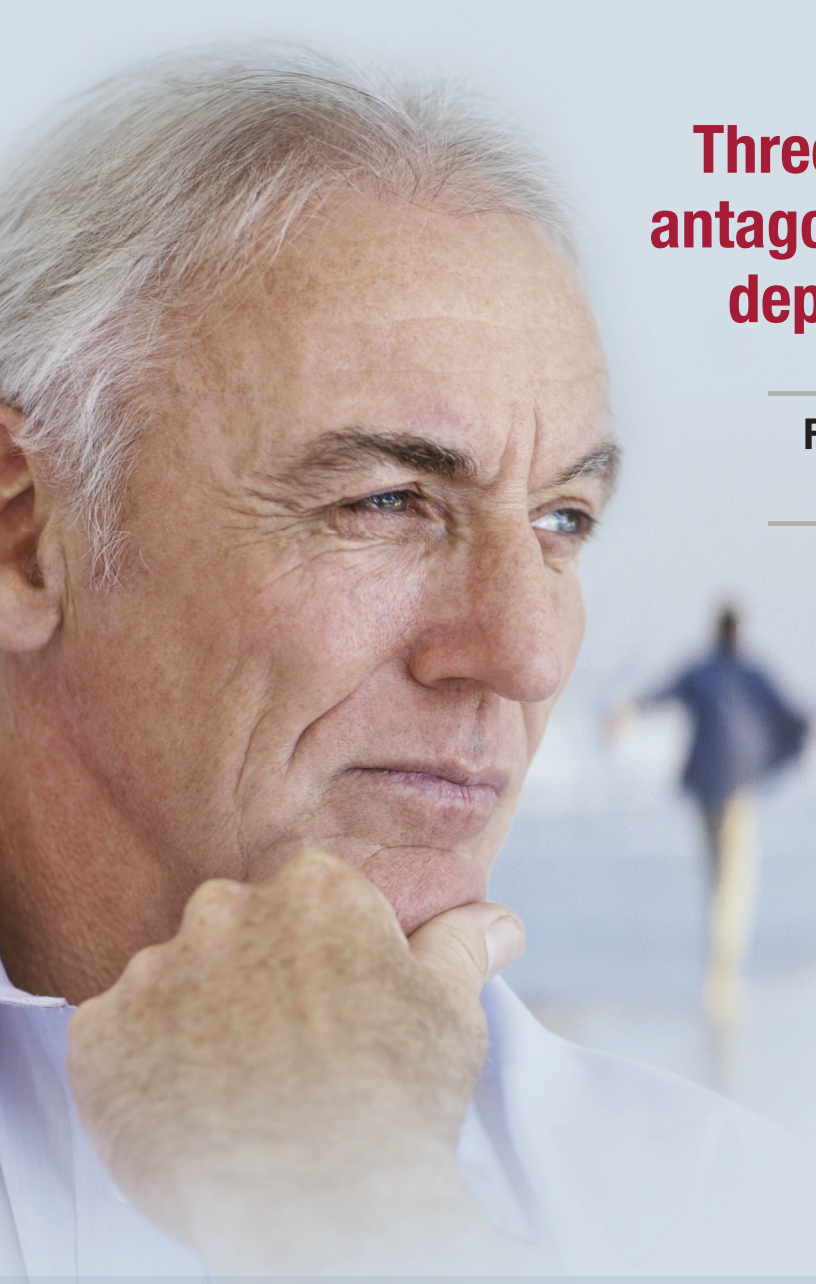
Prof Dr Richard Gaston, Bordeaux, France

EAU Prostate Cancer Research Award 2014

For the best paper published on clinical or experimental studies in prostate cancer.
Supported by an unrestricted educational grant from the FRITZ H. SCHRÖDER FOUNDATION.

Prof Dr Zoran Culig, Innsbruck, Austria

Epithelial-to-Mesenchymal Transition Leads to Docetaxel Resistance in Prostate Cancer and Is Mediated by Reduced Expression of miR-200c and miR-205.



Three good reasons to use an antagonist in advanced hormone dependent prostate cancer

Firmagon® - Overall better disease control compared to LHRH agonists[1]

- Significantly faster reduction in prostate specific antigen (PSA) compared to leuprorelin[2]
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  In those patients at higher risk of PSA failure (PSA>20ng/ml) degarelix delayed progression or death by 7 months compared with leuprorelin[4]
- Better serum alkaline phosphatase (S-ALP) control and potentially longer control of skeletal metastases[5]

IN ADDITION:

- Novel mode of action and the only GnRH antagonist licensed for advanced hormone-dependent prostate cancer in the UK[6]
- Lower probability of CV events than agonists in patients with a history of cardiovascular disease at baseline[7]
- Decreased joint, musculoskeletal and urinary tract events[8]

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References: 1. Miller K. Disease control-related outcomes from an analysis of six comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone (LHRH) agonists. Poster presented at EAU March 2013. **2.** Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson B, *et al.* The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. Br J Urol Int 2008; 1531-1538. **3.** Tombal B, Miller K, Boccon-Gibot L, Schröder F, Shore N, *et al.* Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. Eur Urol 2010; 57(5): 836-842 **4.** Van Poppel H. *et al.* Int J Urol 10.1111/k.1442-2042.2012. **5.** Schröder FH, Tombal B, Miller K, Boccon-Gibod L, Shore ND, *et al.* Changes in alkaline phosphatase levels in patients with prostate cancer receiving degarelix or leuprolide: results from a 12-month, comparative, phase III study. Br J Urol Int 2009;106:182-187. **6.** Firmagon® 80-120mg injection summary of product characteristics. Ferring Pharmaceuticals Ltd. November 2013 (last accessed on emc website March 2014). **7.** Albertsen P, Klotz L, Tombal B, *et al.* Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol 2014; 65(3):565-73. **8.** Klotz L, Miller K, Crawford Ec, *et al.* Disease control outcomes from analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. Eur Urol 2014; In press.

Prescribing Information: Firmagon®(degarelix) 120mg and 80mg powder and solvent for solution for injection. **Please consult the full Summary of Product Characteristics before prescribing. Name of Product:** Firmagon 120mg and 80mg powder and solvent for solution for injection. **Composition:** Each vial contains 120mg or 80mg degarelix (as acetate). **Indication:** Firmagon is a gonadotrophin releasing hormone (GnRH) antagonist indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer. **Dosage and administration:** For subcutaneous use only. Starting dose – 240mg administered as two subcutaneous injections of 120mg each. Maintenance dose – 80mg administered monthly as one subcutaneous injection. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special Warnings and Precautions:** Long-term androgen deprivation therapy may prolong the QT interval. The benefit/risk ratio must be thoroughly appraised in patients with a history of a corrected QT interval over 450 msec, in patients with a history of or risk factors for torsades de pointes and in patients receiving concomitant medicinal products that might prolong the QT interval as Firmagon has not been studied in these patients. A thorough QT study showed that there was no intrinsic effect of Firmagon on QT/QTc interval. Monitoring of liver function in patients with known or suspected hepatic disorder is advised during treatment. Firmagon has not been studied in patients with severe renal impairment, patients with a history of severe untreated asthma, anaphylactic reactions or severe urticaria, or angioedema. It can be anticipated that long periods of testosterone suppression in men will have effects on bone density. Diabetic patients may require more frequent monitoring of blood glucose when receiving androgen deprivation therapy. Cardiovascular disease such as stroke and myocardial infarction has been reported in the medical literature in patients with androgen deprivation therapy. Therefore, all cardiovascular risk factors should be taken into account. **Side effects:** *Very Common:* hot flush, injection site adverse reactions. *Common:* anaemia, weight increase, insomnia, dizziness, headache, diarrhoea, nausea, liver transaminases increased, hyperhidrosis (incl. night sweats), rash, musculoskeletal pain and discomfort, gynaecomastia, testicular atrophy, erectile dysfunction, chills, pyrexia, fatigue, Influenza-like illness. *Uncommon:* hypersensitivity, hyperglycemia/ diabetes mellitus, cholesterol increased, weight decreased, appetite decreased, changes in blood calcium, depression, libido decreased, mental impairment, hypoaesthesia, vision blurred, cardiac arrhythmia (incl. atrial fibrillation), palpitations, QT prolongation, hypertension, vasovagal reaction (incl. hypotension), dyspnoea, constipation, vomiting, abdominal pain, abdominal discomfort, dry mouth, bilirubin increased, alkaline phosphatase increased, urticaria, skin nodule, alopecia, pruritus, erythema, osteoporosis/osteopenia, arthralgia, muscular weakness, muscle spasms, joint swelling/stiffness, pollakiuria, micturition urgency, dysuria, nocturia, renal impairment, incontinence, testicular pain, breast pain, pelvic pain, genital irritation, ejaculation failure, malaise, peripheral oedema. *Rare:* neutropenic fever, anaphylactic reactions, myocardial infarction, cardiac failure. Please consult the full Summary of Product Characteristics for further information about side effects. **Presentation:** Firmagon 120mg contains 2 vials of 120mg powder for solution for injection and 2 solvent pre-filled syringes, 2 vial adaptors and 2 administration needles. Firmagon 80mg contains 1 vial of 80mg powder for solution for injection and 1 solvent pre-filled syringe, 1 vial adaptor and administration needle. Solvent for both 120mg and 80mg: Water for injection. **Marketing Authorisation Number:** 80mg: EU/1/08/504/001, 120mg: EU/1/08/504/002. **Marketing Authorisation Holder:** Ferring Pharmaceuticals A/S, Kay Fiskers Plads 11, DK-2300 Copenhagen S, Denmark. **Legal category:** POM. **Basic NHS price:** Firmagon 120mg - £260.00; Firmagon 80mg - £129.37 **Date of preparation:** January 2014. Firmagon® is a registered trademark. **PI Job Code:** FN/648/2012/UK(3)

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THE MANY FACES OF MCRPC: ASSESSING PATIENT PROFILES AND TAILORING TREATMENT IN A CHANGING THERAPEUTIC LANDSCAPE

Summary of Presentations from the Bayer Healthcare Symposium, held at the 29th Annual EAU Congress, Stockholm, Sweden, on 11th April 2014

Chairperson

Manfred Wirth[1]

Speakers

Fred Saad,[2] Joe O'Sullivan,[3] Anders Bjartell,[4] Wolfgang Loidl[5]

1. University Hospital Carl Gustav Carus Dresden and Technical University of Dresden, Dresden, Germany
2. Centre Hospitalier de l'Université de Montréal, Montréal, Canada
3. Centre for Cancer Research and Cell Biology, Queen's University Belfast and Northern Ireland Cancer Centre, Belfast, UK
4. Lund University, Malmö, Sweden
5. St Vincent's Hospital, Linz, Austria

Disclosure: Speakers participating in this symposium received honorarium from Bayer Healthcare.
Acknowledgements: Writing assistance provided by Dr Tabasum Mughal.
Support: The publication of this article was funded by Bayer Healthcare. The views and opinions expressed are those of the authors and not necessarily of Bayer Healthcare.
Citation: EMJ Urol. 2014;1:28-32.

MEETING SUMMARY

The Bayer-sponsored satellite symposium brought together a range of experts in the field of metastatic castrate-resistant prostate cancer (mCRPC), including Professors Fred Saad, Joe O'Sullivan, Anders Bjartell, Wolfgang Loidl, and Manfred Wirth. This distinguished faculty came together to discuss the changing paradigm and therapeutic options available in the management of mCRPC, offering the opportunity for interactive audience participation to discuss the current treatment landscape.

Understanding the Unmet Needs and Treatment Options in mCRPC: A Rapidly Changing Field

Professor Fred Saad

Prof Fred Saad began his presentation by introducing the audience to the different prostate cancer disease states. These range from patients with localised prostate cancer to those experiencing advanced disease with primary prostate-specific antigen (PSA) failure, and those who progress to develop CRPC following second PSA failure.

Treatment options available before 2010 constituted largely supportive agents including androgen deprivation therapy (ADT) and docetaxel, which was the first agent to show improvements in overall survival; ultimately however, patients would eventually succumb to mCRPC.[1] Recently, the treatment of mCRPC has evolved with Phase III studies showing efficacy as well as improvements in both quality of life and survival with several drugs that precede docetaxel or that may be used as a replacement.

Prof Saad presented data from the pivotal TAX327 study in which docetaxel (plus prednisolone)

demonstrated improved long-term survival when given to patients every 3 weeks versus mitoxantrone and prednisone.[2] In addition to these data, administration of cabazitaxel (plus prednisolone) in patients previously treated with docetaxel resulted in a 30% reduction in the risk of death, and a 2.4 month improvement in overall survival in patients who were currently taking docetaxel or had previously taken docetaxel.[3] Similarly, the administration of abiraterone and prednisolone in mCRPC patients who have already received chemotherapy, resulted in a 4.6 month improvement on overall survival with a 26% reduction in the risk of death.[4] The 2012 AFFIRM study confirmed that targeting the androgen receptor is a reasonable approach; use of enzalutamide after chemotherapy led to a 36% reduction in the risk of death and a 4.8 month improvement in overall survival.[5]

Prof Saad went on to present recent data from a Phase III study during which chemotherapy-naïve patients received abiraterone in combination with prednisolone. This not only showed a 5 month improvement in overall survival, but also doubled radiographic progression-free survival (PFS) when compared to prednisolone alone; however, the results did not achieve statistical significance.[6] Most recently, the PREVAIL study, which included asymptomatic or slightly symptomatic patients treated with enzalutamide versus placebo has reported an increased overall survival of 2.2 months and an 81% improvement in radiographic PFS.[7] Prof Saad also considered results from the IMPACT trial; in asymptomatic or slightly symptomatic patients, sipuleucel-T increased overall survival; however, in contrast to enzalutamide, there was no effect on PFS or PSA response.[8] Finally, in the ALSYMPCA trial, Radium-223 showed a 3.6-month improvement in median overall survival, providing a meaningful option for patients pre or post-chemotherapy.

Bone metastasis is a recurrent problem in patients with mCRPC, occurring in 90% of this patient population. The consequences of bone metastases are skeletal related events (SREs), which are associated with increased mortality, increased pain and hospitalisation, and decreased mobility and quality of life.[9,10] Therefore, reducing the rate of SREs is an important step in improving disease burden in patients with CRPC, supported by data that suggest that fractures negatively affect survival.[11,12]

Prof Saad concluded his talk by summarising the current available therapeutic agents, emphasising that clinical trials remain an important and active area of research. He emphasised that combining these various therapies and using them correctly on an individual patient basis is the key to reducing complications of CRPC and improving long-term survival.

Energising the Treatment Landscape: Efficacy and Safety of a New Alpha-Emitting Radiopharmaceutical in mCRPC

Professor Joe O'Sullivan

Prof Joe O'Sullivan began his presentation by introducing Radium-223, an alpha-emitting pharmaceutical, which is a radioactive isotope of radium and a calcium mimetic. It is able to target bone metastasis by generating highly localised, intense radiation zones that induce non-repairable, double-strand DNA breaks.[13]

He went on to describe data from ALSYMPCA, a Phase III clinical trial in which mCRPC patients, with at least two symptomatic bone metastases, were treated with Radium-223 and best standard of care versus best standard of care alone.[11] Treatment duration was 6 months and patients were followed-up for 3 years. Results showed that treatment with Radium-223 significantly reduced the risk of death by 30% and improved overall survival by 3.6 months, regardless of previous treatment received. In addition to this, systematic skeletal events (SSEs) were delayed by 5.8 months in these patients. There was an increase in quality of life scores as assessed by the FACT-P scoring system.[14] Examination of adverse events in this trial revealed that Radium-223 is very well tolerated: Grade 3/4 side-effects were comparable between the Radium-223 and the placebo group.

Prof O'Sullivan concluded his talk by suggesting that Radium-223 may provide a new standard of care for the treatment of patients with CRPC and bone metastasis. By targeting bone metastases, Radium-223 has shown improved overall survival and time to SSE, reduced pain, and increased QoL. In particular, its high affinity for osteoblastic bone metastases and predominant gastrointestinal excretion, as well as no close-contact restrictions required after therapy, make it an ideal first-in-class candidate for mCRPC.

Examining Biomarkers in the Management and Treatment of Patients with mCRPC

Professor Anders Bjartell

Prof Anders Bjartell opened his session by introducing the idea of the use of predictive biomarkers in improving disease outcomes in mCRPC. The presentation began on an interactive platform during which the audience were asked if they used either alkaline phosphatase (ALP) or PSA as a prognostic or predictive biomarker in the mCRPC setting. It continued with a discussion about the correlation between these two markers and the subsequent therapeutic success.

The PSA response rate to therapy is limited and varies greatly with different therapies, ranging from 54% with enzalutamide to just 3% with sipuleucel-T, suggesting that clinical benefit may not necessarily correlate with PSA decline.[5,8] This variation is largely dependent on the mechanism of action of the therapy used; therapies that target androgen action may result in higher levels of PSA decline as PSA is directly regulated by androgen receptors.[15] Therefore, PSA should be used with other prognostic markers in order to establish a patient's response to therapy.[1,16,17]

Another prognostic marker, ALP, is elevated in most patients with bone metastases and baseline ALP provided prognostic information in mCRPC, with reductions in total ALP reflecting biological changes in bone turnover and osteoblastic activity.[18] Despite this, it remains to be determined whether elevations in ALP levels are a true predictor of the benefits of a therapy that treats bone metastases.[19] Prof Bjartell presented results from the pivotal ALSYMPCA study, in which Radium-223 treatment significantly reduced total ALP and PSA levels by 30%.[11] In addition to this, ALP decline was associated with an overall increase in survival in patients treated with Radium-223.[20]

Prof Bjartell concluded that ALP may provide important prognostic information in mCRPC and that further ongoing analyses may shed further light on whether this biomarker is indeed a useful indicator for treatment response.

Exploring the Patient Journey in mCRPC via Interactive Case Studies

Professor Wolfgang Loidl

Prof Wolfgang Loidl commenced his talk by outlining the treatment journey in Austria, where there is an established PSA screening programme to detect early CRPC. However, PSA testing has been reported to decline over the past 2 years due to unqualified controversy in the media. Within his presentation, Prof Loidl utilised his own clinical cases to illustrate key points of the discussion.

Prof Loidl went on to discuss a patient case study of a 60-year-old male patient diagnosed with CRPC in 1991. At this time only very limited therapeutic options were available. The patient was subsequently treated with a regimen of radiotherapy to the prostate and pelvic lymph nodes but the tumour returned. The patient received hormone therapy and PSA levels were brought down to 0.0 ng/mL. In 2009, the tumour returned again with a PSA of 1.8 ng/mL. As a regime of hormone and radiation therapy and surgical intervention was ineffective, the patient was given a second round of hormone therapy (bicalutamide and gonadotropin-releasing hormone [GnRH]). Although the patient had no symptoms, a single spot was still observed in the ileum and he was subsequently treated with docetaxel (plus prednisolone) and denosumab, which brought his PSA levels down from 5.5 ng/mL to 2.0 ng/mL. Clinicians in the audience were invited to discuss the treatment plan that they would embark on in the case of this patient, with varied responses ranging from continuing therapy to re-assessment of the patient's condition. Chemotherapy was stopped after three cycles, following which PSA levels rose to 30 ng/mL. This was followed by two more cycles of docetaxel (plus prednisolone) therapy after which the patient requested a break from chemotherapy.

After this break, the patient returned to the clinic with a PSA of 122 ng/mL and heavy pain; however, the patient refused chemotherapy. The audience went on to discuss treatment options available to patients who are averse to chemotherapy. Providing a follow-up, Prof Loidl informed that unfortunately the patient subsequently died of mCRPC a few months later.

Professor Loidl continued with the presentation of a second case of a 68-year-old male diagnosed with CRPC in 2007. The patient received ADT in combination with radiotherapy. His PSA levels were 0.9 ng/mL 1 year following the commencement of therapy. These rose from 1.5 ng/mL to 4.1 ng/mL, prompting a restart of ADT. Within a year, his PSA levels were down to 0.7 ng/mL. Within 2 years, the patient showed multiple lesions in the spine and a PSA level of 10 ng/mL. The audience was asked how best to proceed with this patient and concerns were raised about the lack of correlation between PSA levels and the severity of disease, with a possible indication that the patient may have neuroendocrine differentiation.

Continuing with the case, the audience learned that the patient went on to receive docetaxel (plus prednisolone) but requested a break from chemotherapy for 2 months. The patient's PSA levels increased to 35 ng/mL and bone pain returned. Docetaxel (plus prednisolone) therapy was then resumed following the progression of bone metastasis and increasing pain. The PSA level of the patient continued to rise and was accompanied by increasing pain. In contrast to the previous case, at this time several new therapies provided treatment options for this patient. From April to September 2013, the patient received abiraterone therapy (plus prednisolone); however, he continued to experience pain and increasing PSA levels. Cabazitaxel (plus prednisolone) therapy was initiated from September to November 2013 resulting in a further increase in PSA levels from 353 to 1,232 ng/mL. Circulating tumour cell counts (CTCs) were 155 and the patient was in pain. In December 2013, Radium-223 therapy was initiated. Previously, Radium-223 was not available as European Medicines Agency (EMA) approval was obtained in November 2013 and the product was launched for the first time in Austria in December 2013. After only three cycles of Radium-223 therapy, PSA levels for this patient decreased from 1,232 to 709 ng/mL, a reduction in CTCs was seen from 155 to 22, and there was a marked reduction in pain. The positron emission tomography computed tomography scan showed stabilisation of bone lesions. Prof Loidl concluded his talk by summarising the patient's treatment journey, highlighting Radium-223 as a potential therapeutic option for patients with mCRPC and symptomatic bone metastases.

The mCRPC Treatment Continuum: Analysing Typical Patient Profiles. Questions from the Floor, Final Remarks, and Meeting Close

Professor Manfred Wirth

Prof Manfred Wirth concluded this session on mCRPC management with an overview of the currently available therapies. Similar survival benefits for newer therapies range from 3.6 months to 5.8 months in chemo-naïve and chemo-treated patients, respectively.[11,12,14] Prof Wirth compared the newer available agents with those that are currently best in standard of care, showing data which suggest that although both sets of agents have similar survival benefit in mCRPC patients, they have very different safety profiles.[2,7,8] These similar levels of overall survival are important when considering adjusting a patient's treatment regime.

In particular, the encouraging efficacy and safety profile of Radium-223 suggests that this agent may be considered as a potent anti-tumour agent for patients with mCRPC and symptomatic bone metastases. Its ability to significantly improve overall survival, prolong time-to-first symptomatic skeletal event, and increase quality of life, make it a promising future therapy, as recommended by the EAU and the National Comprehensive Cancer Network.[21,22]

Prof Wirth drew this session to a close by stating that the changing treatment modalities in mCRPC therapy have given clinicians and patients multiple treatment options. Treatment decisions should ideally include consideration of the patient profile, clinical symptoms, and patient preference in order to develop a regime that can offer optimal clinical benefit.

This symposium highlighted important treatments in the field of mCRPC that are continually evolving. In particular, the treatment of bone metastasis, which is a major cause of morbidity and mortality in mCRPC patients, has been shown to improve long-term survival. The ongoing clinical development of newer therapies will increase understanding of the best way to optimise treatment in patients with metastatic cancers.

REFERENCES

1. Saad F, Hotte SJ. Guidelines for the management of castrate-resistant prostate cancer. Can Urol Assoc J. 2010;4(6):380–4.

2. Berthold DR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol. 2008;26(2):242–5.

3. de Bono JS et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147–54.

4. de Bono JS et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995–2005.

5. Scher HI et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187–97.

6. Ryan CJ et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368(2):138–48.

7. Beer T et al. Oral presentation at ASCO Genitourinary Cancers Symposium, 30 January–01 February 2014, San Francisco, USA. Abstract LBA1; J Clin Oncol 2014;32(suppl 4): abstract LBA1.

8. Kantoff PW et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411–22.

9. Saad F et al. Continuing benefit of zoledronic acid in preventing skeletal complications in patients with bone metastases. Clin Genitourin Cancer. 2007;5(19):390–6.

10. Saad F et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94:1458–68.

11. Parker C et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213–23.

12. Pezaro CJ et al. Visceral disease in castration-resistant prostate cancer. Eur Urol. 2014;65:270–3.

13. Henriksen G et al. Significant antitumor effect from bone-seeking, alpha-particle-emitting (223)Ra demonstrated in an experimental skeletal metastases model.

Cancer Res. 2002;62:3120–5.

14. Parker C et al. Updated survival, quality of life (QOL), and safety data of radium-223 chloride (Ra-223) in patients with castration-resistant prostate cancer (CRPC) with bone metastases from the phase 3 double-blind, randomized, multinational study (ALSYMPCA). Presented at ESMO, 28 September–02 October 2012, Vienna, Austria. Poster 898PD.

15. Balk SP et al. Biology of prostate-specific antigen. J Clin Oncol. 2003;21:383–91.

16. EAU guidelines on prostate cancer 2013. Available at: http://www.uroweb.org/guidelines/online-guidelines/. Accessed 07 May 2014.

17. National Comprehensive Cancer Network clinical practice guidelines in oncology (NCCN Guideline®) prostate cancer v.3.2012. Available at: www.nccn.org. Accessed 07 May 2014.

18. Sonpavde G et al. Serum alkaline phosphatase changes predict survival independent of PSA changes in men with castration-resistant prostate cancer and bone metastasis receiving chemotherapy. Urol Oncol. 2012;30:607–13.

19. Armstrong AJ et al. Biomarkers in the management and treatment of men with metastatic castration-resistant prostate cancer. Eur Urol. 2012;61:549–59.

20. Sartor O et al. Correlation between baseline variables and survival in the radium-223 dichloride (Ra-223) phase III ALSYMPCA trial with attention to total ALP changes. J Clin Oncol. 2013;(suppl; abstract 5080).

21. Heidenreich A et al. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65:467–79.

22. Mohler JL et al. Prostate cancer, version 1.2014. J Natl Compr Cancer Netw. 2013;11:1471–9.

INNOVATIVE APPROACHES IN UROLOGICAL CANCERS

Summary of Presentations from the Ipsen Symposium, held at the 29th Annual EAU Congress, Stockholm, Sweden, on 12th April 2014

Chairperson

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Disclosure: Speakers participating in this symposium received honorarium from Ipsen. The views and opinions expressed are exclusively those of the authors.
Acknowledgements: Writing assistance provided by ApotheCom ScopeMedical.
Support: The publication of this article was funded by Ipsen.
Citation: EMJ Urol. 2014;1:33-40.

How to Better Identify Non-Muscle Invasive Bladder Cancer?

Professor Joan Palou Redorta

With approximately 150,000 new cases of bladder cancer diagnosed each year, and two-thirds of these being non-muscle invasive bladder cancer (NMIBC), it is important to perform an accurate diagnosis using cystoscopy, ensuring that the whole bladder is scrutinised.[1] Knowledge of a positive cytology improves tumour detection rates and may lead to a more thorough cystoscopy.[2]

Recurrence of NMIBC occurs for a variety of reasons, including persistence from residual tumour, due to incomplete transurethral resection of bladder tumour (TURBT), or new tumour growth.[3] TURBT quality is of great importance; from tumour detection by systematic inspection of the bladder to complete removal of tumour margins in order to minimise residual tumour tissue in the bladder.[4] Improved tumour detection and resection may lead to improved TURBT results and ultimately reduce recurrence rates for NMIBC.

Photodynamic diagnosis (PDD) relies on the instillation of a solution of hexaminolevulinate (HAL) into the bladder, which interferes with the heme biosynthetic pathway. This leads to intracellular selective accumulation of photoactive porphyrins (PAPs), particularly protoporphyrin IX (PpIX), in tumour cells. Under subsequent blue light (BL) illumination, the PAPs emit red light, enabling specific and accurate visualisation of the tumour.

Several studies have described how improvements in tumour detection and resection has led to a decrease in recurrence rates. One study showed a recurrence rate at 9 months of 47% in the PDD HAL arm (HAL BL cystoscopy [BLC]) compared with 56% in the white light cystoscopy (WLC) arm.[5] A long-term follow-up of this trial has shown an increase in recurrence-free survival (RFS) from 9.4 months with WLC to 16.4 months with HAL BLC.[6] In addition, a review of current literature found 44 studies which compared BLC with WLC and showed an increase of 7–30% in the detection of papillary tumours and carcinoma *in situ* (CIS), a 20% decrease in the presence of residual tumour after TURBT and prolonged RFS at 12 months by 10.9–27.0%.[7] A meta-analysis of nine studies also showed that HAL BLC was associated with improved detection of bladder tumours, with 25% of tumours being only detected with HAL BLC.[8] This resulted in reduced recurrence rates using BLC compared with WLC.[8]

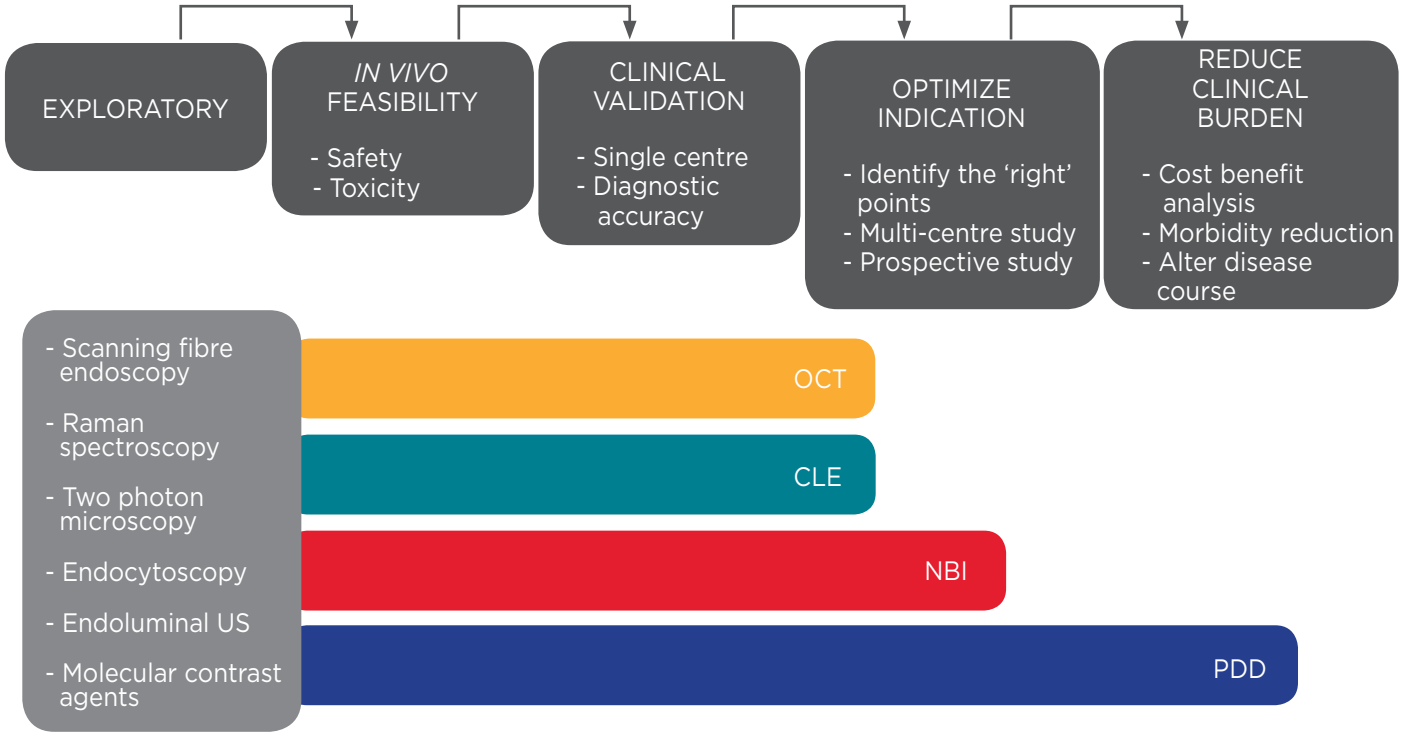

Figure 1: New optical imaging technologies for bladder cancer.
Adapted from Liu et al.[15]

Despite the number of missed tumours, there was still an overall improvement in recurrence rates. This could be explained by the use of adjuvant chemo/immunotherapy, which impacts on the outcome of tumours that are missed by TURBT[7] and leads to reduced disease recurrence rates.[9] In Prof Palou's own clinic, re-TURBT detected residual disease in 17% of cases. However, this translated to an 11% recurrence rate at 3 months.[10] In this case the discrepancy was attributed to adjuvant Bacille Calmette-Guérin (BCG) immunotherapy reducing the number of recurrent tumours.[10]

BLC is also useful in those patients with positive urine cytology but negative WLC. In one of two studies, of 77 patients with positive urine cytology but no evidence of disease under WLC, 82% were diagnosed with urothelial cell carcinoma (UCC) of the bladder or preneoplastic lesions after BLC.[11] In a second study, of 23 patients with a positive urine cytology who were negative after WLC, 26% were subsequently diagnosed with UCC of the bladder or preneoplastic lesions, with additional pathology detected in 32% of these patients after HAL BLC.[12]

As a result of these findings, the EAU 2013 guidelines state that multiple biopsies of the bladder (MBB) are to be performed in the presence of positive cytology, even if the tumour cannot be visualised.[1] Biopsies are also recommended if the tumour has a non-papillary appearance, or if the urothelium appears abnormal.[1] As prostatic urethra involvement has been found to be a prognostic factor for NMIBC,[13] and PDD is not useful in this setting, the EAU has a Grade C recommendation that MBB of the prostatic urethra should be undertaken.[1] Cold-cup biopsy of the prostatic urethra should be performed if CIS is suspected due to the possibility of stromal invasion, and obtained during TURBT at follow-up.[14] The EAU guidelines assign a Grade B recommendation for a PDD-guided biopsy to be performed instead of random biopsies when bladder CIS or high-grade tumour is suspected, such as a tumour with positive cytology or a recurrent tumour with a previous history of a high-grade lesion.[1]

Other optical imaging technologies are available for bladder cancer diagnosis,[15] including confocal laser endomicroscopy and optical coherence tomography, which are still used for clinical validation and to provide diagnostic accuracy (Figure 1).[15] In addition, narrow-band imaging (NBI), a contrast-enhancing technique, can be used to increase the visibility of capillaries and

other delicate surface structures to identify areas of increased vascularisation, which are indicative of tumour invasion.[16] In a study of 427 patients evaluated for tumour recurrence by WLC followed by NBI cystoscopy, 24% of the patients had tumour recurrences, with 87% of these detected by both WLC and NBI cystoscopy; however, 100% were detected by NBI cystoscopy alone.[17] Of the detection technologies available, studies have shown that PDD can lead to an overall reduction in clinical burden, but further evaluation is needed to determine whether this is the case for the other visualisation methods described here.[15]

In conclusion, tumour recurrence is not due to tumour biology alone, and cystoscopy as well as TURBT procedures need to be conducted thoroughly. HAL BLC is one of the imaging methods available, but the efficacy of plain imaging methods such as NBI will require further evaluation.

Evolution of Individualised Medicine with GnRHa Treatment in mCRPC: Concept of Backbone Therapy

Professor Peter Hammerer

Despite changes in treatment patterns, androgen deprivation therapy (ADT) remains the mainstay for the management of advanced prostate cancer.[18] However, results of a recent poll showed that 72% of urologists and oncologists halt ADT when using chemotherapy following diagnosis of castration-resistant prostate cancer (CRPC).[19] In addition, 31% of this group would initially prescribe this chemotherapy without a gonadotrophin-releasing hormone agonist (GnRHa), even though several national and international guidelines recommend hormone therapy when prescribing additional treatment.[19]

There is much discussion concerning ADT and the optimal levels of testosterone in castrated men. EAU guidelines recommend levels of <50 ng/dL;[20] however, one study showed that 44% of patients had very low levels of testosterone (<20 ng/dL), and that, in terms of prognosis as measured by progression-free survival, there was a cut-off at approximately 32 ng/dL, suggesting that the optimal levels of testosterone could be lowered.[21] This study comprised of only 73 patients.

There is also debate around whether or not complete androgen blockade is needed. A meta-analysis of 27 randomised trials of men with metastatic or locally advanced prostate cancer compared the effects on survival of androgen suppression alone, or with an anti-androgen such as nilutamide, flutamide, or cyproterone acetate. The addition of an anti-androgen improved 5-year survival by 2–3%; however, the range of uncertainty regarding the actual benefit of this increase was between 0-5%.[22]

In addition to recommending testosterone levels <50 ng/dL and the addition of an anti-androgen, the EAU guidelines also state that three consecutive rises of prostate-specific antigen (PSA) over a nadir of 2 ng/mL is required in order to define prostate cancer as castration-resistant. This definition also requires PSA progression despite hormonal manipulations, or the progression of osseous lesions.[23–25] The recommendation for ADT despite PSA progression comes from a study of patients refractory to orchiectomy and testosterone levels <50 ng/dL. Patients stimulated with a synthetic androgen and then treated with chemotherapy showed reduced survival compared to non-stimulated patients receiving chemotherapy, suggesting a need to suppress the androgen pathway.[24] A retrospective trial also came to a similar conclusion of continuing ADT, due to its association with a median survival advantage of 2–6 months.[26]

Prostate cancer progresses despite a low testosterone environment. ADT leads to widespread apoptosis of prostate luminal androgen-receptor (AR)-positive cells. Following this, growth can resume via several routes, including adaptation of cells for growth in a low testosterone environment and clonal expansion of AR-negative cells.[27] In addition, tumours can progress as a result of local testosterone production by the prostate tumour cells due to AR modifications.[28] Medical castration reduces tissue androgen by approximately 75% and reduces the expression of some, but not all, androgen-regulated genes. This suboptimal suppression of tumour androgen leads to adaptive cellular changes, allowing prostate cancer cell survival in a low testosterone environment; therefore testosterone levels should be kept low even in men with CRPC.

Several novel therapies are currently entering the market for CRPC, including inhibitors of the enzyme CYP17, which has been shown to be expressed in high levels in CRPC.[29] This enzyme is involved in steroidal biosynthesis, catalysing the

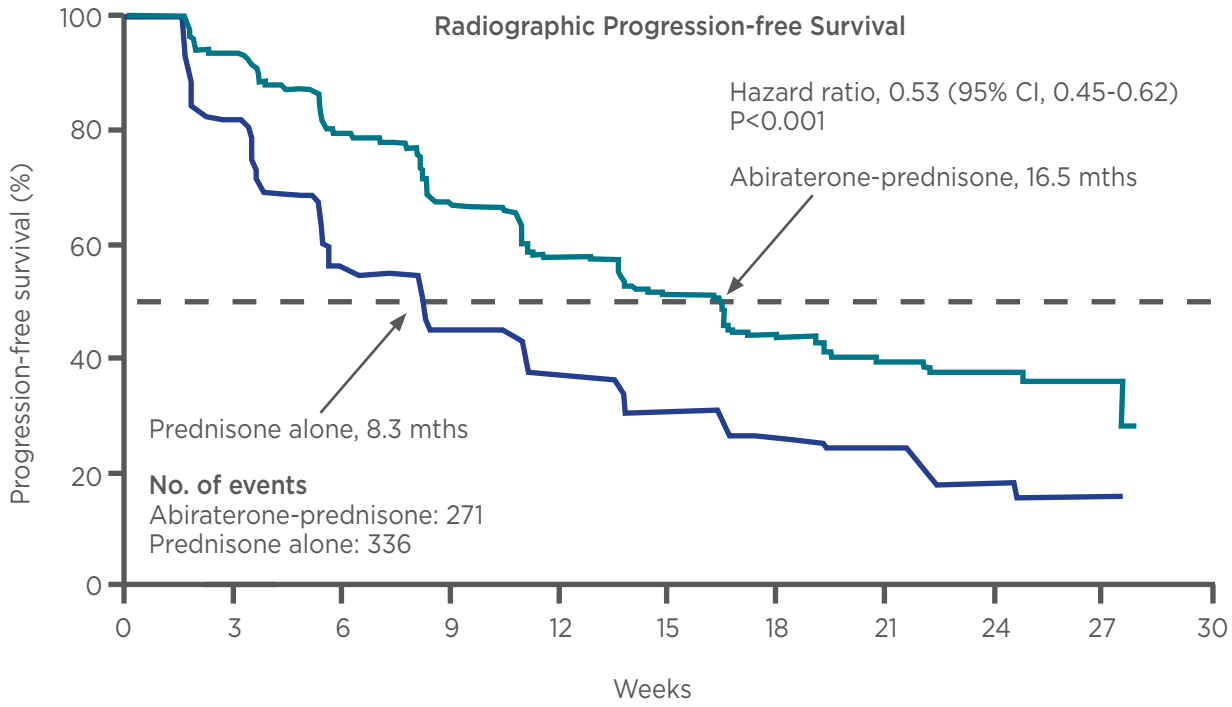

Figure 2: Abiraterone in chemotherapy-naïve patients with metastatic CRPC.
Adapted from Ryan et al.[32]

conversion of pregnenolone and progesterone to dehydroepiandrostenedione and androstenedione, which in turn are converted to androgens further along the pathway. As such, inhibition of this enzyme provides a mechanism of reducing androgen synthesis.[29] Abiraterone, a selective and irreversible CYP17 inhibitor approved by both the FDA and EMA, increased survival of CRPC patients on ADT backbone therapy (Figure 2)[31] or of those who have progressed after docetaxel treatment.[32] The androgen receptor antagonist enzalutamide improved overall survival in patients with progressive metastatic CRPC in the AFFIRM trial; this study also included ADT as backbone therapy.[33]

Recently published US National Comprehensive Cancer Network (NCCN) guidelines for patients with CRPC and metastases state backbone ADT should be continued to maintain castrate serum testosterone levels. If the patient is symptomatic, chemotherapy, mitoxantrone, abiraterone, or other therapies can be administered; if non-symptomatic, therapies include sipuleucel-T and secondary hormone therapy.[34]

Backbone therapy with ADT should remain the mainstay of therapy in all men with advanced prostate cancer. With the introduction of new agents, therapy combinations, and the earlier use of drugs, individualised therapy will likely become the standard. This will be facilitated by improved phenotyping and genomic-driven therapeutic decisions.

'Thinking Out of the Box' Targeting the Tumour Microenvironment to Improve Prostate Cancer Management

Professor Shahrokh F. Shariat

The immune system plays a central role in the elimination of tumours.[35,36] An example of this is in patients under immunosuppressive therapy as a result of organ transplantation, or in those who are immunocompromised, for example by HIV. These patients are at a higher risk of developing malignancies, and HIV-infected patients in particular have a high risk of developing non-AIDS-defining cancers, including Hodgkin's lymphoma, anal, vaginal, and liver cancers. The increased rate of malignancies in these patients therefore demonstrates the major role the immune system plays in keeping cancer in check.[37–39]

Until recently it was well established and generally accepted that early oncogenesis was driven by

cell-intrinsic phenomena. The biological capabilities acquired by tumours that enable their development were described around the year 2000 as the six cell-intrinsic hallmarks of cancer. They were the sustaining of proliferative signalling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, and resisting cell death.[40] It was 10 years later before the avoidance of immune system destruction was recognised as a hallmark of cancer. This led to a change in the definition of cancer, such that it was no longer a disease intrinsic to tumour cells, and that cell-extrinsic factors also played a critical role in the development of malignancies.[41] These factors are the deregulation of cellular energetics, the avoidance of immune destruction, genome instability and mutation, and tumour-promoting inflammation.[41]

The immune system is capable of directly identifying and eliminating tumour cells.[42] The key cells of the immune system, which include granulocytes, macrophages, and dendritic cells, develop from progenitor cells in the bone marrow and aid T cell response. T cells and other immune cells are involved in the immunosurveillance process and in the elimination of tumour cells in the early stages of the disease. If tumour cells escape these mechanisms, they continue to be held in check by the immune system in an equilibrium phase, whereby tumour cells can remain dormant or continue to accumulate changes due to DNA mutations or changes in gene expression patterns.[42] During this phase the immune system exerts a selective pressure on developing tumours, which are eliminated where possible. However, tumours may develop despite a functioning immune system with the change from normal to transformed tissue being driven by carcinogens, infection, or genetic changes. Transformed cells escape intrinsic tumour suppressor mechanisms, and tumour cells gain a selective advantage where they are able to resist, avoid, or suppress the anti-tumour immune response. This leads to progressive tumour growth and proliferation.[42,43]

The tumour microenvironment (TME) plays a central role in these mechanisms. In addition to the proliferating tumour cells, the TME includes tumour stromal cells, blood vessels to provide nutritional support for the tumour cells, and infiltrating inflammatory and immune cells.[44] Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature cells to which macrophage, neutrophil, and dendritic cell progenitors belong. MDSCs are released from the bone marrow in response to cytokine signals and serve to inhibit T cell activation and function. This normal physiological role is co-opted by

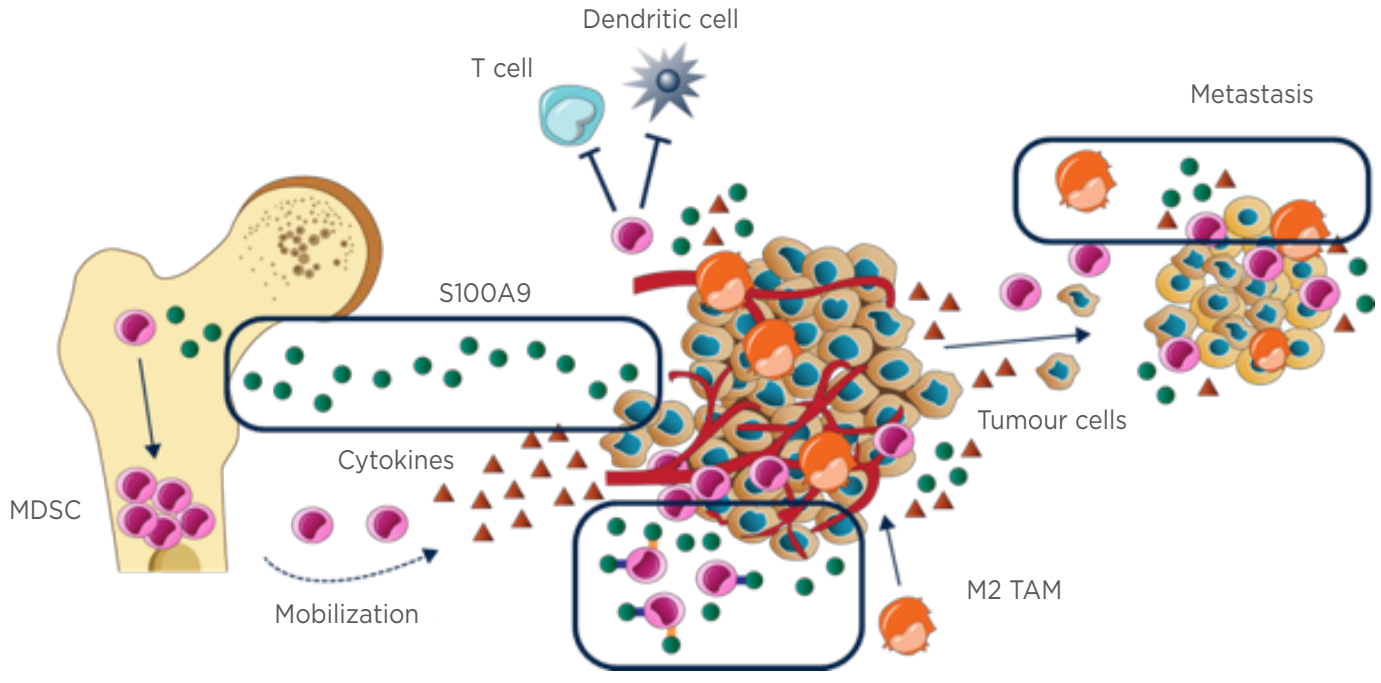

Figure 3: The role of S100A9 in tumour progression and metastasis.
Adapted from Cheng et al.[50]

the tumour, as the cytokines it releases lead to immune suppression in the TME through the accumulation of MDSCs.[45]

The TME is also infiltrated by other immune cells such as macrophages, which have two phenotypes. M1 macrophages are immunoactive, possessing inflammatory, phagocytic, and anti-tumour properties. M2 macrophages are associated with tissue repair but in the context of the TME promote tumour development and angiogenesis. In the TME, macrophages primarily consist of M2 macrophages, and infiltrating macrophages are polarised to a M2 phenotype.[46] As with the MDSCs, the TME subverts the role of anti-tumour cells. Together the MDSCs and M2 TAMs promote angiogenesis and suppress the immune system, supporting tumour cell invasion and metastases.[45,46]

The presence of MDSC and TAM M2 cells in the TME promote immune escape of prostate cancer cells, which is considered to be due to the release of immunosuppressive cytokines that suppress the adaptive immune response.[46-49] In addition, MDSC and M2 TAM cells have been shown to release cytokines, which promote angiogenesis and vascular remodelling, resulting in prostate tumour growth.[48,49] This mechanism is also involved in metastatic spread of the tumour where components of the TME travel and recruit stem cells and MDSC at the metastatic site.[48,49] These processes involve the chemokine, S100A9, which is expressed as a heterodimer on myeloid cells and has an immunosuppressive function.[50] S100A9 is important for the accumulation and regulation of function of MDSCs in the TME and metastatic sites (Figure 3).[50] Studies have shown that prostate cancer patients have much higher S100A9 levels compared with healthy men, or men with benign prostatic hyperplasia (BPH).[51]

Targeting myeloid cells via S100A9 may inhibit the growth and metastasis of prostate cancer. In a mouse model of prostate cancer, tumour growth was found to be delayed in those that lacked S100A9 expression.[52] S100A9 is a ligand for the pro-inflammatory receptors Receptor for Advanced Glycation End products (RAGE) and Toll-like receptor 4 (TLR4).[52] Novel therapies are being developed that target S100A9, to inhibit its interaction with TLR4 and RAGE, thus reducing infiltration of MDSCs and M2 TAM polarisation into the TME (Figure 4).[52] Results of clinical studies using these novel agents are highly anticipated.

There is a need to consider the complex interplay between tumour cells, and other components of the TME, alongside the hormonal axis in the pathophysiology of prostate cancer. Understanding interactions between immune and tumour cells in the development of new therapies will be paramount in overcoming tumour-associated immunosuppression, inhibiting angiogenesis, tumour growth, and metastasis in CRPC.

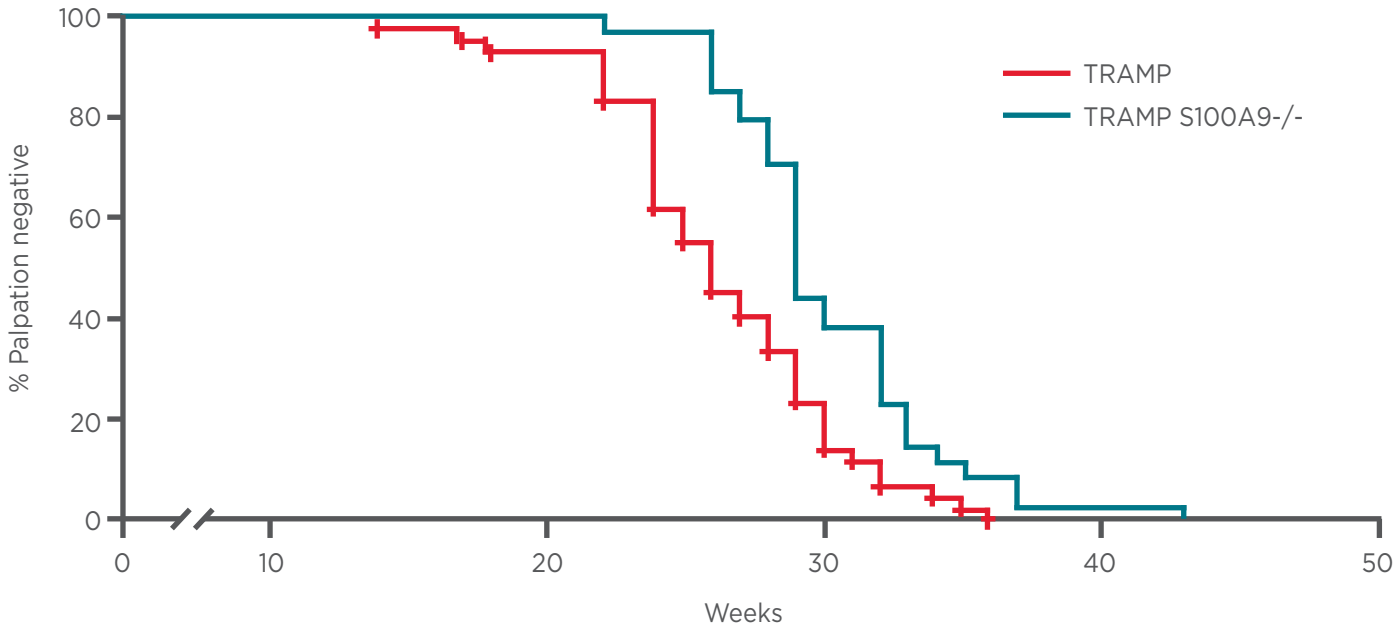

Figure 4: Targeting myeloid cells through S100A9 to inhibit the growth and metastasis of prostate cancer. *Adapted from Kallberg et al.*[52]

Concluding Remarks

Professor Hendrik Van Poppel

Several key messages can be taken from this symposium:

• Persistence of disease following TURBT is a key prognostic indicator for patients with NMIBC. Advances in tumour visualisation have improved resection procedures and reduced the risk of recurrence.

• It is important to maintain castrate levels of testosterone and continue ADT in CRPC. As new treatments become available, it is essential to optimise regimens according to the needs of the individual patient.

• Tumour progression involves the immune system as well as genetic and metabolic changes. As new treatments become available they should be optimised according to individual patient needs so that outcomes can continue to improve for patients with urological cancers.

REFERENCES

1. Babjuk M et al. EAU 2013 Guidelines on NMIBC (TaT1 and CIS): http://www.uroweb.org/gls/pdf/05_TaT1_Bladder_Cancer_LR.pdf. Accessed 29 April 2014.

2. van der Aa MN et al. Cystoscopy revisited as the gold standard for detecting bladder cancer recurrence: diagnostic review bias in the randomized, prospective CEFUB trial. J Urol. 2010;183:76–80.

3. Sarosdy MF. Principles of intravesical chemotherapy and immunotherapy. Urol Clin N Amer. 1992;19:509–19.

4. Kolozsky Z. Histopathological "self control" in transurethral resection of bladder tumours. Brit J Urol. 1991;67:162–4.

5. Stenzl A et al. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. J Urol. 2010;184:1907–13.

6. Grossman HB et al. Long-term decrease in bladder cancer recurrence with hexaminolevulinate enabled fluorescence cystoscopy. J Urol. 2012;188:58–62.

7. Rink M et al. Hexyl aminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: a critical review of the current literature. Eur Urol. 2013;64:624–38.

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

9. Bono AV et al. Chemoresection in Ta-T1 bladder cancer. Members of the EORTC Genito-Urinary Group. Eur Urol. 1996;29:385–90.

10. Pieras A et al. [Cytoscopic follow-up of initial G3T1 bladder tumors treated with BCG]. Arch Esp Urol. 2001;54:211–7.

11. Karl A et al. Positive urine cytology but negative white-light cystoscopy: an indication for fluorescence cystoscopy? BJU Int. 2009;103:484–7.

12. Ray ER et al. Hexylaminolaevulinate 'blue light' fluorescence cystoscopy in the investigation of clinically unconfirmed positive urine cytology. BJU Int. 2009;103:1363–7.

13. Palou J et al. ICUD-EAU International Consultation on Bladder Cancer 2012: Urothelial carcinoma of the prostate. Eur Urol. 2013;63:81–7.

14. Huguet J et al. Cystectomy in patients with high risk superficial bladder tumors who fail intravesical BCG therapy: pre-cystectomy prostate involvement as a prognostic factor. Eur Urol. 2005;48:53–9.

15. Liu J et al. New optical imaging technologies for bladder cancer: considerations and perspectives. J Urol. 2012;188:361–8.

16. Bryan RT et al. Narrow-band imaging flexible cystoscopy in the detection of recurrent urothelial cancer of the bladder. BJU Int. 2008;101:702–6.

17. Herr H, Nonat SM. A comparison of white-light cystoscopy and narrow-band imaging cystoscopy to detect bladder tumour recurrences. BJU Int. 2008;102:1111–4.

18. Alcaraz A. Management of the hormone sensitivity of prostate cancer: where are we now? Eur Urol. 2008;54:247-50.

19. Sternberg CN et al. Treatment patterns and characteristics of European patients with castration-resistant prostate cancer. BMC Urol. 2013;13:58.

20. Heidenreich A et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65:467–79.

21. Morote J et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. J Urol. 2007;178:1290–5.

22. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Lancet. 2000;355:1491–8.

23. Heidenreich A et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol. 2014;65:467–79.

24. Manni A et al. Androgen priming and chemotherapy in advanced prostate cancer: evaluation of determinants of clinical outcome. J Clin Oncol. 1988;6:1456–66.

25. D'Amico AV et al. Interval to testosterone recovery after hormonal therapy for prostate cancer and risk of death. Int J Radiat Oncol Biol Phys. 2009;75:10–5.

26. Taylor CD et al. Importance of continued testicular suppression in hormone-refractory prostate cancer. J Clin Oncol. 1993;11:2167–72.

27. Tombal B et al. What is the pathophysiology of a hormone-resistant prostate tumour? Eur J Cancer. 2011;47:179–88.

28. Mostaghel E et al. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. Cancer Res. 2007;67:5033–41.

29. Montgomery RB et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res. 2008;68:4447–54.

30. Molina A, Belldegrun A. Novel therapeutic strategies for castration resistant prostate cancer: inhibition of persistent androgen production and androgen receptor mediated signaling. J

Urol. 2011;185:787–94.

31. Fizazi K et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncology. 2012;13:983–92.

32. Ryan CJ et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2012;368:138–48.

33. Saad F. Evidence for the efficacy of enzalutamide in postchemotherapy metastatic castrate-resistant prostate cancer. Ther Adv Urol. 2013;5:201–10.

34. NCCN Guidelines Version 2.2014 Prostate Cancer. Available: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#prostate. Accessed: 29 April 2014.

35. Dunn GP et al. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002;3:991–8.

36. Burnet FM. The concept of immunological surveillance. Prog Exp Tumor Res. 1970;13:1–27.

37. Penn I. Chemical immunosuppression and human cancer. Cancer. 1974;34: 1474–80.

38. Patel P et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med. 2008;148:728–36.

39. Derhovanessian E et al. Immunity, ageing and cancer. Immun Ageing. 2008;5:11.

40. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57–70.

41. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74.

42. Swann JB, Smyth MJ. Immune surveillance of tumors. J Clin Invest. 2007;117:1137–46.

43. Zitvogel L et al. Cancer despite immunosurveillance: immunoselection and immunosubversion. Nature Immunol. 2006;6:715–27.

44. Sounni NE, Noel A. Targeting the tumor microenvironment for cancer therapy. Clin Chem. 2013;59:85–93.

45. Schmid MC, Varner JA. Myeloid cells in the tumor microenvironment: modulation of tumor angiogenesis and tumor inflammation. J Oncol. 2010;201026.

46. Solinas G et al. Tumor-associated macrophages (TAM) as major players of the cancer-related inflammation. J Leukocyte Biol. 2009;86:1065–73.

47. Ostrand-Rosenberg S, Sinha P. Myeloid-derived suppressor cells: linking inflammation and cancer. J Immunol. 2009;182:4499–506.

48. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nature Med. 2013;19:1423–37.

49. Hao N et al. Macrophages in tumor microenvironments and the progression of tumors. Clin Dev Immunol. 2012;2012:948098.

50. Cheng P et al. Inhibition of dendritic cell differentiation and accumulation of myeloid-derived suppressor cells in cancer is regulated by S100A9 protein. J Exp Med. 2008;205:2235–49.

51. Hermani A et al. Calcium-binding proteins S100A8 and S100A9 as novel diagnostic markers in human prostate cancer. Clin Cancer Res. 2005;11:5146–52.

52. Kallberg E et al. S100A9 interaction with TLR4 promotes tumor growth. PLoS One. 2012;7:e34207.

GLYCOSAMINOGLYCAN-REPLENISHMENT THERAPY: RATIONALE FOR USE AND CURRENT EVIDENCE

Summary of Presentations from the IBSA Institut Biochimique SA Symposium, held at the 29th Annual EAU Congress, Stockholm, Sweden, on 12th April 2014

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Disclosure: The authors are invited speakers for IBSA Institut Biochimique SA and declare no conflicts of interest.
Acknowledgements: Writing assistance provided by Dr Tabasum Mughal.
Support: The publication of this article was funded by IBSA Institut Biochimique SA. The views and opinions expressed are those of the authors and not necessarily of IBSA Institut Biochimique SA.
Citation: EMJ Urol. 2014;1:41-47.

Introduction by the Chairman

Professor Phillip E. Van Kerrebroeck

The glycosaminoglycan (GAG) layer of the bladder represents a mucous layer on the surface of the urothelium. Acting as an antibacterial defence mechanism, the layer contains chondroitin sulphate, dermatan sulphate, and heparan sulphate.[1] Pathophysiological changes in this layer (including a lack of chondroitin sulphate), changes occurring after bacterial cystitis, chemo or radiation therapy, and overactive bladder (OAB) lead to the development of interstitial cystitis (IC).[2] The symposium presentations discussed the rationale for the use of GAG replenishment therapy in patients with bladder problems and outlined the challenges faced by clinicians when administering GAG therapy in the clinic.

The Physiological Function of the Urothelium – More than a Simple Barrier

Professor Paulo Dinis Oliveira

The bladder wall is composed of three main structures: the detrusor muscle, the suburothelium, and the urothelium. Sensory nervous innervation is abundant in the subendothelium, and fibres inclusively penetrate through the urothelium layer. This former layer also contains connective tissue, inflammatory cells, interstitial cells, and blood vessels, all of which sit on a layer of muscle cells. All of the elements of the sub-urothelial layer interact actively among them and with urothelial cells, forming a dynamic sensory organ participating in bladder function. The urothelial barrier is made up of a layer of mucopolysaccharides, the GAG layer, and the urothelium umbrella cells layer, both contributing to its function as one of the tightest epithelial barriers in the body.[3] Surface plaques are constituted by proteins known as uroplakins, and make up the so-called asymmetric unit membrane,

as the cellular membrane at the apical surface is thicker on the luminal side, and are important for transcellular permeability.[4] Surrounding the apical cells is a continuous network of tight junctions, predominantly made up of zona occludens-1 proteins, adhesins, and claudins. The GAG layer, also known as the mucous layer, is an important factor in cellular permeability. It is composed of a uniform mantle of GAGs and proteoglycans covering the luminal surface of the urothelium. Damage to this layer results in exposure of the underlying urothelial cells and can lead to bladder dysfunction.

GAGs are long chains of disaccharides, the most important of which are chondroitin sulphate, dermatan sulphate, and hyaluronic acid (HA). These GAGs rarely exist freely and are usually attached to a core transmembrane protein chain with a cytoplasmic tail. The attachment of several GAGs to this core protein chain makes up a structure known as a proteoglycan, which plays a principal role in various physical and chemical processes.

The GAG chain has the ability to retain water molecules, resulting in a 'gel-like' layer over the urothelium, which forms a seal giving protection against damage by cations and bacterial invasion. Proteoglycans are also involved in cell-cell adhesion, cell proliferation, cell differentiation, wound healing, and tissue remodelling. A recent study identifying urothelial GAGs has shown that chondroitin sulphate covers the layer of umbrella cells on the luminal side and is also present in the subendothelium, while heparan sulphate is only seen in the subendothelial space.[4]

Urothelial cells have neuron-like properties and produce neuromediators, which have autocrine and paracrine functions. These include acetylcholine, adenosine triphosphate, nitric oxide, nerve growth factor, substance P, and prostaglandins.[5–10] Under normal physiological conditions, signalling via these neuromediators regulates normal bladder function; however, under pathophysiological conditions, this signalling can lead to hyper or hyporeflexia, pain, and neurogenic inflammation.

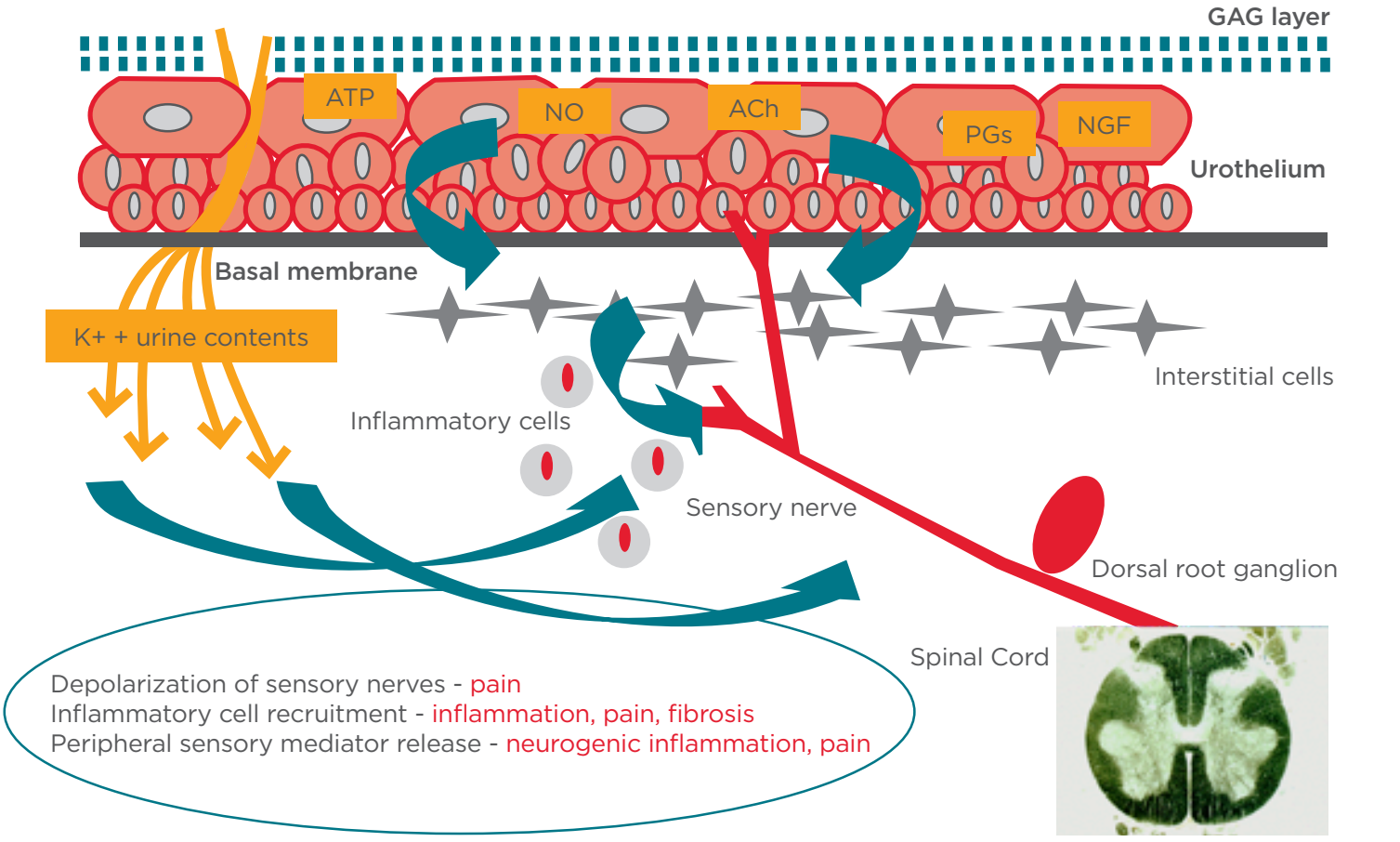

Figure 1: Glycosaminoglycan (GAG) layer/urothelium damage.
ATP: adenosine triphosphate; NO: nitric oxide; ACh: acetylcholine; PG: proteoglycans; NGF: nerve growth factor. From Paulo Dinis' presentation at this symposium.

A damaged GAG layer (Figure 1) is increasingly permeable to urine and its contents, in particular, potassium. An influx of potassium into the suburothelium leads to the depolarisation of afferent nerves that, in turn, leads to pain and neurogenic inflammation with subsequent recruitment of inflammatory cells. This cycle of events may at first be associated with acute pain and inflammation, but with time can lead to both chronic pain and inflammation, accompanying extensive damage to the GAG layer, with marked decreases in chondroitin and heparan sulphate.[11] Examination of urothelium and GAG layer in patients with bladder pain syndrome (BPS)/IC has shown a decrease in differentiation markers, such as chondroitin sulphate, E-cadherin, and tight junction proteins. This indicates a differentiation defect that can lead to a leaky urothelium due to increased permeability in these patients.[12] This increase in permeability is also apparent in the clinical setting.[13] A comparison of urinary potassium levels in patients newly diagnosed with BPS/IC and those previously treated for BPS/IC with GAG replenishment showed that the latter had higher levels of urinary potassium than newly diagnosed patients. This suggests that damage to this layer can be alleviated with GAG layer replenishment therapy, thus preventing potassium reabsorption.[13] Leakiness of the urothelium, as measured by the potassium sensitivity test, is also present in other diseases including: chronic pelvic pain, dyspareunia, vulvodynia, endometriosis, recurrent urinary tract infection (UTI), radiation cystitis, and some patients with bladder hyperactivity.[14]

Additional evidence suggests that application of an external GAG restores normal permeability by adhering to the damaged barrier whilst also inhibiting inflammatory cell recruitment.[2] The urothelium is therefore a complex structure with barrier and neuron-like properties that work in concert to regulate bladder function. GAG layer integrity is paramount to maintain normal urothelium and respective functions.

Economic Burden of Urothelium Dysfunction: The Case of Uncomplicated UTIs

Doctor Rosanna Tarricone

Recurrent UTIs (RUTIs) not only place a strain on patients but are also associated with increased demands on healthcare systems. This economic burden can be assessed from recent results of the ongoing RAISC-RUTI study.

Epidemiological data available on the occurrence of UTIs among females show that women with a previous history of UTIs have an increased risk of RUTI; 20–50% of initial episodes being followed by a second infection within 6 months.[16] UTI and RUTI episodes have a significant impact on quality of life (QoL) and adequate long-term treatments are not currently available. In recent years, development of newer therapies that work by replenishing the GAG layer offer a promising alternative to existing antimicrobial therapy. Although these alternative therapies are available, the economic costs and potential strain that they may place on already struggling healthcare systems must be carefully considered by policymakers.

An EU-based, multicentre, retrospective, case-control study sought to assess the costs and effectiveness of combined HA and CS (Ialuril®) versus the current standard management of RUTIs in adult women. In total, the study involved nine participating centres across four different countries. Baseline data included measurement of QoL using standard instruments including EQ-5D, the female sexual function index (FSFI), and the short-form 36 health survey (SF-36). Primary outcomes of this study included the occurrence of objective UTI recurrence, and secondary outcomes included the occurrence of symptomatic UTI recurrence and the mean direct overall costs associated with the two treatments over the two groups. Economic cost incurred by the two groups of patients will be calculated by assessing the use of resources associated with the two treatments. Preliminary data from this study are available from four of the nine study centres.

Preliminary results indicate a trend in favour of Ialuril; patients in this group had a 34% reduced risk of bacteriologically confirmed recurrence and a 23% reduced risk of having a symptom-based recurrence, compared to control (Table 1). Time-to-recurrence of bacteriologically confirmed recurrence was 357 days with Ialuril versus 302 days with standard of care.

Preliminary cost-effectiveness analysis has shown that laboratory examination and instrumental costs are slightly higher for Ialuril treatment versus the standard of care treatment. In contrast, the cost of hospitalisation and additional medical

Table 1: Retrospective case-control study of effectiveness of Ialuril versus the current standard management of reoccurring urinary tract infections in adult women.

Recurrence (binary) bacteriologically confirmed	OR (95%CI)	Adj OR (95%CI)*
Standard of care	*Reference*	*Reference*
Ialuril	0.66 (0.31-1.38)	0.63 (0.28-1.38)
**Adjusted for age, dyspareunia and EQ-5D*		
Recurrence (binary) clinical/symptoms based	**OR (95%CI)**	**Adj OR (95%CI)***
Standard of care	*Reference*	*Reference*
Ialuril	0.77 (0.37-1.60)	0.73 (0.34-1.61)
**Adjusted for age, dyspareunia and EQ-5D*		

From Rosanna Tarricone's presentation at this symposium.

therapies were lower for the group treated with Ialuril. It should be noted that these are preliminary data that represent a subset of patients in the study. Other factors to consider include the organisation of the different healthcare systems of the four participating countries in which these preliminary data were obtained, which may affect the overall cost incurred within each treatment group. However, the results emphasise the importance of assessing the cost-effectiveness of new treatments for policymakers.

Clinical Utility of GAG-Replenishment with IALURIL

Doctor Salvador Arlandis Guzman

Chemically-induced cystitis as a result of cyclophosphamide treatment, ketamine abuse, or Bacillus Calmette–Guérin (BCG) therapy for high-grade bladder tumours results in urothelium lesions and long-term damage to this layer. Similarly, radiation-induced cystitis can also lead to urothelium damage, as well as damage to the connective tissue and surrounding vasculature. The aetiology of IC/BPS is unknown but is thought to be multifactorial. Factors that may contribute to urothelium damage include allergy, infection, hypoxia, and autoimmune reaction. The disruption of the GAG layer, such as that seen during UTI, increases bacterial adherence and perpetuates the risk of further recurrence of UTIs. Therefore, replenishing the damaged GAG layer may offer a defence against further infection, and may play a role in chemical and radiation-induced cystitis and IC/BPS.

The rationale for using GAGs replacement therapy in RUTI comes from studies in rats treated for 5 days with HA, CS, or a combination of HA and CS, inoculated with *Escherichia coli* and sacrificed 3 days later for bladder examination. Animals that had received a combination of HA and CS showed increased bacterial resistance accompanied by a thicker transitional epithelium, providing promising results for the use of this therapy in humans. Other clinically relevant studies have shown promising data from the use of GAG replenishment therapy in patients with IC/BPS. Patients treated with Ialuril, which consists of a combination of HA and CS, for 8 weeks showed a significant improvement in pain, urgency, and frequency (PUF) score and a significant improvement in interstitial cystitis symptoms index (ICSI) score.[18] These results were also seen in a second study where combined intravesical therapy with HA and CS resulted in significant improvements in PUF score and the O'Leary–Sant score, which is used as a measure of symptoms associated with IC.[19] A 3-year follow-up study showed that GAG replenishment therapy has long-term benefits for PUF score and beneficial effects on all domains of the O'Leary–Sant questionnaire, including the bother index and the symptoms index.[20]

GAG replenishment therapy has also been shown to be beneficial in RUTI, with a 77% reduction in the occurrence of RUTIs versus placebo.[21] 48% of treated patients were relapse-free at the end of the study, whereas patients receiving placebo relapsed on average of 50 days; however, those receiving therapy were free from relapse for up to 6 months. Data from a systematic review showed reduced rates of UTI occurrence per year with

GAG replenishment, as well as a decrease in UTI recurrence and improvements in PUF score.[22]

There is a paucity of evidence available in the literature for GAG replenishment therapy in patients who have undergone radiation therapy. However, there is evidence showing that HA administration lowers bladder toxicity in patients who have undergone high-dose brachytherapy.[23] Similarly, CS instillation in patients who have received radiation therapy for gynaecological malignancies also reduces overactive bladder symptoms.[24] An investigation of 25 patients who had undergone radiation therapy, assigned patients to receive either HA or CS weekly for 6 weeks, and then once every 2 weeks for 2 months. Significant improvement was seen in International Prostate Symptom Score (IPSS), with improvements observed in International Consultation on Incontinence Questionnaire - Short Form (ICIQ-SF), the bladder pain/interstitial cystitis symptom score (BPIC-SS), and QoL scores.[24] In addition, Ialuril therapy in patients undergoing treatment for BCG also showed a significant reduction in IPSS, indicating that Ialuril treatment in these patients could be used to counteract the chemical cystitis associated with this treatment.[25] Preliminary data on 25 patients show that Ialuril (once-weekly instillation for 12 weeks, with a mean follow-up of 6 months) significantly reduces visual analogue scale (VAS) pain scores and BPIC-SS. Improved responses were observed with primary treatments (in GAG therapy-naïve patients) versus rescue treatments (previous failure treatment with HA or DMSO); in the primary treatment group a 38% and 27% reduction was observed in VAS and BPIC-SS, respectively (Table 2).[26]

In order to choose the appropriate treatment in BPS/IC, characterisation of patient phenotype is of great importance. Identifying patients with urothelium dysfunction and GAG layer damage should improve outcomes after GAG replenishment therapy. Maintenance instillation policy may be

Table 2: Reduction in VAS pain scores and BPIC-SS with Ialuril in patients undergoing treatment for BCG.

Results				
Mean Age years (range)	**Time diagnosis** months (range)	**Primary/Rescue** (n/%)	**VAS pre** Mean ± sd	**BPIC-SS pre** Mean ± sd
60.4 (31-82)	20 (7.9-45.1)	15 (60%)/10 (40%)	6 ± 2.79	22.1 ± 8.2
			VAS post Mean ± sd	**BPIC-SS post** Mean ± sd
			5.3 ± 2.8	17,6 ± 10,3
			11.6% red. p=0.006	20.3% red. p=0.054
Primary versus rescue				
	VAS difference (pre-post)		**BPIC-SS difference (pre-post)**	
Primary	2.6 ± 2.1		7.1 ± 6	
Rescue	- 0.4 ± 1.9		- 0.3 ± 3.5	
p	0.005		0.023	
Primary versus treatment				
	Primary Treatment Group		**% Reduction**	**P**
VAS pre	6.9 ± 2.2		38%	<0.0001
VAS post	4.3 ± 3.2			
BPIC-SS pre	24.8 ± 5.8		27%	0.013
BPIC-SS post	18.1 ± 9.7			

Preliminary internal data non published, SURF HUP La Fe 2014

VAS: visual analogue scale; BPIC-SS: bladder pain/interstitial cystitis symptom score.
From Salvador Arlandis Guzman's presentation at this symposium.

useful, especially in patients who are refractory to previous treatments, but more studies are needed to confirm this hypothesis. Future lines of investigation should include new administration schedules (self-administration, daily), new indications (OAB, RUTI in neurogenic patients), and cost-effectiveness and cost-utility studies.

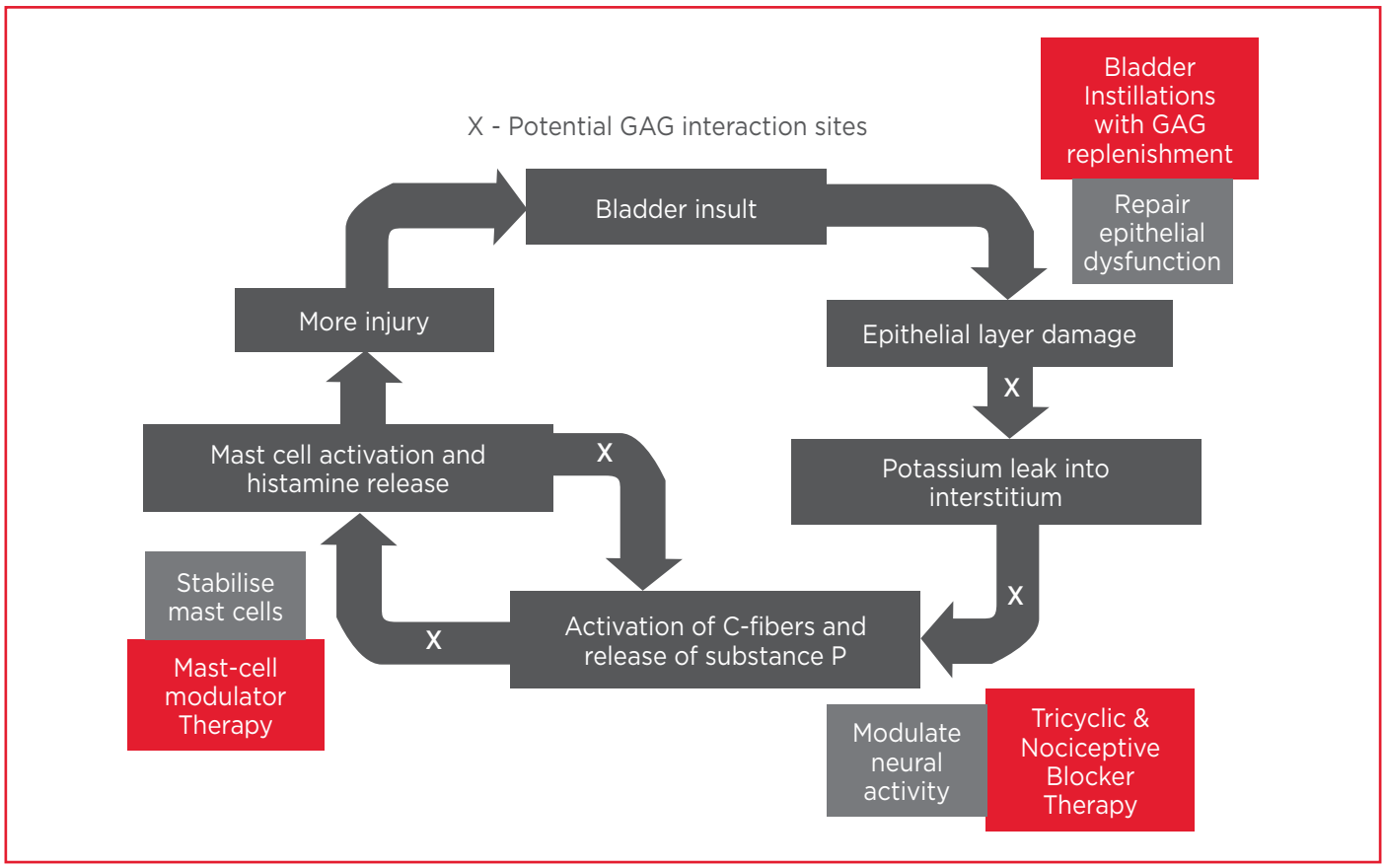

Figure 2: Principles of BPS/IC Therapy.
BPS: bladder pain syndrome; IC: interstitial cystitis; GAG: glycosaminoglycan.
From Mauro Cervigni's presentation at this symposium.
Modified from Evans RJ.[27]

Final Remarks

Professor Mauro Cervigni

The combination of HA and CS has overall beneficial effects on the GAG layer; HA reduces the pain in BPS patients while CS has similar effects in IC patients. The high concentration of HA and CS in Ialuril explains the therapeutic benefit of this treatment in patients who have a damaged GAG layer (Figure 2). It is important to identify the correct treatment regime, which is based on individual patient needs for optimal therapeutic benefit. In addition, the economic impact of the use of this therapy needs to be considered; whilst more expensive than the current standard of care, the therapeutic benefit that it could provide may outweigh the cost.

REFERENCES

1. Parsons CL et al. The primary antibacterial defense mechanism of the bladder. Invest Urol. 1975;72–78.
2. Hurst RE et al. A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis. Urology. 1996;48:817–21.
3. Hauser PJ et al. Restoring barrier function to acid damaged bladder by intravesical chondroitin sulfate. J Urol. 2009;182:2477–82.
4. Janssen DA et al. The distribution

and function of chondroitin sulfate and other sulfated glycosaminoglycans in the human bladder and their contribution to the protective bladder barrier. J Urol. 2013;189:336–42.

5. Ferguson DR et al. ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes--a possible sensory mechanism? J Physiol. 1997;505:503–11.

6. Vlaskovska M et al. P2X3 knock-out mice reveal a major sensory role for urothelially released ATP. J Neurosci. 2001;21:5670–7.

7. Birder LA et al. Adrenergic- and capsaicin-evoked nitric oxide release from urothelium and afferent nerves in urinary bladder. Am J Physiol. 1998;275:F226–9.

8. Micera A et al. Nerve growth factor and tissue repair remodeling: trkA(NGFR) and p75(NTR), two receptors one fate. Cytokine Growth Factor Rev. 2007;18: 245–56.

9. Birder LA et al. Feline interstitial cystitis results in mechanical hypersensitivity and altered ATP release from bladder urothelium. Am J Physiol Renal Physiol. 2003;285:F423–9.

10. Chess-Williams R et al. Oral presentation at the 36th Annual Meeting of the International Continence Society, 27 November–1 December, 2006, Christchurch, New Zealand. Abstract 70. Neurourol Urodyn. 2006;25:593–594.

11. Hauser PJ et al. Abnormal expression of differentiation related proteins and proteoglycan core proteins in the urothelium of patients with interstitial cystitis. J Urol. 2008;179:764–9.

12. Slobodov G et al. Abnormal expression of molecular markers for bladder impermeability and differentiation in the urothelium of patients with interstitial cystitis. J Urol. 2004;171:1554–8.

13. Parsons CL et al. Abnormal urinary potassium metabolism in patients with interstitial cystitis. J Urol. 2005;173:1182–5.

14. Parsons CL. Changing concepts in interstitial cystitis. J Urol. 1997;158:794.

15. Engles CD et al. Intravesical chondroitin sulfate inhibits recruitment of inflammatory cells in an acute acid damage "leaky bladder" model of cystitis. Urology. 2012;79(2):483.e13–7.

16. Ciani O et al. An economic perspective on urinary tract infection: the 'costs of resignation'. Clin Drug Investig. 2013;33:255–61.

17. Tasdemir S et al. Intravesical hyaluronic acid and chondroitin sulfate alone and in combination for urinary tract infection: assessment of protective effects in a rat model. Int J Urol. 2012;19:1108–12.

18. Porru D et al. Impact of intravesical hyaluronic acid and chondroitin sulfate on bladder pain syndrome/interstitial cystitis. Int Urogynecol J. 2012;23:1193–9.

19. Cervigni M. A combined intravesical therapy with hyaluronic acid and chondroitin for refractory painful bladder syndrome/interstitial cystitis. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19;7:943–7.

20. Cervigni M. Intravesical hyaluronic acid and chondroitin sulphate for bladder pain syndrome/interstitial cystitis: long-term treatment results. Int Urogynecol J. 2012;23:1187–92.

21. Damiano R et al. Prevention of recurrent urinary tract infections by intravesical administration of hyaluronic acid and chondroitin sulphate: a placebo-controlled randomised trial. Eur Urol. 2011;59:645–51.

22. Samper Ots PM et al. Vesical instillations of hyaluronic acid to reduce the acute vesical toxicity caused by high-dose brachytherapy do not affect the survival: a five-year follow-up study. Clin Transl Oncol. 2009;11:828–34.

23. Hazewinkel MH et al. Prophylactic vesical instillations with 0.2% chondroitin sulfate may reduce symptoms of acute radiation cystitis in patients undergoing radiotherapy for gynecological malignancies. Int Urogynecol J. 2011;22:725–30.

24. Collado A et al. Tratamiento de la sintomatología miccional de llenado inducida tras radioterapia pélvica mediante instilaciones endovesicales de condroitin sulfato o hialuronato sódico: resultados preliminaries. 48th Valencian Community Urological Society Meeting, Segorbe, Spain, 21–22 February 2014.

25. Li Marzi V et al. Do preoperative urodynamics still have a role in female stress urinary incontinence? Poster presented at the 37th Annual Congress of the Italian Urodynamic Society, 20–22 June, 2013, Latina, Italy. Abstract 2. Neurourol Urodyn. 2013;32(Suppl S1–S2).

26. Arlandis S et al. HUP La Fe Valencia, Spain. Unpublished data.

27. Evans RJ. Treatment approaches for interstitial cystitis: multimodality therapy. Rev Urol. 2002;4(Suppl 1):S16-20.

PROSTATE CANCER: A STATE OF THE HEART

Summary of Presentations from the Ferring Pharmaceuticals Sponsored Symposium, held at the 29th Annual EAU Congress, Stockholm, Sweden, on 13th April 2014

Chairperson

Laurence Klotz[1]

Speakers

Alberto Briganti,[2] Jan Nilsson,[3] Alexandre de la Taille[4]

1. University of Toronto, Toronto, Canada
2. University Vita-Salute San Raffaele, Milan, Italy
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4. CHU Mondor, Créteil, France

Disclosure: LK – Speaker or advisor: Amgen, Astellas, Dendreon, Ferring, GSK, Janssen, Profound Medical, and Sanofi Aventis; AB – Nothing to disclose; AdlT – Consultant or advisor: Astellas, Ferring, Ipsen, Takeda, and PFM; JN – Consultant or advisor: Boehringer Ingelheim, Probi AB.

Acknowledgements: Writing assistance provided by Dr Tabasum Mughal.

Support: Ferring Pharmaceuticals sponsored this symposium. The views and opinions expressed are those of the authors.

Citation: EMJ Urol. 2014;1:48-53.

MEETING SUMMARY

This symposium was focused on reviewing androgen deprivation therapy (ADT) in prostate cancer, highlighting the implications of this therapy in clinical practice and including a focus on the cardiovascular (CV) risk associated with ADT therapy.

Introduction: Current Challenges with ADT for Prostate Cancer

Professor Laurence Klotz

Prof Laurence Klotz began this session by giving a brief history of ADT, starting in 1780 when John Hunter discovered that castration resulted in the regression of the prostate. In 1940, Charles Huggins was awarded the first Nobel Prize in this area for the discovery that orchiectomy and oestrogen caused the regression of prostate cancer. Discovery of synthetic oestrogens and the development of first and second-generation, non-steroidal anti-androgens followed. A second Nobel Prize was awarded to Andrew Schally for the discovery of luteinising hormone-releasing hormone (LHRH) and the development of the first agonist, with the subsequent development of several first and second anti-androgen therapies. The recent arrival of gonadotropin-releasing hormone (GnRH) antagonists marks the evolution of drugs in prostate cancer management.

Prof Klotz then discussed developments in understanding the mechanism of castration resistance over the past decade, with reference to the cellular synthesis of androgens in an androgen-depleted environment. He emphasised the importance of testosterone as well as the timing of therapy in predicting patient outcomes; findings indicate that delayed therapy produces the same outcome as early therapy.

Prof Klotz stated that a focus of the session was the systemic, metabolic, and CV effects of ADT, as well as the role hormones play in atherosclerosis plaque formation and rupture. The ability of prostate cancer cells to synthesise their own androgen

hormones, also known as the back door pathway, allows them to proliferate by binding to the androgen response element in the genome to trigger various signal transduction pathways; findings that have changed the understanding of castration resistance. Non-genomic signalling, via MAP kinases/ERK and PI3K pathways, results in the direct stimulation of prostate cancer cells; the complexity of this signalling cross talk, in addition to the thousands of genes that are regulated by the androgen receptor, allows for potential therapeutic intervention at various stages.

Prof Klotz then discussed management challenges, and emphasis was placed on the decisions for initiation and duration of therapy and the choice of either intermittent or continuous therapy.

A Patient-Centred Approach to Making Treatment Decisions

Professor Alberto Briganti

Prof Alberto Briganti's presentation began with the case of a 57-year-old male diagnosed with a 4 + 3 bilateral extended prostate cancer. The patient displayed some CV risk factors, including diabetes and obesity. Following staging, the patient appeared to have no systemic disease in the bone or in the abdomen and pelvis; however, a prostate magnetic resonance imaging (MRI) scan showed a suspicious area of minimal extracapsular extension at the right apex. Prostate-specific antigen (PSA) levels were 21.6 ng/mL, indicating that he was a high-risk patient. He consequently underwent bilateral extended pelvic lymph node dissection (PLND). The final pathological report revealed that the patient had a Gleason score of 8, 2/21 positive lymph nodes, and a positive surgical margin, with complete recovery of urinary continence at 4 weeks after surgery. Post-surgery evaluation showed that the patient had a PSA of 0.07 ng/mL, had no spontaneous erections, and did not require a protective pad at 40 days.

Postoperative patient management was discussed and Prof Briganti concluded he would opt for a combination of radiotherapy and hormonal therapy for 3 years. However, he indicated that there were no guidelines on the duration of therapy and that a case for a shorter or longer duration of therapy could be made. The experts agreed, in particular given the patient's young age.

Follow-up after 2 years revealed that this patient had a PSA of 1.98 ng/mL 15 months post-therapy with a PSA doubling time of 2.08 months. Prof Briganti stated that the patient underwent imaging and discussed the use of this technique in guiding future therapy use.[1] He continued by explaining that specifically the patient underwent PLND and 14 nodes were removed, 3 of which were positive. PSA levels 6 weeks post-surgery were 0.11 ng/mL; 6 months post-salvage LND these rose to 0.91 ng/mL. At this point the patient also suffered a myocardial infarction and was treated with a percutaneous coronary intervention and drug-eluting stent. The patient was kept under observation and 16 months post-salvage had a PSA level of 6.58 ng/mL. A bone scan revealed malignancy in the left ischiopubic ramus, despite the patient being asymptomatic and selected for ADT.[2]

Using this case by way of example, Prof Briganti ended by asking the experts what should be considered when selecting and optimising ADT.

Hormonal Therapy: Selecting the Optimal Agent

Professor Laurence Klotz

Surgical castration, oestrogens, LHRH agonists and GnRH antagonists, anti-androgens, combined androgen blockade (CAB), and 17,20-lyase inhibitors are some of the treatment options available to a patient with CV risk factors and known metastatic disease. Due to the high rate of thromboembolic events with oral oestrogen, it has somewhat been abandoned as a therapy. The oestrogen patch, however, is not thought to induce thromboembolic events. Prof Klotz described a study comparing a LHRH agonist and a transdermal oestrogen patch in which the use of the patch did not increase the number of CV events versus the LHRH agonist, suggesting that this may be regarded as a potential therapeutic option.[3] LHRH agonists have a number of disadvantages including testosterone surge, the flare in patients with advanced disease that may accelerate disease, adverse systemic, and CV effects.[4–9]

Hormone-naïve patients are unlikely to display disease flare, particularly in countries with PSA screening; however, incidence of clinical disease flare in LHRH agonist trials has been shown to be up to 63%, despite CAB.[10] In a preclinical study,

men treated with CAB (LHRH agonist + anti-androgen) displayed massive bone metastasis perfusion associated with a flare, which does not occur with the GnRH antagonist (degarelix), indicating that CAB may not reduce tumour size.

A comparison of five studies in patients after orchiectomy was presented, which showed that LHRH agonists are associated with a breakthrough of testosterone levels, with 20% of patients unable to consistently drop their levels below 0.7 nmol/L (20 ng/dL).[11-13] Prof Klotz then went on to describe the importance of lower testosterone levels and shared evidence supporting a higher chance of PSA progression in patients with testosterone levels ≥50 ng/dL.[14,15]

Furthermore, analysis of patients on the continuous arm of the NCIC/SWOG/UK CCR PR-7 study,[16] with measurement of testosterone levels every 3 months, revealed that patients who failed to drop their testosterone below 1.7 nmol/L (50 ng/dL) had a greater chance of progression to castrate-resistance, supporting the idea that testosterone is important in prostate cancer progression.[16]

Prof Klotz continued his presentation by sharing data from the Phase III CS21 trial, evaluating the efficacy and safety of degarelix in 610 patients with prostate cancer requiring androgen therapy in comparison with leuprolide.[17] Treatment with the GnRH antagonist degarelix resulted in an immediate drop in testosterone levels and maintained the median levels below castration levels (≤0.5 ng/mL) from day 28 to day 364. Longer-term follow-up of up to 5 years showed that degarelix was able to control testosterone and PSA levels for a longer period of time.[18]

Prof Klotz also presented data from a pooled analysis (1,925 patients) showing that overall PSA progression-free survival was better in patients treated with degarelix versus LHRH agonists, accompanied by a lower probability of musculoskeletal events. There was also a lower probability of urinary tract events with degarelix.[19] This may be explained by previous data that have shown increased regression in men receiving degarelix.

Conventional wisdom dictates that morbidity associated with LHRH agonists is related tommetabolic syndrome (MetS); however, other factors such as the presence of GnRH receptors in inflammatory cells, follicle-stimulating hormone (FSH) receptor activity in the endothelium, adipocytes, and effects on bone mineral density, as well as oestrogen deficiency, may all contribute. Degarelix treatment is associated with a decrease in FSH levels of 88.5% versus 54.8% with leuprolide at year 1 of treatment;[17,20] this is of particular significance as FSH receptors are expressed in normal prostate, but expression is enhanced in prostate cancer and cardiomyocytes.[21] Prostate tumour blood vessels have also been shown to express FSH receptors, so lowering FSH levels may decrease vascularisation of prostate tumours.[22] FSH activation of osteoclast NF-kB causes hypogonadal bone loss and directly increases osteoclastogenesis and resorption; as such, antagonising this hormone may result in positive disease outcomes.[23] Comparison of necrotic plaque size in response to orchiectomy, leuprolide, and degarelix in a murine model has shown that the necrotic plaque area is significantly reduced in animals in the degarelix group.[24] This is of particular significance as plaque size is often a predictor of downstream CV events, supporting the hypothesis that these drugs have different effects on CV physiology.

Prof Klotz concluded his presentation by stating that degarelix is a superior treatment over LHRH agonist therapy as a result of possessing a longer time to PSA failure and improved overall survival and control of bone metastasis.

Getting to the Heart of the Matter: CV Risk and ADT

Professor Alexandre de la Taille and Professor Jan Nilsson

Prof Jan Nilsson began this session by explaining the epidemiology of CV disease (CVD) worldwide. There were nearly 17 million deaths due to CVD in 2011,[25] with most acute events caused by vulnerable atherosclerotic plaque rupture. Degradation of the fibrous plaque results in an occluding thrombus and consequently a myocardial infarction. Age is an important factor in the incidence of CVD events with older men having the highest incidence of CV events.[26] Identification and reduction of CVD risk factors are likely to have a significant impact in reducing CV-related mortality.[27,28]

Prof de la Taille then led a discussion on the incidence of CV disease in patients with prostate

cancer. A cohort study of 30,721 patients with incident prostate cancer revealed that overall mortality was 20% higher in prostate cancer patients with pre-existing CVD compared to those without ischaemic heart disease (IHD) or stroke.[29]

Management of prostate cancer has a long history of treatment with androgen therapy as well as being associated with an increased risk of CV-related side-effects. A pivotal study from 1967 in which 2,052 patients were treated using radical prostatectomy or orchiectomy, with or without oestrogen, reported several interesting findings.[30] Survival was significantly shorter in patients with Stage 1–3 prostate cancer receiving oestrogens, with a significant increase in deaths due to CVD.[30] Similar findings have been observed with LHRH agonists, CAB, and orchiectomy, where the incidence of CVD is higher in patients treated with these therapies.[31] CV risk has been observed to increase with age and comorbidities; men aged ≥65 years and receiving 6 months of ADT had shorter times to fatal myocardial infarction compared to those receiving radiotherapy alone.[32] This increase in CVD in men treated with ADT (orchiectomy, oestrogen, or LHRH agonists) appears to be 20–25%, making it an important health issue compounded by the fact that CVD is the second most common cause of death in men with prostate cancer. Different types of ADT result in different CV effects depending on the treatment administered to the patient.[31]

Prof de la Taille then presented pooled data from six randomised Phase III/IIIb trials of degarelix versus LHRH agonists in 2,328 patients, where patients were treated with degarelix, leuprolide, or goserelin. Outcome measures included death from any cause and CV events. Baseline data between groups were similar, with no differences in age or body mass index; however, at least one-third of patients had CVD history at inclusion.[33] Findings confirmed previous results presented by Prof Klotz; there was better overall survival in patients treated with degarelix than those treated with LHRH.[19] The overall incidence of CV events was lower in the degarelix-treated group (2.8% degarelix versus 4.4% of LHRH agonist patients) as was the risk of serious CV events. Patients with pre-existing CVD had significantly fewer CV events during the first year of treatment compared with the LHRH agonist-treated patients; they had relative risk reduction of 56% and absolute risk reduction of 8.2%. Pooling all CV risk factors in a multivariate analysis revealed that degarelix had a lower risk of a CV event.[33]

Prof Nilsson suggested that these differences in CV risk could be due to differences in the effect of different ADT. Conventional ADT has been associated with metabolic change, insulin resistance, accumulation of subcutaneous fat, and decreased lean body mass, leading to MetS that increases the risk of developing CVD. However, it must be noted that MetS and the metabolic changes induced by ADT are different. Low testosterone is implicated in MetS as it increases fat deposition with increasing insulin resistance.[34,35]

Plaque instability is a predictor of CV event risk; stable plaques will have a thick fibrous plaque, with less infiltration by inflammatory cells. Conversely, a vulnerable plaque will have a thin fibrous cap, increased amounts of lipids and inflammatory cells but will also be able to maintain lumen size. Events further destabilising this plaque will ultimately lead to a CV event. Inflammatory events during plaque rupture include the production of various cytokines. These activate macrophages degrade the fibrous cap. Ultimately, this leads to plaque instability and increases the risk of thromboembolic complications and CV events.[36] The presence of GnRH receptors in T cells allows GnRH or LHRH agonist binding, which leads to the increased proliferation and activity of these cells, causing fibrous cap disruption and plaque instability. In contrast, GnRH antagonists do not activate T cell proliferation and activity, and thus are not likely to contribute to plaque destabilisation through this mechanism.[37–40]

A comparison of leuprolide, degarelix, and orchiectomy in a preclinical study has shown that FSH and LH levels are significantly lower with degarelix than leuprolide, with significantly lower triglyceride levels and better glucose tolerance. Atherosclerotic plaque surface area is also smaller with degarelix than leuprolide or orchiectomy, which may clarify potential differences between types of ADT and CV risk.[24,41]

Prof de la Taille explained that, as a urologist, the first and foremost concern with treatment is the effectiveness of the therapy to treat prostate cancer and control disease symptoms while minimising side-effects. However, in the presence of CV risk, including obesity, diabetes, and prior myocardial infarction, degarelix may be the preferred treatment of choice.

As a cardiologist, Prof Nilsson concluded this session with the following advice; the correct management of prostate cancer patients with accompanying changes in lifestyle including exercise, smoking cessation, and controlling alcohol intake, as well as medical intervention such as statin therapy and therapy to manage diabetes, hypertension, and risk of thrombosis, are all important.[42] The presentation concluded that ADT is associated with an increased risk of CV events; however, the GnRH antagonist degarelix may be a promising drug, offering increased survival in the total patient analysis and significant risk reduction of CV events in patients with pre-existing CVD, due to its different mechanism of action. Risk assessment of CVD needs to be assessed prior to using ADT.

This session provided the attending physicians with an informative discussion on the management of CVD risk in patients with prostate cancer.

Prof Klotz then concluded the symposium. The choices regarding therapy should take CVD and risk factors into account and consider each patient individually, offering a tailored approach. Promising new therapies, including degarelix, offer clinicians increasing effective options with improved side-effect profiles.

REFERENCES

1. Rigatti P et al. Pelvic/retroperitoneal salvage lymph node dissection for patients treated with radical prostatectomy with biochemical recurrence and nodal recurrence detected by [11C]choline positron emission tomography/computed tomography. Eur Urol. 2011;60:935-43.

2. Picchio M et al. [11C]Choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. Eur J Nucl Mol Imaging. 2012;39:13–26.

3. Langley RE et al. Cardiovascular outcomes in patients with locally advanced and metastatic prostate cancer treated with luteinising-hormone-releasing-hormone agonists or transdermal oestrogen: the randomised, phase 2 MRC PATCH trial (PR09). Lancet Oncol. 2013;14:306–16.

4. Thompson IM. Flare Associated with LHRH-Agonist Therapy. Rev Urol. 2001;3(suppl 3):S10–4.

5. Heidenreich A et al. EAU Guidelines on prostate cancer 2007.

Available at: www.uroweb.org. Accessed April 2014.

6. Sharifi N et al. Androgen deprivation therapy for prostate cancer. JAMA. 2005;294:238–44.

7. Morote J et al. Failure to maintain a suppressed level of serum testosterone during long-acting depot luteinizing hormone-releasing hormone agonist therapy in patients with advanced prostate cancer. Urol Int. 2006;77:135–8.

8. Tombal B. Eur Urol Suppl. 2008;7: 477–83.

9. Arcadi JA. Rapid drop in serum testosterone after bilateral subcapsular orchiectomy. J Surg Oncol. 1992;49:35–8.

10. Bubley GJ. Is the flare phenomenon clinically significant? Urology. 2001;58 (2 suppl 1):5–9.

11. Pickles T et al. How often do breakthroughs of testosterone suppression occur while on an lhrh analogue (lhrha), and are they of importance? Presented at: CARO Annual Scientific Meeting, 22–25 September 2010, Vancouver, Canada. Paper session 2, oral 24.

12. Casey R et al. 2012 CUA Abstracts. Can Urol Assoc J. 2012;6(3 Suppl 1):S3–S103.

13. Niazi T et al. Does testosterone breakthrough impact biochemical failure in prostate cancer patients? Presented at: European Cancer Congress, 27 September–1 October 2013, Amsterdam, the Netherlands. Abstract 2912.

14. Morote J et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. J Urol. 2007;178:1290–5.

15. Bertaglia V et al. Effects of serum testosterone levels after 6 months of androgen deprivation therapy on the outcome of patients with prostate cancer. Clin Genitourin Cancer. 2013;11:325–30.

16. Klotz L et al. Intermittent androgen suppression for rising PSA levls after radiotherapy. Presented at: 29th Annual Congress of the European Association of Urology, 11–15 April 2014, Stockholm, Sweden. Poster 973

17. Klotz L et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int. 2008;102:1531–8.

18. Crawford ED et al. Long-term tolerability and efficacy of degarelix: 5-year results from a Phase III extension trial with a 1-Arm crossover from leuprolide to degarelix. Oncology. 2014;83(5):1122-8.

19. Klotz L et al. Disease Control Outcomes from Analysis of Pooled Individual Patient Data from Five Comparative Randomised Clinical Trials of Degarelix Versus Luteinising Hormone-releasing Hormone Agonists. Eur Urol. 2014;doi:10.1016/j.eururo.2013.12.063. [Epub ahead of print].

20. Crawford ED et al. A phase III extension trial with a 1-arm crossover from leuprolide to degarelix: comparison of gonadotropin releasing hormone agonist and antagonist effect on prostate cancer. J Urol. 2011;186:889-97.

21. Mariani S et al. Expression and cellular localization of follicle-stimulating hormone receptor in normal human prostate, benign prostatic hyperplasia and prostate cancer. J Urol. 2006;175:2072–7.

22. Radu A et al. Expression of follicle-stimulating hormone receptor in tumor blood vessels. N Engl J Med. 2010;363:1621–30.

23. Sun L et al. FSH directly regulates bone mass. Cell. 2006;125:247–60.

24. Pinthus JH et al. The role of FSH in castration-induced adipogenesis: highlighting differences between orchiectomy, GNRH agonists, and antagonists. Presented at: the ASCO GU Congress, 30 January-February 1, 2013, San Francisco, USA, Abstract 191.

25. World Health Organization. The top 10 causes of death. July 2013. Available at: http://www.who.int/mediacentre/factsheets/fs310/en/. Accessed 7 May, 2014.

26. Driver JA et al. Incidence of cardiovascular disease and cancer in advanced age: prospective cohort study. BMJ. 2008;337:a2467.

27. Sytkowski PA et al. Changes in risk

factors and the decline in mortality from cardiovascular disease. The Framingham Heart Study. N Engl J Med. 1990;322: 1635–41.

28. Keil U. [The Worldwide WHO MONICA Project: results and perspectives]. Gesundheitswesen. 2005;67(suppl 1):S38–45.

29. Jespersen CG et al. The influence of cardiovascular morbidity on the prognosis in prostate cancer. Experience from a 12-year nationwide Danish population-based cohort study. BMC Cancer. 2011;11:519.

30. Treatment and survival of patients with cancer of the prostate. The Veterans Administration Co-operative Urological Research Group. Surg Gynecol Obstet. 1967;124:1011–7.

31. Keating NL et al. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Can Inst. 2010;102:39–46.

32. D'Amico AV et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol. 2007;25:2420–5.

33. Albertsen PC et al. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol. 2014:65;565–73.

34. Kelly DM, Jones TH. Testosterone: a vascular hormone in health and disease. J Endocrinol. 2013;217:R47–71.

35. Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. J Urol. 2009;181:1998–2006.

36. Libby P. Molecular bases of the acute coronary syndromes. Circulation. 1995;91:2844–50.

37. Chen HF et al. Human peripheral blood mononuclear cells express gonadotropin-releasing hormone (GnRH), GnRH receptor, and interleukin-2 receptor gamma-chain messenger ribonucleic acids that are regulated by GnRH in vitro. J Clin Endocrinol Metab. 1999;84:743–50.

38. Tanriverdi F et al. GnRH-I and GnRH-II have differential modulatory effects on human peripheral blood mononuclear cell proliferation and interleukin-2 receptor gamma-chain mRNA expression in healthy males. Clin Exp Immunol. 2005;142:103–10.

39. Grasso G et al. The effect of LHRH and TRH on human interferon-gamma production in vivo and in vitro. Life Sci. 1998;62:2005–14.

40. Jacobson JD et al. Modulation of the expression of murine lupus by gonadotropin-releasing hormone analogs. Endocrinol. 1994;134:2516–23.

41. Duivenvoorden WCM et al. The role of FSH in castration-induced weight gain and cardiovascular disease: Differences between orchiectomy, GnRH agonists and antagonists. Presented at EAU, 11–15 April 2014, Stockholm, Sweden. Poster 308.

42. Perk J et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33:1635–701.

HEALTH AND WELLBEING IMPACT AND TREATMENT OF NOCTURIA – A REVIEW OF THE LITERATURE

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Disclosure: No potential conflict of interest.
Received: 20.02.14 **Accepted:** 01.04.14
Citation: EMJ Urol. 2014;1:54-59.

ABSTRACT

Nocturia is a prevalent and highly bothersome lower urinary tract symptom (LUTS) affecting men and women of all ages. In waking to void there is disruption to an individual's sleep that can lead to daytime tiredness and a loss of vitality. This may significantly impact upon physical, mental, and social wellbeing. It is recognised that nocturia has a multifactorial aetiopathogenesis that encompasses systemic, psychogenic, as well as lower urinary tract factors, necessitating separate evaluation to other LUTS. In particular, nocturnal polyuria is an under-recognised cause of nocturia that may respond well to anti-diuretic pharmacotherapy.

Keywords: Nocturia, nocturnal polyuria, lower urinary tract symptoms, desmopressin.

INTRODUCTION

Nocturia is one of the most common and pragmatic of all the lower urinary tract symptoms (LUTS). It is defined by the International Continence Society (ICS) as: "The complaint that an individual has to wake one or more times to void...each void preceded and followed by sleep."[1] In waking to void there is fragmentation of the sleep cycle, which can have profound consequences on an individual's wellbeing and quality of life (QoL). Epidemiological studies have consistently demonstrated a high prevalence in both men and women, particularly in the elderly where there is a correlation with falls and fall-related morbidity.[2,3] The economic costs associated with nocturia are substantial; they are estimated to be over $60 billion per annum in the US on the basis of lost productivity alone.[4] In this review, we discuss the evidence relating to the impact of nocturia on health and wellbeing in addition to the contemporary therapeutic approaches, with a focus on the role of antidiuretic pharmacotherapy.

NOCTURIA

Definition

Nocturia is defined by the ICS as: "The complaint that an individual has to wake one or more times to void...each void preceded and followed by sleep."[1] The validity of this definition has been questioned as - for many people - waking up once at night to void is normal and not perceived as bothersome.[5] Tikkinen and colleagues[5] demonstrated a correlation between the number of night time voids and the grade of symptoms: up to 1 void per night results in no impact on QoL, 2 voids are followed by little discomfort, and ≥3 voids in a night causes moderate-to-severe impact upon sleep. Therefore, clinically relevant nocturia is probably ≥2 voids; however, it should be emphasised that it is the impact upon sleep that is likely to be the most critical factor determining bother, rather than the exact number of voids.[6]

Prevalence

The prevalence of nocturia was recently summarised in a meta-analysis including >40

population studies. Using the clinically relevant definition of nocturia as ≥2 voids, in young women (in the 2nd or 3rd decade) prevalence was 4.4-18%, whilst in older women (7th or 8th decade) the range was 28.3-61.5%. In men, the corresponding age groups demonstrated a prevalence of 2-16.6%, whereas in the older group this rose to 29-59.3%.[7]

Aetiology

The aetiological factors implicated in nocturia can be classified as affecting urine storage, urine production, and unrelated conditions that impact upon sleep. Lower urinary tract dysfunctions that lead to a failure to store urine may result in nocturia. Most commonly this occurs in the context of overactive bladder syndrome (OAB), which is variably correlated to underlying detrusor overactivity (DOA). Urinary urgency, the pivotal symptom of OAB, is correlated with nocturia (OR=1.70), as is urinary incontinence.[8] OAB is present in one-third of individuals with nocturia,[9,10] whilst approximately 50% of those with OAB have nocturia.[10,11] Benign prostatic hyperplasia (BPH) is also associated with nocturia; however, this association may be age related.[12] BPH may lead to a reduction in the functional bladder capacity at night by impairing bladder emptying, leading to a raised post-voiding residual. DOA may also occur due to bladder outlet obstruction as a consequence of BPH. In the past, nocturia was considered by many to result primarily as a consequence of BPH, however it often failed to resolve after outlet surgery, suggesting that other factors were implicated.[13,14]

It is now recognised that the volume of nocturnal urine produced is a critical aetiological factor in many individuals with nocturia. Global polyuria (GPu) is the overproduction of urine occurring over 24 hours (>2.8 litres of urine/24 hr or >40 ml/kg). A common cause is diabetes mellitus, where high circulating glucose levels lead to an osmotic diuresis. In diabetes insipidus (DI) the kidneys are unable to sufficiently concentrate the urine due to a lack of arginine vasopressin (AVP) (or anti-diuretic hormone) production in the posterior pituitary gland (cranial DI), or loss of renal sensitivity to the hormone (renal DI). Other causes include excessive drinking (either habitual or due to psychiatric causes) and an excessive intake of protein drinks, causing an osmotic diuresis.

Nocturnal Polyuria (NPu) is relative overproduction of urine during the night, defined by the ICS as a night time volume of >20% of the daily total in younger patients (<65 years) and >33% in the elderly (>65 years).[15] Using these definitions it is highly prevalent in patients with nocturia: 66-83% of patients <65 years and in 90-93% ≥65 years.[16] However, recently published results from the Krimpen study[17] challenge the clinical utility of the ICS definitions; 70.1% of men without clinically significant nocturia (defined as ≥2 voids) had NPu according to the ICS definitions compared to 91.9% of men with nocturia. NPu is thought to occur due to age-related alterations in renal function and a loss of the normal diurnal variation in the release of AVP, albeit this is incompletely understood.[18-20] Obstructive sleep apnoea can cause NPu[21] due to the release of atrial natriuretic peptide from the atrial walls as a secondary effect of a more negative intrathoracic pressure, generated by upper airway obstruction.[22] Conditions that cause the third spacing of fluid peripherally (e.g. cardiac failure or venous insufficiency) may also contribute to NPu due to the redistribution of this fluid into the circulation when the patient becomes recumbent.

Certain conditions that cause disturbance of sleep are associated with nocturia, including: insomnia,[23] depression and anxiety,[24] pruritus,[25] snoring,[26] burning mouth syndrome,[27] and chronic pain.[28] In such situations it can be difficult to determine whether nocturia is a primary or a secondary phenomenon (convenience voids).

IMPACT OF NOCTURIA

Quality of Sleep

Nocturia is commonly unrecognised as a reason for poor sleep.[23] Although there is a positive correlation between the actual number of night time voids and the degree of bother,[29] it is probably more useful to consider bother as a product of the relative sleep deficit. The timing of voids is likely to be important. Restorative slow wave pattern sleep occurs during the first half of the night's sleep, hence awakening during this period is more likely to lead to negative consequences.[30] Individuals who find it easier to fall asleep and return to sleep after awakening are less likely to incur a significant degree of bother.[31]

QoL

Sleep deficit leads to daytime tiredness and may impair physical and mental functioning,

impacting on QoL. The Boston Area Community Health (BACH) study (USA) demonstrated that significant reductions in QoL scores independently correlated with nocturia, with an inverse correlation between score and number of night time voids.[32] Similarly, data from Finland showed that nocturia (≥2 voids) was associated with reductions in 14 out of 15 domains of health-related QoL (all except eating).[5]

Greater nocturnal urinary frequency is associated with a greater degree of bother.[29] However, it is likely that the relationship between nocturia and sleep disturbance is more complex and a product of the relative deficit in sleep. Shorter interval to initiation of sleep is associated with less bother from nocturia,[33] whilst those with difficulty initiating sleep and returning to sleep after waking up are more likely to be bothered.[31]

Morbidity and Mortality

Older people with nocturia have an increased risk of falling.[34-36] This risk appears to increase with greater episodes of nocturia (>2, OR=1.84 and >3, OR 2.15).[37] Unsurprisingly, an increased risk of fracture is also correlated with nocturia.[3,34,38] An age-independent relationship between the number of nocturia episodes and risk of hip fracture was found in men: nocturia ≥2 and ≥3 (OR=1.36 and 1.80, respectively).[38] Nocturia has also been correlated to an increased risk of mortality in several studies;[3,39] however, this may potentially be explained by confounding factors, particularly age.[40] Chung et al.,[41] however, found that severe nocturia had a significant association with mortality (6.1% versus 2.4% in those without severe nocturia, p=0.001), which was independent of age or disease duration in patients with diabetes mellitus.

ASSESSMENT AND TREATMENT

Contemporary clinical assessment of nocturia entails an evaluation of the severity of symptoms, impact upon QoL, and the identification of contributory/causative factors. The frequency volume chart is a fundamental part of assessment, providing an objective measure of number of voids and volumes passed, allowing the estimation of nocturnal bladder capacity and the identification of NPu. Current treatment for nocturia entails lifestyle modification and pharmacotherapies for OAB, LUTS/BPH, and NPu.

Outcome Measures

A major limitation of most drug trials for LUTS has been the inadequate assessment of nocturia due to a failure to use voiding diaries or to assess the impact of nocturia on sleep and QoL. Nocturia is often assessed in terms of an absolute reduction in number of voids or by the use of 'question 7' of the international prostate symptoms score (IPSS): "How many times did you typically get up to urinate?" These methods do not assess associated bother, impact on quality of sleep, or QoL. Consequently, methods to more comprehensively assess nocturia are being introduced. The hours of undisturbed sleep (HUS) is the time from falling asleep to first waking,[42] its use being based on the finding that the most restorative hours in a night's sleep are the initial 3-4.[43] The Nocturia Quality of Life module (ICIQ-NQoL)[44] is a validated nocturia-specific QoL questionnaire that assesses three domains: sleep/energy, bother/concern, and overall QoL.

Lifestyle Changes

Lifestyle modification measures include avoidance of caffeine and alcohol, limiting evening fluid, leg elevation, and interventions aimed at improving sleep (e.g. exercise, warm temperature). A combination of these measures has been found to significantly reduce nocturia episodes (from 2.6 to 1.9 [p<0.001]) and quality of sleep.[33] The use of sedatives (e.g. hypnotics)[45] to promote sleep can provide helpful palliation, although side-effect profiles and risk of dependence limit longer term usage.

OAB Pharmacotherapy

Muscarinic antagonists, the mainstay of drug therapy for OAB, have often demonstrated little impact upon nocturia in clinical trials. This may be attributable to the inclusion of a significant number of individuals with NPu. Even when patients with NPu are excluded, improvements in nocturia are modest. A post-hoc analysis of four Phase III trials of solifenacin in men and women with OAB[46] found a statistically significant reduction in night time voids of 35.5% in subjects randomised to solifenacin 5 mg and of 36.4% in subjects taking solifenacin 10 mg. By comparison, those receiving placebo experienced a 25.0% reduction in night time voids. In numerical terms, this equated to a 0.18 and 0.08 advantage over placebo for the 5 mg and 10 mg doses, respectively. Similar findings were found in other studies.[47,48]

LUTS/BPH Pharmacotherapy

Alpha-blockers are the most commonly used first-line drug treatment of LUTS associated with BPH. Where voiding diaries have been used, statistically significant reductions in nocturnal voids are commonly reported. Johnson et al.[50] performed a subset analysis in the medical therapy of prostate symptoms study (MTOPS). Doxazosin led to a mean reduction of 0.77 voids compared to placebo, 0.61, at 1 year, a statistically significant advantage ($p<0.05$). Similar findings were seen in trials of Alfuzosin[49] and Terazosin.[50] The clinical significance of such reductions is doubtful. Furthermore, given recall bias and the subjective quantification of the level of bother, the IPSS questionnaire is unlikely to be a sensitive measure of nocturia.

Desmopressin Therapy

Desmopressin acetate, a synthetic analogue of AVP, causes the production of smaller volumes of more concentrated urine.[51] It acts as a selective V2 receptor inhibitor (i.e. in the renal collecting system) and thus avoids vasopressor effects associated with V1 receptor agonism. It has Grade A recommendation for use in patients with NPu.[52] Currently available preparations include an oral tablet, an oral disintegrating tablet, a sublingual spray, and an intranasal spray.

The safety and efficacy of desmopressin therapy is supported by level I evidence.[51,53,54] A recent meta-analysis by Cornu et al.[55] demonstrated significant reductions in night time voids and an increase in HUS in five trials (lasting several weeks), primarily assessing the efficacy of desmopressin in non-neurogenic patients. The mean difference in night time voids between desmopressin and placebo across the studies was -0.54 (-0.8 to -0.28). In terms of HUS, desmopressin had a 53.56 (31.67-75.45) minutes mean advantage compared to placebo. open label extension studies up to 1 year showed a durable effect.[56-58] Moreover, randomisation periods were short (up to 4 weeks) and most studies included a dose titration period, which excluded non-responders and subjects who had adverse effects.

A dose finding study by Weiss and colleagues[54] investigated four doses of the oral disintegrating preparation of desmopressin (from 10 to 100 μg) in 757 men and women. An increasing dosage was associated with increased effect in terms of reduction in night time voids and length of HUS, and voided volume, greater proportions of subjects with >33% reduction in nocturnal voids, and increased duration of first sleep period. The minimal dosage required to attain a significant advantage over placebo in both night time voids and HUS was 25 μg in women and 100 μg in men, suggesting that women are more sensitive to desmopressin therapy.

Desmopressin therapy was well tolerated in most studies and did not indicate any safety concerns other than the expected potential for hyponatraemia. An overall incidence of clinically significant hyponatraemia (Na <130 mmol/L) of 3% has been reported.[54] Hyponatraemia is most likely to occur in women, the elderly, and at higher doses. When hyponatraemia occurs, it is usually on initiation of treatment and within the first week. Subsequently, the risk of hyponatraemia does not appear to increase with time (up to 1 year).[56] Current guidance advises checking sodium levels on days 3 and 7[59,60] in order to identify those patients at risk of developing symptomatic hyponatraemia. Desmopressin is an effective treatment for nocturnal polyuria. It prolongs the first sleep period and thereby improves patient quality of life.

When NPu is due to obstructive sleep apnoea, continuous positive airway pressure (CPAP) treatment overnight is the treatment of choice; Margel et al.[61] demonstrated mean nocturnal voids were reduced from 2.6-0.7 with CPAP ($p<0.001$).

CONCLUSION

Nocturia is a highly prevalent problem that is under-appreciated in clinical practice. It has a multifactorial aetiology necessitating a comprehensive evaluation not confined to LUTS. The voiding diary is fundamental to the identification of the underlying pathophysiological mechanism, particularly NPu. There has been a failure to use adequate measures of the impact of nocturia in most clinical studies for LUTS pharmacotherapies. The available evidence suggests statistically significant reductions in night time voids with traditional agents used in the treatment of OAB and LUTS due to BPH unlikely to translate into meaningful clinical improvements. There is a growing body of evidence to support the safety and efficacy of desmopressin preparations in patients with underlying NPu; however, optimal dosages and long-term efficacy need to be established.

REFERENCES

1. Abrams P et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21:167-78.

2. Vaughan CP et al. The association of nocturia with incident falls in an elderly community-dwelling cohort. Int J Clin Pract. 2010;64:577-83.

3. Nakagawa H et al. Impact of nocturia on bone fracture and mortality in older individuals: a Japanese longitudinal cohort study. J Urol. 2010;184:1413-8.

4. Holm-Larsen TWJ, Langkilde LK. Economic burden of nocturia in the US adult population. J Urol. 2010;183:e1.

5. Tikkinen KA et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol. 2010;57:488-96.

6. van Dijk L et al. Nocturia: impact on quality of life in a Dutch adult population. BJU Int. 2004;93:1001-4.

7. Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol. 2010;184: 440-6.

8. Rembratt A et al. Nocturia and associated morbidity in a community-dwelling elderly population. BJU Int. 2003;92:726-30.

9. Schatzl G et al. Cross-sectional study of nocturia in both sexes: analysis of a voluntary health screening project. Urology. 2000;56:71-5.

10. Weiss JP et al. Age related pathogenesis of nocturia in patients with overactive bladder. J Urol. 2007;178:548-51; discussion 551.

11. Irwin DE et al. Understanding the elements of overactive bladder: questions raised by the EPIC study. BJU Int. 2008;101:1381-7.

12. Yoshimura K. Correlates for nocturia: a review of epidemiological studies. Int J Urol. 2012;19:317-29.

13. Castleden CM et al. A postal survey evaluation of prostatectomy. J Public Health Med. 1994;16:275-8.

14. Homma Y et al. Significance of nocturia in the International Prostate Symptom Score for benign prostatic hyperplasia. J Urol. 2002;167:172-6.

15. van Kerrebroeck P et al. The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn. 2002;21:179-83.

16. Weiss JP et al. Excessive nocturnal urine production is a major contributing factor to the etiology of nocturia. J Urol. 2011;186:1358-63.

17. van Doorn B et al. Prevalence, incidence, and resolution of nocturnal polyuria in a longitudinal community-based study in older men: the Krimpen study. Eur Urol. 2013;63:542-7.

18. Asplund R, Aberg H. Diurnal variation in the levels of antidiuretic hormone in the elderly. J Intern Med. 1991;229:131-4.

19. Ouslander JG et al. Arginine vasopressin levels in nursing home residents with nighttime urinary incontinence. J Am Geriatr Soc. 1998;46:1274-9.

20. Hvistendahl GM et al. Gender differences in nighttime plasma arginine vasopressin and delayed compensatory urine output in the elderly population after desmopressin. J Urol. 2007;178: 2671-6.

21. Kaynak H et al. Does frequency of nocturnal urination reflect the severity of sleep-disordered breathing? J Sleep Res. 2004;13:173-6.

22. Yalkut D et al. Mechanism of atrial natriuretic peptide release with increased inspiratory resistance. J Lab Clin Med. 1996;128:322-8.

23. Bliwise DL et al. Nocturia and disturbed sleep in the elderly. Sleep Med. 2009;10:540-8.

24. Asplund R et al. Nocturia and depression. BJU Int. 2004;93:1253-6.

25. Anderson RT, Rajagopalan R. Effects of allergic dermatosis on health-related quality of life. Curr Allergy Asthma Rep. 2001;1:309-15.

26. Tikkinen KA et al. A systematic evaluation of factors associated with nocturia--the population-based FINNO study. Am J Epidemiol. 2009;170:361-8.

27. Asplund R. Nocturia and the burning mouth syndrome (BMS) in the elderly. Arch Gerontol Geriatr. 2005;41:255-60.

28. Menefee LA et al. Sleep disturbance and nonmalignant chronic pain: a comprehensive review of the literature. Pain Med. 2000;1:156-72.

29. Asplund R, Aberg H. Health of the elderly with regard to sleep and nocturnal micturition. Scand J Prim Health Care. 1992;10:98-104.

30. Chartier-Kastler EC, Chapple CR. LUTS/BPH in clinical practice: the importance of nocturia and quality of sleep. BJU international. 2006;98:3-8.

31. Vaughan CP et al. Self-rated sleep characteristics and bother from nocturia. Int J Clin Pract. 2012;66:369-73.

32. Kupelian V et al. Nocturia and quality of life: results from the Boston area community health survey. Eur Urol. 2012;61:78-84.

33. Vaughan CP et al. A multicomponent behavioural and drug intervention for nocturia in elderly men: rationale and pilot results. BJU international. 2009;104: 69-74.

34. Asplund R. Hip fractures, nocturia, and nocturnal polyuria in the elderly. Arch Gerontol Geriatr. 2006;43:319-26.

35. Brown JS et al. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc. 2000;48:721-5.

36. Jensen J et al. Falls among frail older people in residential care. Scand J Public Health. 2002;30:54-61.

37. Stewart RB et al. Nocturia: a risk factor for falls in the elderly. J Am Geriatr Soc. 1992;40:1217-20.

38. Temml C et al. Nocturia is an age-independent risk factor for hip-fractures in men. Neurourol Urodyn. 2009;28: 949-52.

39. Kupelian V et al. Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. J Urol. 2011;185:571-7.

40. van Doorn B et al. Mortality in older men with nocturia. A 15-year follow-up of the Krimpen study. J Urol. 2012;187: 1727-31.

41. Chung MS et al. Prevalence and associated risk factors of nocturia and subsequent mortality in 1,301 patients with type 2 diabetes. Int Urol Nephrol. 2014. [Epub ahead of print].

42. Djavan B MS et al. The impact of tamsulosin oral controlled absorption system (OCAS) on nocturia and the quality of sleep: preliminary results of a pilot study. Eur Urol Suppl. 2005;4:61–8.

43. Kobelt G et al. Productivity, vitality and utility in a group of healthy professionally active individuals with nocturia. BJU international. 2003;91:190-5.

44. Abraham L et al. Development and validation of a quality-of-life measure for men with nocturia. Urology. 2004;63: 481-6.

45. Weiss JP et al. The evaluation and treatment of nocturia: a consensus statement. BJU Int. 2011;108:6-21.

46. Brubaker L, FitzGerald MP. Nocturnal polyuria and nocturia relief in patients treated with solifenacin for overactive bladder symptoms. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18:737-41.

47. Vardy MD et al. Effects of solifenacin on overactive bladder symptoms, symptom bother and other patient-reported outcomes: results from VIBRANT - a double-blind, placebo-controlled trial. Int J Clin Pract. 2009;63:1702-14.

48. Cardozo L et al. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. J Urol. 2004;172(5 Pt 1):1919-24.

49. Roehrborn CG et al. Safety and efficacy of alfuzosin 10 mg once-daily in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. BJU Int. 2003;92:257-61.

50. Johnson TM et al. Changes in nocturia from medical treatment of benign prostatic hyperplasia: secondary analysis of the Department of Veterans Affairs Cooperative Study Trial. J Urol. 2003;170:145-8.

51. Lose G et al. Efficacy of desmopressin (Minirin) in the treatment of nocturia: a double-blind placebo-controlled study in women. Am J Obstet Gynecol. 2003;189:1106-13.

52. Andersson KE et al. Pharmacological treatment of urinary incontinence. Continence. Paris: Health Publications Ltd. pp. 631-99.

53. Mattiasson A et al. Efficacy of desmopressin in the treatment of nocturia: a double-blind placebo-controlled study in men. BJU Int. 2002;89:855-62.

54. Weiss JP et al. Desmopressin orally disintegrating tablet effectively reduces nocturia: Results of a randomized, double-blind, placebo-controlled trial. Neurourol Urodyn. 2012;31:441-7.

55. Cornu JN et al. A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management--a systematic review and meta-analysis. Eur Urol. 2012;62:877-90.

56. Weiss JP, Daneshgari F. Desmopressin orally disintegrating tablet effectively reduces symptoms of nocturia and prolongs undisturbed sleep in patients with nocturia: results of a large randomized trial. Neurourol Urodyn. 2010;29:805;abstract 19.

57. Lose G et al. Clinical experiences with desmopressin for long-term treatment of nocturia. J Urol. 2004;172:1021-5.

58. Wang CJ et al. Low dose oral desmopressin for nocturnal polyuria in patients with benign prostatic hyperplasia: a double-blind, placebo controlled, randomized study. J Urol. 2011;185:219-23.

59. NICE. The management of lower urinary tract symptoms in men. National Institute for Health and Clinical Excellence. Available: http://www.nice.org.uk/usingguidance/commissioningguides/luts/LUTS.jsp.

60. Oelke M et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol. 2013;64:118-40.

61. Margel D et al. Continuous positive airway pressure reduces nocturia in patients with obstructive sleep apnea. Urology. 2006;67:974-7.

INCREASED HYALURONAN ACID BINDING ABILITY OF SPERMATOZOA INDICATING A BETTER MATURITY, MORPHOLOGY, AND HIGHER DNA INTEGRITY AFTER MICRONUTRIENT SUPPLEMENTATION

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Disclosure: No potential conflict of interest.
Received: 19.01.14 **Accepted:** 01.04.14
Citation: EMJ Urol. 2014;1:60-65.

ABSTRACT

Measuring the hyaluronan-binding ability of spermatozoa is useful in predicting the ability of spermatozoa to fertilise oocytes during *in vitro* fertilisation (IVF). Recent publications discuss an influence of micronutrients on sperm quality. The objective of this paper was to evaluate the effect of a non-prescription nutraceutical containing eight micronutrients on sperm-hyaluronan binding assay (SHBA) values among males with idiopathic sub-/infertility, using an open comparative pilot study. The study took place at the Outpatient Fertility Centre IMI, Vienna, Austria, and involved 67 sub-/infertile males. Sub-/infertile males were invited to participate and take two daily capsules of the active compound for a 3-month period between the first and the follow-up semen analysis. Each capsule contained L-carnitine, L-arginine, zinc, vitamin E, glutathione, selenium, coenzyme Q10 (CoQ10), and folic acid (Profertil®). 40 sub-/infertile men receiving no active treatment served as controls; this was measured by change in SHBA after 3 months. It was found that SHBA values significantly increased after 3 months of treatment with the active compound, from a median baseline value of 56.0% to 74% ($p<0.05$). This represented a 19.7% increase compared to baseline, which was significantly higher than the 2.1% decrease observed in the control group. The rate of subjects displaying an increase in SHBA values after 3 months was significantly higher in the active group (74.6% versus 30.0%, $p=0.0001$), which showed that sub-/infertile men treated with the active micronutrient compound displayed increased SHBA ability. However, more research is necessary to get detailed information on this specific subject.

Keywords: Sperm, micronutrients, sperm DNA integrity, idiopathic male infertility, sub-fertility.

INTRODUCTION

Birth rates in Western countries are decreasing; 10-17% of all couples experience primary or secondary sub-/infertility,[1] defined as the failure to conceive after 1 year of regular, unprotected intercourse with the same partner. Sub-/infertility resulting in permanent childlessness can be a very difficult situation for couples.[2] These couples try to conceive by all possible means, including assisted reproduction (AR), which obviously does not necessarily treat the cause of sub-/infertility.

Factors related to the male partner account for nearly 25-30% of all sub-/infertility causes.[1,3] Several treatable conditions have been identified: hypogonadism, varicocele, gonadotropin deficiency, genital tract infections and obstructions, or sperm

autoimmunity. In about 50% of all sub-/infertile men with seminal abnormalities seeking treatment, no specific cause is found. Despite this, 15% of couples suffering from male factor sub-/infertility have normal sperm parameters, indicating that definitive diagnosis cannot be determined through routine semen analysis.[4]

There is growing evidence highlighting the role of sperm nuclear DNA integrity in male factor sub-/infertility. Reports indicate that a higher amount of DNA damage is associated with a negative effect on fertility potential.[5-7] While sub-/infertile men with poor semen parameters tend to have high levels of sperm DNA damage, increased DNA fragmentation can also be seen in 8% of men with normal semen analysis.[7] Sperm DNA integrity can be estimated by various methods, the sperm-hyaluronan binding assay (SHBA) is one option. Only sperm which have gone through all stages of development are able to recognise hyaluronan as a component of the human zona pellucida. For this reason, DNA integrity is higher in hyaluronan-recognising mature sperm. This is believed to be the main reason for the significant correlation between high SHBA values, good embryonic quality, and lower miscarriage rates. Exposure to environmental and industrial toxins, oxidative stress, smoking, and genetic factors are known to cause sperm DNA fragmentation.[8,9]

Developing an effective treatment for male idiopathic sub/-infertility is not easy. Various agents have been used in an attempt to increase the fertility potential of men with decreased semen quality; nevertheless, studies have rendered heterogeneous results, and the effect of gonadotropins or antioestrogens on pregnancy rates remains controversial.[1] Hence, to date there is still no proven therapy for the improvement of semen quality in this large group of men.[10]

A key factor of major therapeutic interest is nutrition. Most of the essential compounds required for DNA synthesis and spermatogenesis are derived from the diet. Therefore, concentration of required nutrients and other relevant factors may have substantial effects on sperm quality and reproduction.[11,12] A number of nutrients such as trace elements, vitamins, amino acids, and other agents involved in spermatogenesis have been examined and advocated as a way of optimising sperm production and quality. A Cochrane review stated that antioxidant supplementation in sub-/infertile men may improve reproductive outcomes (i.e. live births and pregnancy rates) among couples undergoing ART cycles.[13]

Studies examining the effect of a combination of several of the aforementioned elements and their effect over SHBA are still lacking. Hence, the aim of the present pilot study was to evaluate the effect of a non-prescription nutraceutical containing eight micronutrients on values indicated by the SHBA (maturity, strict morphology, high DNA integrity, and reduced chromosomal aneuploidies) among males with idiopathic sub-/infertility. Micronutrients included in the preparation were L-carnitine, L-arginine, zinc, vitamin E, glutathione, selenium, coenzyme Q10 (CoQ10), and folic acid. The treatment time of 3 months was selected according to the period of 74 days for spermatogenesis and the common interval between first and usual follow-up semen analysis.

MATERIALS AND METHODS

Study Design and Participants

The present open comparative pilot study was performed from January 2007 to October 2010 at the Outpatient Fertility Centre IMI, Vienna, Austria. Men with at least 1 year of sub-/infertility and at least one prior and one recent abnormal semen analysis were invited to participate and take two daily capsules of the proposed nutraceutical for 3 months, after which a follow-up semen analysis was performed (active treatment group). Exclusion criteria were azoospermia, aspermia, varicocele, and recent urogenital infections. Participants in the active treatment group were requested to provide written consent after being informed of the study, its aims, and methodology. Sub-/infertile men attending the Department of Urology of the Medical University of Vienna, Austria, who did not take the active compound during the study period, served as controls. Investigations were approved by the local ethical committee (Vienna) and written consent was obtained from patients.

Preparation (Nutraceutical)

Two capsules of the active compound (PROfertil®) contained: L-carnitine (440 mg), L-arginine (250 mg), zinc (40 mg), vitamin E (120 mg), glutathione (80 mg), selenium (60 µg), CoQ10 (15 mg), and folic acid (800 µg), and were provided by Lenus Pharma GmbH, Vienna, Austria.

Primary Outcome Assessment: SHBA Values

The present study used the SHBA® (Biocoat, Inc., Horsham, PA, USA). The assay kit consists of SHBA® test slides, Cell-Vu® gridded cover slips, and the product instruction. Following 2-3 days of abstinence, semen samples were obtained by masturbation. The samples were stored at 20-30°C for about 30 minutes until liquefaction was complete. Then, 7-10 µl of the obtained semen were pipetted into the centre of the test chamber of the slides. Cell-Vu® gridded cover slips were then installed without entrapping air bubbles. After incubating the slides for about 10 minutes, unbound motile and bound motile sperm cells in the same grid squares were counted. In order to achieve good assay precision the count of bound and unbound sperm cells in each assessed sample was between 100 and 200. This test measures sperm hyaluronan binding (expressed as percentage). The percentage of binding was calculated as 100 x bound motile sperm/(bound motile sperm + unbound motile sperm). A SHBA® score of ≥80% is indicative of normal maturity and physiological function whereas a value of <80% indicates a diminished maturity and physiological function.

Statistical Analysis

Statistical analysis was performed using SPSS version 19 (IBM, Armonk, NY, USA). Data are presented as medians [interquartile ranges], minimum/maximum values, and percentages. The Kolmogorov-Smirnov test was used to determine the normality of data distribution. According to this, differences between groups were analysed with the Mann Whitney test (continuous non parametric data) and the chi-square test (percentages). Changes within each studied group were evaluated with the Wilcoxon rank test. A value of $p<0.05$ was considered as statistically significant.

RESULTS

During the study period a total of 76 eligible sub-/infertile men attending the Fertility Clinic IMI, Vienna, Austria, were enrolled and took the active compound. 9 men withdrew from study participation, leaving 67 subjects who completed 3 months of treatment and provided data for full analysis. The control group included 40 sub-/infertile men. The median age of men taking the active compound was 34 years (minimum/maximum: 18-43 years), whereas in the control group this was 38 years (minimum/maximum: 22-52 years).

SHBA value significantly increased after 3 months of treatment with the active compound, from a median baseline value of 56.0-74.0% ($p<0.05$) (Table 1). This represented a 19.7% increase compared to baseline, which was significantly

Table 1: Sperm hyaluronan binding assay results of the changes between treatment group after 3 months of treatment and control group. The rate of patients displaying an increase in SHBA values is significantly higher in the treatment group.

Parameter	Treatment group n=67	Control group n=40	p value*
Percent of sperm-hyaluronan binding at baseline	56.0 [41.0]	69.5 [23.3]	0.02
Percent of sperm-hyaluronan binding after 3 months	74.0 [21.0] **p=0.0001	64.5 [20.8] **p=0.03	0.01
Median percent change compared to baseline	19.7 [64.8]	-2.1 [7.6]	0.0001
Increase after 3 months *n* (%)	50 (74.6)	12 (30.0)	0.0001
Neutral after 3 months *n* (%)	2 (3.0)	2 (5)	0.99
Decrease after 3 months *n* (%)	15 (22.4)	26 (65.0)	0.0001

Data are presented as medians [interquartile ranges] and frequencies *n* (%).
* p value after comparing groups using the Mann Whitney test or the chi-square test.
** p value when compared to baseline (intragroup comparison) using the Wilcoxon rank test.

higher than the 2.1% decrease observed in the control group (Table 1). The rate of subjects displaying an increase in SHBA values after 3 months was significantly higher in the active group (74.6% versus 30.0%, p=0.0001) (Table 1).

DISCUSSION

The investigated nutrient combination was designed to treat idiopathic male sub-/infertility through the supplementation of several vitamins, enzymes, and trace elements required for optimal sperm cell metabolism, DNA-synthesis during spermatogenesis, proliferation, and anti-oxidative protection. In consideration of their biochemical function, these ingredients are of great significance for male reproduction. A deficiency of these nutrients may result in male fertility disturbances. The studied composition was based on the rationale that each ingredient has been shown to improve sperm factors that may contribute to fertility.

L-carnitine is the energy substrate of spermatozoa. Free L-carnitine is positively correlated with sperm count, motility, and motile sperm density.[14] Although two controlled trials have reported a positive effect of L-carnitine over each of the mentioned parameters,[15,16] a recent study performed on men with idiopathic asthenozoospermia found no significant effect.[17]

Nitric oxide (NO) is beneficial for sperm viability and motility in both fertile and infertile individuals;[18] L-Arginine is the immediate precursor of NO. L-arginine improved sperm motility in infertile men with normal cell counts[19] and displayed a beneficial *in vitro* effect on sperm motility of asthenozoospermic men.[20]

Vitamin E improved sperm motility and enabled fertility in asthenozoospermic men,[21] and also significantly improved the *in vitro* function of human spermatozoa in single studies.[22] In combination with selenium, vitamin E increased sperm motility and normal morphology rates.[23] Selenium is an essential component of the enzyme glutathione peroxidase, and is required for the production of this enzyme when glutathione is supplemented. Testicles contain high selenium concentrations, and sperm quantity and quality are decreased in selenium-deficient humans.[24] Despite this, studies regarding selenium supplementation have rendered contradictory results.[25,26] Zinc is involved in DNA transcription, protein synthesis, testicular development, and sperm maturation, and it is thought to extend functional life span of ejaculated spermatozoa.[27] Low seminal zinc levels have been correlated to decreased fertility potential;[27] zinc supplementation has shown positive effects on sperm counts and other measures.[28] Folic acid is required for DNA synthesis and thus is important for spermatogenesis.[11] Nevertheless, the underlying mechanisms are still unknown. The supplementation of folic acid alone failed to show beneficial effects on sperm concentration in normal and oligo-zoospermic men.[29]

Glutathione plays a key role in protein and DNA synthesis. Lower glutathione levels have been reported in sub-/infertile men and related to abnormal sperm motility and morphology.[30] A positive effect of glutathione supplementation on sperm motility and morphology, and furthermore an oral bioavailability, has been reported.[31,32] CoQ10 is deeply involved in body energy metabolism; 95% of all ATP is converted with the aid of CoQ10.[33] This defines a role for CoQ10 in male infertility, which has been confirmed by increased sperm motility in asthenozoospermic men.[34] Spermatozoa are particularly sensitive to oxidative and electrophilic stress. Moreover, reactive oxygen species have been implicated in both male and female reproductive functions.[35] The oral bioavailability of CoQ10 in the right formulation is documented.[36] Despite this, the role of antioxidants in sperm quality improvement is still controversial, mainly due to the low quality of most studies and to the use of different antioxidants (different combinations, doses, and durations). Pregnancy, the most relevant outcome, was reported in only a few studies.[37]

As extensively described above, each micronutrient alone or in combination have reported positive effects on semen parameters in sub-/infertile men. However, to date no study has reported on the use of a combination of eight of these nutrients (as performed in this pilot study) and its effect on SHBA values. Yagci et al.[38] showed that hyaluronan acid shows a high degree of selectivity for sperm with high DNA integrity. As Breznik et al.[39] stated, the HBA-slide is found to be useful in predicting the ability of spermatozoa to fertilise oocytes in IVF and is helpful in distinguishing semen samples suitable for IVF and intra-cytoplasmic sperm injection. These studies indeed demonstrated that the SHBA can be used for indirect measurement

of sperm DNA integrity. An increase of hyaluronan acid-binding ability means that more motile and morphologically normal sperm with high DNA integrity are binding, which means a higher possibility of achieving an effective fertilisation and a subsequent normal pregnancy. This seems to be an important approach in treating sub-/infertile couples as low DNA integrity values are associated with a lower probability of natural conception, a lower fertilising potential of sperm used in AR techniques, a higher rate of disrupted embryonic development and miscarriages, and a higher probability of diseases in newborns.[40]

The examined preparation was well tolerated by all participants and no adverse reactions appeared. All ingredients have been thoroughly examined for decades and toxicological data show that they exert no negative health effects or potential hazards, even at higher dosages than those used in the present study.

CONCLUSION

We recognise the non-randomised, placebo-controlled design of our study is a limitation, as well as the differences between the controls, such that they did not receive the investigational active compound. However, a double-blind, randomised, placebo-controlled study is currently on its way to support these preliminary results. Despite these limitations, and in light of the fact that therapies for sub-/infertile men are still missing, the investigated compound seems to be a promising therapeutic approach for improving hyaluronic acid-binding ability of spermatozoa in order to enable natural conception among couples with idiopathic male sub-/infertility. In conclusion, hyaluronic acid-binding ability of spermatozoa is improved in sub-/infertile men after treatment with the active micronutrient compound without any adverse effects. More research, however, is warranted in this regard.

Acknowledgements

We kindly thank Lenus Pharma GmbH, Vienna, Austria for supporting this initiative and providing the active compound without any charge, and Adebar Fertility Clinic for their invaluable scientific mentoring.

REFERENCES

1. Templeton A. Infertility – epidemiology, aetiology and effective management. Health Bull (Edinb). 1995;53:294-8.

2. Downey J et al. Mood disorders, psychiatric symptoms, and distress in women presenting for infertility evaluation. Fertil Steril. 1989;52:425-32.

3. Isidori AM et al. Medical treatment to improve sperm quality. Reprod Biomed Online. 2006;12:704-14.

4. Agarwal A, Allamaneni SS. Sperm DNA damage assessment: a test whose time has come. Fertil Steril. 2005;84:850-3.

5. Venkatesh S et al. Clinical significance of sperm DNA damage threshold value in the assessment of male infertility. Reprod Sci. 2011;18:1005-13.

6. Zini A et al. Biologic variability of sperm DNA denaturation in infertile men. Urology. 2001;58:258-61.

7. Zini A et al. Correlations between two markers of sperm DNA integrity, DNA denaturation and DNA fragmentation, in fertile and infertile men. Fertil Steril. 2001;75:674-7.

8. Saleh RA et al. Effect of cigarette smoking on levels of seminal oxidative stress in infertile men: a prospective study. Fertil Steril. 2002;78:491-9.

9. Wang X et al. Oxidative stress is associated with increased apoptosis leading to spermatozoa DNA damage in patients with male factor infertility. Fertil Steri. 2003;80:531-5.

10. Baker HW. Management of male infertility. Baillieres Best Pract Res Clin Endocrinol Metab. 2000;14:409-22.

11. Wong WY et al. Male factor subfertility: possible causes and the impact of nutritional factors. Fertil Steril. 2000;73:435-42.

12. Ebisch IM et al. The importance of folate, zinc and antioxidants in the pathogenesis and prevention of subfertility. Hum Reprod Update. 2007;13:163-74.

13. Showell MG et al. Antioxidants for male subfertility. Cochrane Database Syst Rev. 2011;(1):CD007411.

14. Menchini-Fabris GF et al. Free L-carnitine in human semen: its variability in different andrologic pathologies. Fertil Steril. 1984;42:263-7.

15. Lenzi A et al. A placebo-controlled double-blind randomized trial of the use of combined l-carnitine and l-acetyl-carnitine treatment in men with asthenozoospermia. Fertil Steril. 2004;81:1578-84.

16. Balercia G et al. Placebo-controlled double-blind randomized trial on the use of L-carnitine, L-acetylcarnitine, or combined L-carnitine and L-acetylcarnitine in men with idiopathic asthenozoospermia. Fertil Steril. 2005;84:662-71.

17. Sigman M et al. Carnitine for the treatment of idiopathic asthenospermia: a randomized, double-blind, placebo-controlled trial. Fertil Steril. 2006;85: 1409-14.

18. Zhang H, Zheng RL. Possible role of nitric oxide on fertile and asthenozoospermic infertile human sperm functions. Free Rad Res. 1996;25:347-54.

19. Scibona M et al. L-arginine and male infertility. Minerva Urol Nefrol. 1994;46:251-3.

20. Morales ME et al. [Progressive motility increase caused by L-arginine and polyamines in sperm from patients with idiopathic and diabetic asthenozoospermia]. Ginecol Obstet Mex. 2003;71:297-303.

21. Suleiman SA et al. Lipid peroxidation and human sperm motility: protective role of vitamin E. J Androl. 1996;17:530-7.

22. Kessopoulou E et al. A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. Fertil Steril. 1995;64:825-31.

23. Vezina D et al. Selenium-vitamin E supplementation in infertile men. Effects on semen parameters and micronutrient levels and distribution. Biol Trace Elem Res. 1996;53:65-83.

24. Oldereid NB et al. Selenium in human male reproductive organs. Hum Reprod. 1998;13:2172-6.

25. Scott R et al. The effect of oral selenium supplementation on human sperm motility. Br J Urol. 1998;82:76-80.

26. Iwanier K, Zachara BA. Selenium supplementation enhances the element concentration in blood and seminal fluid but does not change the spermatozoal quality characteristics in subfertile men. J Androl. 1995;16:441-7.

27. Kvist U et al. Seminal fluid from men with agenesis of the Wolffian ducts: zinc-binding properties and effects on sperm chromatin stability. Int J Androl. 1990;13:245-52.

28. Omu AE et al. Treatment of asthenozoospermia with zinc sulphate: andrological, immunological and obstetric outcome. Eur J Obstet Gynecol Reprod Biol. 1998;79:179-84.

29. Landau B et al. Folic acid levels in blood and seminal plasma of normo- and oligospermic patients prior and following folic acid treatment. Experientia. 1978;34:1301-2.

30. Raijmakers MT et al. Glutathione and glutathione S-transferases A1-1 and P1-1 in seminal plasma may play a role in protecting against oxidative damage to spermatozoa. Fertil Steril. 2003;79: 169-72.

31. Lenzi A et al. Placebo-controlled, double-blind, cross-over trial of glutathione therapy in male infertility. Hum Reprod. 1993;8:1657-62.

32. Favilli F et al. Effect of orally administered glutathione on glutathione levels in some organs of rats: role of specific transporters. Br J Nutr. 1997;78:293-300.

33. Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. Biochim Biophys Acta. 1995;1271:195-204.

34. Mancini A et al. An update of Coenzyme Q10. Implications in male infertility: biochemical and therapeutic aspects. Biofactors. 2005;25:165-74.

35. De Lamirande E, Gagnon C. Reactive oxygen species (ROS) and reproduction. Adv Exp Med Biol. 1994;366:185-97.

36. Weis M et al. Bioavailability of four oral coenzyme Q10 formulations in healthy volunteers. Mol Aspects Med. 1994;15: 273-80.

37. Agarwal A et al. Role of antioxidants in treatment of male infertility: an overview of the literature. Reprod Biomed Online. 2004;8:616-27.

38. Yagci A et al. Spermatozoa bound to solid state hyaluronic acid show chromatin structure with high DNA chain intergrity: an acridine orange fluorescence study. J Androl. 2010;31(6):566-72.

39. Pregl Breznik B et al. Are sperm DNA fragmentation, hyperactivation, and hyaluronan-binding ability predictive for fertilization and embryo development in in vitro fertilization and intracytoplasmic sperm injection? Fertil Steril. 2013;99(5):1233-41.

40. Aitken RJ, De Iuliis GN. On the possible origins of DNA damage in human spermatozoa. Mol Hum Reprod. 2010; 16:3-13.

PREVENTION OF CATHETER-ASSOCIATED URINARY TRACT INFECTION FOLLOWING GYNAECOLOGIC SURGERY: A SYSTEMATIC REVIEW

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Disclosure: No potential conflict of interest.
Received: 25.01.14 **Accepted:** 28.02.14
Citation: EMJ Urol. 2014;1:66-73.

ABSTRACT

Catheter-associated urinary tract infection (CAUTI) is the most common postoperative infection associated with gynaecologic procedures, and results in increased risks to patients and costs for hospitals. Currently, there is great variation in chemoprophylaxis used for prevention of postoperative CAUTI. The objective of this paper was to systematically review the efficacy of chemoprophylaxis for the prevention of CAUTI during short-term catheterisation following gynaecologic surgery. Evidence acquisition was undertaken by performing a systematic review of PubMed/Medline, Scopus, and the Cochrane Library in November 2013 according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. Quality assessment was performed using the Jadad and Newcastle-Ontario Scales. Nine studies met criteria for inclusion. Included publications used either antibiotics or methenamine hippurate for chemoprophylaxis. Chemoprophylaxis during catheterisation resulted in a statistically significant decrease in significant bacteriuria as compared to control groups in the majority of the studies. Symptomatic bacteriuria was also significantly decreased. A recommendation of a specific regimen for chemoprophylaxis cannot be made due to heterogeneity in study quality, dose, and duration of chemoprophylaxis, timing of urine culture, and study endpoints. Evidence examining cost-effectiveness and antibiotic resistance was limited. We reviewed the use of either antibiotics or methenamine hippurate for the prevention of CAUTI after gynaecologic surgery. Evidence suggests that chemoprophylaxis results in a decreased rate of bacteriuria and UTIs postoperatively. Further studies are required to determine the optimum regimen. Chemoprophylaxis is useful for the prevention of CAUTI during short-term catheterisation after gynaecologic surgery. Further research to determine the most effective type and dose of chemoprophylaxis, as well as cost-effectiveness and the potential development of antibiotic resistance, is needed.

Keywords: Antibiotic prophylaxis, catheter-associated urinary tract infection, gynaecology, methenamine hippurate, prevention, short-term catheterisation, surgical patients, urinary catheter, urinary tract infection, urogynaecology.

INTRODUCTION

Catheter-associated urinary tract infection (CAUTI) after catheterisation is an increasingly important issue in gynaecology as it is one of the most common infections that occur after gynaecologic surgery.[1,2] Women undergoing urogynaecologic procedures, such as surgery for pelvic organ prolapse and urinary incontinence, are particularly susceptible to post-surgical CAUTI because of urinary tract instrumentation and post-menopausal status, as well as the high rates of transient postoperative urinary retention requiring short-term indwelling catheter use. Rates of urinary tract infection (UTI) within 6 weeks of urogynaecologic surgery were estimated to be 16.8% in patients who failed their void trials, and up to 33.6% within 3 months of mid-urethral sling placement.[3,4]

Significant bacteriuria or positive urine culture is defined as ≥105 colony-forming units per ml of urine with no more than two species of microorganisms.[5,6] Symptomatic UTI is defined as at least one or more signs or symptoms (fever >38°C, suprapubic tenderness, costovertebral angle tenderness, dysuria, urgency, frequency), positive urine dipstick for leukocyte esterase and/or nitrite, or pyuria or microorganisms on microscopy, and a positive urine culture.[5] CAUTI is defined by the Center for Disease Control as symptomatic UTI associated with indwelling catheters in place for at least 2 days, or removed within 2 days of diagnosis of symptomatic UTI.[5] In published studies, there is considerable variation in the combination of symptoms and signs used to define symptomatic UTI; several studies define significant bacteriuria at lower colony counts, and CAUTI as any UTI within 6 weeks of catheter removal.[6]

Prevention of postoperative CAUTI is important for both patients and healthcare systems. UTIs can lead to complications such as pyelonephritis and bacteraemia, which require treatment with antibiotics and increased hospitalisation. CAUTI increases the economic burden on both patients and physicians, as UTI results in 8.3 million office visits a year, and each CAUTI costs approximately $600 per episode.[7] CAUTI has become costly for hospitals as well; in the United States, the Centers for Medicare and Medicaid Services (CMS) have not been compensating hospitals for UTIs related to catheterisation since 1st October, 2008.[8]

Chemoprevention with antibiotics or antiseptics such as methenamine can potentially decrease the chance of UTI after postoperative catheterisation. Both the American Urologic Association (AUA) and the American College of Obstetrics and Gynecology (ACOG) recommend considering prophylactic antibiotics for catheter removal.[8,9] AUA guidelines suggest that antimicrobial use may be warranted "at the time of catheter removal following urinary tract surgery", especially in patients with risk factors such as advanced age, anatomic anomalies, and immunodeficiencies; however, treatment may also be deferred and based on urine culture at catheter removal.[8] According to ACOG guidelines: "Daily antibiotic prophylaxis should be considered in women discharged with an indwelling urinary catheter after urogynaecologic surgery."[9] The above recommendations for chemoprophylaxis for short-term postoperative catheter use are mostly based on non-gynaecologic populations and there are no specific recommendations on the choice and dose of the agent. The aim of this study is to systematically review the efficacy of different types of chemoprophylaxis used to prevent CAUTI after short-term catheterisation following gynaecologic surgery.

MATERIALS AND METHODS

Literature searches were performed using PubMed/Medline, Scopus, and Cochrane Central Register of Controlled Trials for studies published from 1947 to November 2013. With the assistance of a medical librarian, we searched for studies with the following keywords and MeSH terms in different search combinations: "UTI", "catheter-associated UTI", "urinary catheter", "removal", "device removal", "prevention", "prophylaxis", "gynaecology", "urogynaecology", "gynaecologic surgery", "antibiotic", "antibiotic prophylaxis", "anti-infective agents", "anti-infective agents, urinary", "anti-septic", "methenamine", "hippurates", and "Hiprex". We included both English and non-English language studies. Titles and abstracts of eligible studies were screened, and potentially-eligible papers were obtained for full review. These papers were reviewed before inclusion into the review.

Articles were assessed for relevance, and those unrelated to CAUTI and chemoprophylaxis - with either antibiotics or methenamine hippurate - were excluded. Titles and abstracts were excluded if: 1) the study was not a randomised controlled or prospective cohort design; 2) the patients included had not undergone either gynaecologic or urogynaecologic surgery; 3) antibiotics were given at or until the time of catheter removal; and 4) measurement of the outcome of bacteriuria was not performed. Short-term catheterisation was defined as ≤14 days. The primary endpoint for this review was symptomatic UTI, as defined by one sign or symptom of UTI and significant bacteriuria. The secondary outcome was significant bacteriuria as defined in the specific study.

Included articles underwent data abstraction. Information abstracted included: 1) year of publication; 2) study design; 3) number of patients who received chemoprophylaxis; 4) number of patients who did not receive chemoprophylaxis or received placebo; 5) number of days patients underwent indwelling urinary catheterisation; 6) type of chemoprophylaxis; 7) duration and

dose of chemoprophylaxis; 8) duration of post-catheterisation follow-up; 9) proportion of patients who had significant bacteriuria; 10) proportion of patients who had symptomatic bacteriuria, if measured.

Assessment of methodological quality was performed using the Jadad scale for randomised controlled trials (RCTs) and the Newcastle-Ottawa Scale (NOS) for prospective cohort studies. The Jadad scale evaluates three aspects of RCTs: randomisation, blinding, and patient drop-out/withdrawals.[10] All areas except patient drop-out are assigned two points, for a total score of zero (low quality) to five (high quality), with the potential to eliminate points based on the quality of description of the randomisation and blinding processes. It has been found to have high reliability and validity compared to other scales of assessment.[11] The NOS is a commonly used scale for quality evaluation of cohort studies that has been recommended by The Cochrane Collaboration.[12] The NOS contains three parts: selection, comparability, and outcome - with a total of eight questions. Each item can be awarded up to one star, except for comparability, which may earn two; scores, therefore, range from zero to nine.[13]

RESULTS

The study selection process is described in Figure 1. The initial search resulted in 4,708 publications, which, after evaluation of titles and abstracts, led to 60 articles being considered for full evaluation. After the removal of duplicates, 34 articles were considered. However, 7 articles were excluded for study design, 14 studies were excluded for population, and 4 articles were excluded for intervention not consistent with the objectives of this review.

Out of the nine studies that met inclusion criteria, five studies investigated the use of methenamine,[2,14-17] while three studies examined the use of antibiotics as prophylaxis for CAUTIs.[18-20] One study included a comparison of an antibiotic and methenamine.[21] Seven of these studies were RCTs,[2,14,15,17,19-21] while two studies (one on methenamine and one on prulifloxacin) were prospective observational cohort studies.[16,18] Of the RCTs included in the review, three provided description of their randomisation process.[2,19,21] Three studies were conducted as a double-blind, randomised, placebo-controlled study.[2,14,19]

Table 1 shows the rating of the RCTs included in this review according to the Jadad Scale, while Table 2 shows the quality of the prospective cohort studies rated according to the NOS. There was considerable heterogeneity between studies in the chemoprophylaxis regimens, duration of use, and outcomes measured, which prevented us from performing a meta-analysis.

Table 3 (*click here to view table*) shows the study design and outcomes of the nine studies included in this review. Two out of six studies that investigated methenamine were conducted in patients undergoing urogynaecologic procedures only;[17,21] similarly, three out of four studies that investigated the use of antibiotics were performed in patients undergoing urogynaecologic procedures.[18,19,21] All other studies involved a mix of patients undergoing a variety of general gynaecologic and urogynaecologic procedures.[2,14-16,20] Out of all nine studies, eight studies used indwelling catheters; Rogers et al.[19] however, used suprapubic catheters in the postoperative period.

Four studies investigated the use of prophylactic antibiotics for the prevention of CAUTIs.[18-21] Antibiotics used in the studies were quite heterogeneous, and included three different classes of antibiotics (nitrofurantoin, fluoroquinolones, and sulfa antibiotics). Rogers et al.[19] studied the use of nitrofurantoin for prophylaxis, while Ghezzi et al.[18] investigated prulifloxacin. Both Baertschi et al.[20] and Murray et al.[21] examined the use of sulfa antibiotics. However, Murray et al.[21] used sulphamethizole (a bacteriostatic antibiotic) solely, with a total daily dose of 1,000 mg, while Baertschi et al.[20] used trimethoprim-sulfamethoxazole in a daily dose of 320 mg trimethoprim and 1,600 mg sulfamethoxazole.

There was a lack of consistency in antibiotic regimens as well. Ghezzi et al.[18] was the only study to use a one-dose regimen prior to catheter removal. All other studies provided daily prophylaxis at least until catheter removal, but two studies started prophylaxis prior to surgery,[20,21] and one study provided an additional 2-6 days prophylaxis after catheter removal.[20]

Six studies investigated the use of prophylactic methenamine hippurate for the prevention of CAUTIs.[2,14-17,21] Regimens again varied, with the total daily dose ranging from 1-4 g (with most studies using 2 g daily), initiated 1-2 days prior

to surgery, and ending anywhere from catheter removal to 3 days post-catheter removal. Thomlinson et al.[16] added sodium acid phosphate to their methenamine regimen for further urine acidification.

The duration of catheterisation also varied considerably between studies, although duration in all nine studies was similar between treatment and control groups within studies.

Bacteriuria, as measured by urine culture, was reported as an outcome in all studies although there was a considerable difference across studies in the timing of urine collection. Most studies included a pre-surgical specimen (except for Murray et al.[21]). Several studies examined urine collected at catheter removal,[2,18-21] and every study examined urine collected in the post-catheter period (ranging from 2-8 days after catheter removal). Additional follow-up urine cultures, at time periods ranging from 1 week to 6-8 weeks after surgery, was performed in three studies.[2,18-19]

Five of the nine studies did not specify the technique by which urine was collected at each follow-up.[14-16,19,20] Remaining studies provided specific descriptions of follow-up by aseptic catheter collection or mid-stream urine collection.[2,17,18,21] Most studies defined significant bacteriuria as $>10^5$ cfu/ml, although three studies provided lower limits in their definition of significant bacteriuria for catheter-collected specimens (ranging from 10^3 to 10^4 cfu/ml).[2,18,20]

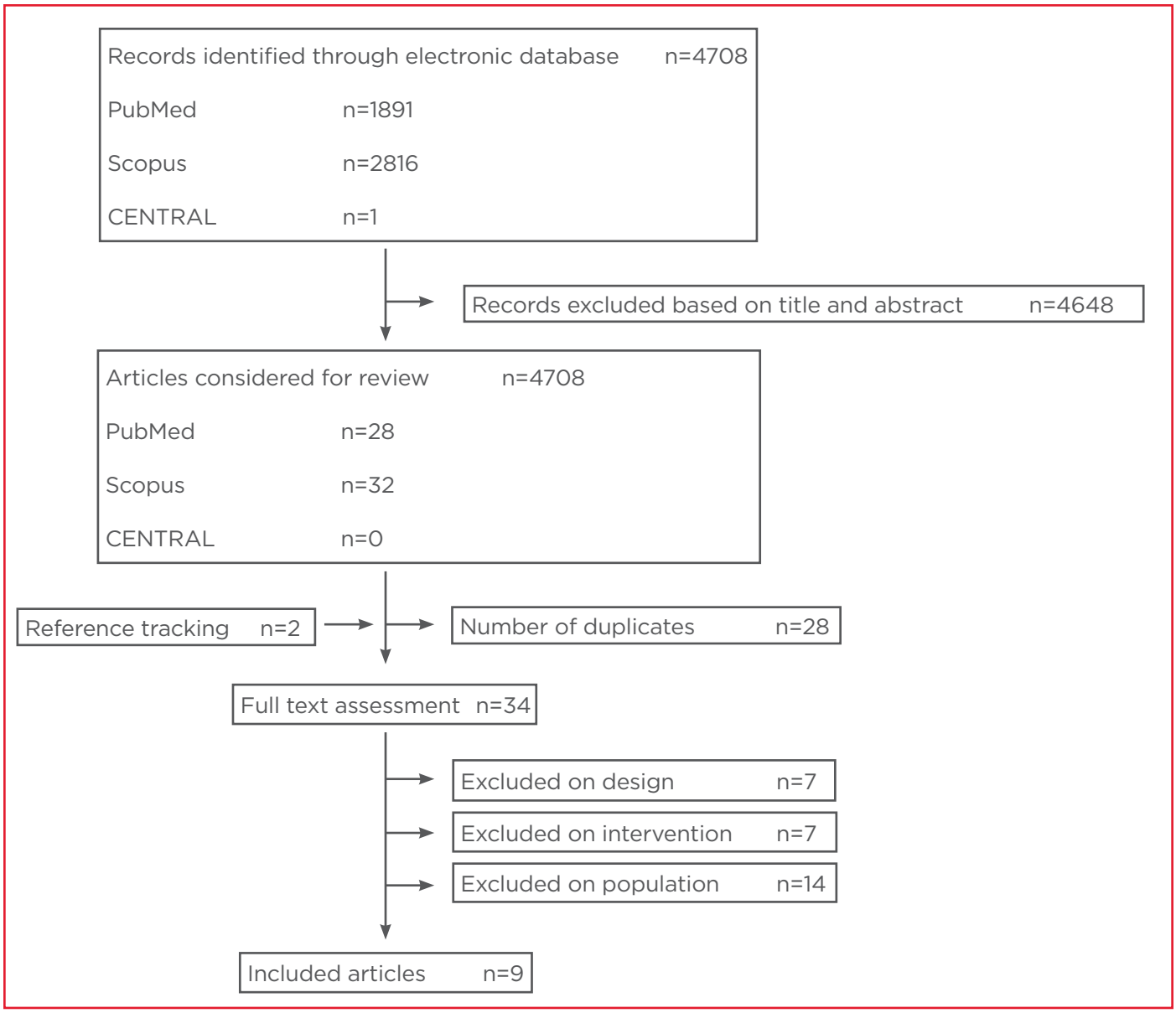

Figure 1: Selection process for the included studies in this systematic review.

Table 1: Rating of randomised controlled trials on chemoprophylaxis for catheter-associated urinary tract infection following gynaecologic surgery (Jadad Scale).

	Random allocation	Blinding	Dropout/Withdrawal	Total
Rogers et al.[19]	2	2	1	5
Baertschi et al.[20]	1	0	1	2
Murray et al.[21]	2	0	1	3
Schiøtz et al.[2]	2	2	1	5
Tyreman et al.[17]	1	0	1	2
Knoff et al.[14]	1	2	1	4
Ladehoff et al.[15]	1	0	1	1

Jadad Scale: scores range from 0-5, with 5 being high quality.

Table 2: Rating of prospective cohort studies on chemoprophylaxis for catheter-associated urinary tract infection following gynaecologic surgery (Newcastle-Ottawa Scale).

	Ghezzi et al.[18]	Thomlinson et al.[16]
Representation of exposed cohort	*	*
Selection of non-exposed cohort	*	*
Ascertainment of exposure	*	*
Demonstration that outcome of interest was not present at the start of the study	*	*
Comparability of cohorts	-	*
Assessment of outcome	*	*
Was follow-up long enough for outcome to occur	*	*
Adequacy of follow-up of cohorts	*	-
Total	7	7

Newcastle-Ottawa Scale: scores range from 0-9, with 9 being high quality; 1 star is awarded for each category except for comparability.

Five studies examined symptomatic bacteriuria (UTI) as a secondary endpoint, usually defined as a positive urine culture with at least one symptom of UTI.[2,14,17-19]

Two of the three studies that investigated treatment with antibiotics reported reduction in the incidence of symptomatic UTI after short-term postoperative indwelling catheter.[18-19] Baertschi et al.[20] did not report the rate of symptomatic UTI after treatment with trimethoprim-sulfamethoxazole. Significant bacteriuria was decreased at the time of catheter removal following treatment with any antibiotic compared to control.[18-20] At additional follow-up cultures after surgery, significant bacteriuria decreased on treatment with any antibiotic; however, this difference did not reach significant levels.[18,19]

The majority of the studies reported that chemoprophylaxis with methenamine resulted in the reduction of both symptomatic bacteriuria and significant bacteriuria. The three studies that examined symptomatic UTI reported a significant decrease in this outcome with the use of methenamine prophylaxis.[2,14,17] Four of five studies found a significant decrease in bacteriuria,[2,15-17] while one study found no significant difference.[17]

In the only study comparing methenamine with an antibiotic agent (sulphamethizole), Murray et al.[21] found no statistically significant difference between the two agents in the incidence of significant bacteriuria.

Side-effects and adverse events secondary to treatment were reported in six studies. A rash was observed in patients treated with methenamine, as well as trimethoprim-sulfamethoxazole.[2,20] Gastrointestinal symptoms were common, including diarrhoea,[18] nausea and vomiting,[2,15,19,20] and gastro-oesophageal reflux disease.[14,20]

Ghezzi et al.[18] also examined the effect of antibiotic use on vaginal microflora through lactobacillary grade on wet mount or culture. In their study, no patients were found to have any significant change in lactobacillary flora 1 week after surgery in either the treatment or placebo group. Tyreman et al.[17] noted decreased UTI due to opportunistic infections in patients treated with methanamine. Only one study examined bacterial resistance in patients with significant bacteriuria, and reported greater frequency of resistance in the treatment group than the placebo group.[20]

DISCUSSION

The majority of the studies included in this review report a statistically significant benefit from the use of chemoprophylaxis, with either antibiotic or methenamine prophylaxis, for the prevention of CAUTI after gynaecological procedures. Our findings are consistent with a recent meta-analysis that investigated antibiotic prophylaxis at catheter removal in patients who have undergone a wide variety of surgical procedures. Unlike this meta-analysis, our review includes chemoprophylaxis with either antibiotic or methenamine, and focuses on CAUTI following gynaecologic surgery.[22] In our review, the six studies that examined symptomatic UTI noted a significant decrease in symptomatic UTIs, ranging from 0-19% after antibiotic use and 2-3% after methenamine hippurate, as compared to 0-41% in controls.[2,14,17-20] Rates of significant bacteriuria were also significantly lower after treatment by antibiotics or methenamine, ranging from 0-46% and 3-35%, respectively, as compared to 4.3-50% in controls.

Though the majority of the studies show that chemoprophylaxis with antibiotics or methenamine is effective in preventing CAUTI, considerable heterogeneity across studies does not allow us to recommend an optimal regimen for chemoprophylaxis. There is a lack of consistency across studies in the dose of chemoprophylactic agent, duration of administration, duration of catheter use, timing and technique of collection of urine specimen, and the primary outcome (bacteriuria versus symptomatic UTI). Additionally, the majority of the studies have a small sample size, and only a few studies[2,18,19] report a sample size calculation. The quality of the studies on prophylactic antibiotics was poor to good, with the Jadad scale score averaging 3.3 while the NOS score of the cohort trial was 7 out of 9. Likewise, the quality of the studies on methenamine ranged widely, with the average Jadad scale averaging 3, and a NOS score of 7 out of 9. Furthermore, as *Escherichia coli* resistance to trimethoprim-sulfamethoxazole and ciprofloxacin is greater than to nitrofurantoin,[23] further studies on nitrofurantoin may be more clinically relevant. Only one study in our review examined the use of nitrofurantoin as a prophylactic agent.[19]

There is also considerable heterogeneity across studies in the outcome used to measure the effectiveness of the chemoprophylactic regimen. Although many studies defined bacteriuria as $>10^5$ colony-forming units per ml, several studies had a lower threshold for catheterised specimens ($>10^{3-4}$). This lower threshold is traditionally used for direct bladder puncture or clean catheterisation, and may not be as useful for indwelling catheters. Irrespective of which definition is used, significant bacteriuria may not be a clinically meaningful endpoint in the prevention of CAUTI. Prior studies suggest that treatment of asymptomatic bacteriuria is not required after minor urologic procedures that do not involve bladder mucosal trauma.[24] In 40% of patients, significant bacteriuria resolves spontaneously, and only about 11-33% of patients with significant bacteriuria became symptomatic.[2,19] Therefore, symptomatic bacteriuria (symptomatic UTI) may be a more clinically relevant endpoint. Half of the studies included in the review did not examine this as an endpoint. Future research should also include the rate of symptomatic UTI after chemoprophylaxis as either a primary or secondary outcome.

Adverse effects, costs, and side-effects are important considerations in the use of prophylaxis at the time of catheter removal. This review shows

that although prophylaxis is not without side-effects, they are generally minor and affect a small number of patients. Though the prescription of chemoprophylaxis would increase costs for hospitals and healthcare systems alike, no studies performed cost-analysis weighing the benefits of the costs of chemoprophylaxis against the benefits of prevention of CAUTI.

Antibiotic resistance is a potentially important complication that could develop with increased antibiotic use for the prevention of CAUTI. Although most studies looked at the type of uropathogen isolated by urine culture, only Baertschi et al.[20] examined the resistance of positive urine cultures to trimethoprim-sulfamethoxazole, and found a higher percentage of uropathogen resistance in the treatment group as compared to placebo. With this in mind, more research is needed on whether the use of prophylactic antibiotics may induce significant resistance in uropathogens. Methenamine is not an antibiotic, but instead is an antiseptic agent that hydrolyses to formaldehyde and ammonia in acidic urine. The combination of hippuric acid, in addition to decreasing urinary pH, also has bacteriostatic effects. The use of methenamine for prophylaxis instead of antibiotics could potentially reduce the rate of antibiotic resistance in prophylaxis for CAUTI. One study in this review noted the presence of fewer opportunistic infections in positive cultures as compared to placebo, and this may be an interesting area for further study of methenamine.[17] Only one randomised control study compared methenamine with antibiotic prophylaxis.[21] This study was small, and did not include the endpoint of symptomatic UTI. In addition, this study used sulphamethizole, which is rarely used alone for prophylaxis or treatment nowadays. Further studies comparing methenamine hippurate to antibiotic prophylaxis would be helpful in determining whether methenamine is equally or more effective than antibiotic use, and whether it would prevent the development of antibiotic resistance.

The strengths of this review include a systematic and comprehensive assessment of published literature, which was performed according to PRISMA guidelines. Though we were unable to perform a meta-analysis due to the considerable heterogeneity between studies, our systematic review indicates that chemoprophylaxis prior to catheter removal is beneficial in gynaecological postoperative patients. Further studies are necessary to define the best agent, dosage, and duration of prophylaxis at catheter removal that would minimise adverse effects, antibiotic resistance, and costs for patients undergoing gynaecologic procedures. Our recommendations for future studies include appropriately powered, randomised controlled studies, comparing an antibiotic (preferably nitrofurantoin) to methenamine hippurate, or comparing a single-dose regimen to a multi-dose regimen, with symptomatic bacteriuria as a primary endpoint. Antibiotic resistance of positive urine cultures and cost-effectiveness should also be examined in order to help us more accurately define a role for chemoprophylaxis in CAUTI prevention after gynaecological procedures.

CONCLUSION

Current literature supports chemoprophylaxis with antibiotics or methenamine hippurate for prevention of symptomatic UTI during short-term catheterisation after gynaecologic surgery. Further adequately powered, randomised controlled studies that compare the effectiveness and cost-effectiveness of methenamine hippurate to placebo, or methenamine hippurate to an antibiotic, for the prevention of symptomatic urinary tract infection following short-term catheterisation for gynaecologic surgery, are required.

REFERENCES

1. Schiøtz HA. Comparison of 1 and 3 days' transurethral Foley catheterization after retropubic incontinence surgery. Int Urogynecol J Pelvic Floor Dysfunct. 1996;7(2):98-101.

2. Schiøtz HA, Guttu K. Value of urinary prophylaxis with methenamine in gynecologic surgery. Acta Obstet Gynecol Scand. 2002;81(8):743-6.

3. Sutkin G et al. Symptomatic urinary tract infections after surgery for prolapse and/or incontinence. Int Urogynecol J. 2010;21(8):955-61.

4. Anger JT et al. Complications of sling surgery among female Medicare beneficiaries. Obstet Gynecol. 2007;109(3):707-14.

5. Centers for Disease Control and Prevention. Catheter-Associated Urinary Tract Infection (CAUTI) Event. http://www.cdc.gov/nhsn/PDFs/pscManual/7pscCAUTIcurrent.pdf. Published January 2014. Accessed February 13, 2014.

6. Pickard R et al. Types of urethral catheter for reducing symptomatic urinary tract infections in hospitalised adults requiring short-term catheterisation: multicentre randomised controlled trial and economic evaluation of antimicrobial- and antiseptic-impregnated urethral catheters (the CATHETER trial). Health Technol Assess. 2012;16(47):1-197.

7. Saint S. Clinical and economic consequences of nosocomial catheter-related bacteriuria. Am J Infect Control. 2000;28(1):68-75.

8. Wolf JS Jr et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. J Urol. 2008;179(4):1379-90.

9. ACOG Committee on Practice Bulletins--Gynecology. ACOG practice bulletin No. 104: antibiotic prophylaxis for gynecologic procedures. Obstet Gynecol. 2009;113(5):1180-9.

10. Jadad AR et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12.

11. Olivo SA et al. Scales to assess the quality of randomized controlled trials: a systematic review. Phys Ther 2008;88(2):156-75.

12. Higgins PT, Green S (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, The Cochrane Collaboration, London, UK (2009). [updated September 2009].

13. Wells GA et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/nos_manual.pdf.

14. Knoff T. Methenamine hippurate. Short-term catheterization in gynecologic surgery. A double-blind comparison of Hiprex and placebo. Tidsskr Nor Laegeforen. 1985;105(7):498-9.

15. Ladehoff P et al. The preventive effect of methenamine hippurate (Haiprex) on urinary infections after short-term catheterization. A clinical study. Ugeskr Laeger. 1984;146(19):1433-4.

16. Thomlinson J et al. Persistence of bacteriuria following gynaecological surgery: a trial of methenamine hippurate. Br J Urol. 1968;40(4):479-82.

17. Tyreman NO et al. Urinary tract infection after vaginal surgery. Effect of prophylactic treatment with methenamine hippurate. Acta Obstet Gynecol Scand. 1986;65(7):731-3.

18. Ghezzi F et al. Prophylactic single-dose prulifloxacin for catheter-associated urinary tract infection after tension-free vaginal tape procedure. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18(7):753-7.

19. Rogers RG et al. A randomized, double-blind, placebo-controlled comparison of the effect of nitrofurantoin monohydrate macrocrystals on the development of urinary tract infections after surgery for pelvic organ prolapse and/or stress urinary incontinence with suprapubic catheterization. Am J Obstet Gynecol. 2004;191(1):182-7.

20. Baertschi U, Kunz J. Comparative study on the question of systemic chemoprophylaxis following gynecological surgery. Schweiz Med Wochenschr. 1976;106(11):380-5.

21. Murray CP, Feeney J. A comparison of hexamine hippurate and sulphamethizolein patients with indwelling catheters following pelvic-floor surgery. Ir Med J. 1977;69(4):97-8.

22. Marschall J et al. CDC Prevention Epicenters Program. Antibiotic prophylaxis for urinary tract infections after removal of urinary catheter: meta-analysis. BMJ. 2013;346:f3147.

23. Zhanel GG et al. Antibiotic resistance in Escherichia coli outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). Int J Antimicrob Agents. 2006;27(6):468-75.

24. Nicolle LE. Asymptomatic bacteriuria. Curr Opin Infect Dis. 2013. [Epub ahead of print].

ATHEROSCLEROSIS AND INFLAMMATORY STATUS IN CHRONIC KIDNEY DISEASE PATIENTS AFTER RENAL TRANSPLANTATION: WHERE ARE WE NOW?

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Disclosure: No potential conflict of interest.
Received: 04.01.14 **Accepted:** 07.04.14
Citation: EMJ Urol. 2014;1:74-82.

ABSTRACT

Cardiovascular diseases are the most common cause of mortality and morbidity in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD), receiving haemodialysis, peritoneal dialysis, and renal transplantation (Rtx). Estimated glomerular filtration rate (eGFR) places Rtx patients in one of the stages of CKD. Therefore, Rtx patients might be considered a subset of CKD patients. Besides the traditional risk factors of hypertension, diabetes, and dyslipidaemia, advanced-age novel risk factors such as endothelial dysfunction, vascular calcification, and increased chronic low-grade inflammation are highly prevalent and seem to play a more important role for vascular disease in CKD and Rtx patients compared to the general population. The role of Rtx in terms of atherogenesis and chronic ongoing low-grade inflammation is still unclear. To date, in the literature, the data are scant regarding the relationship between atherosclerosis, chronic inflammation, and cardiovascular events in Rtx patients with well-functioning kidneys. This review will discuss classical and recent epidemiological, pathophysiological, and clinical aspects of atherosclerosis and inflammation in Rtx patients.

Keywords: Atherosclerosis, inflammation, renal transplantation.

INTRODUCTION

Cardiovascular diseases (CVDs) are the most common cause of mortality and morbidity in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) receiving haemodialysis (HD), peritoneal dialysis (PD), and renal transplantation (Rtx). Cardiovascular (CV) risk is increased even in the early stages of CKD and this heightened risk is also found to be ongoing in ESRD patients who received Rtx.[1,2] Transplant recipients have a lower risk of fatal and non-fatal CV events compared with wait-listed patients on dialysis;[3,4] however, these patients have a much higher risk compared with the general population.[5] 50-60% of post-Rtx deaths were found to be associated with CVD, with an incidence of ischaemic heart disease of approximately one per 100 person-years at risk.[6] CVD is the most common cause of death with graft function after transplant, and accounts for 30% of graft loss from death overall, with the greatest rates early after Rtx.[7]

Rtx is accepted as the optimal renal replacement therapy method; however, CV mortality remains three-to-five times higher in this patient population compared to general population.[8] Despite the improvement in kidney functions of this population after Rtx, estimated glomerular filtration rate (eGFR) places them in one of the stages of CKD.

Besides traditional risk factors including hypertension, diabetes, dyslipidaemia, advanced age, and left ventricular hypertrophy (LVH), novel risk factors such as endothelial dysfunction (ED), vascular calcification (VC), oxidative stress, and inflammation are highly prevalent and seem to play a more important role for vascular disease in renal patients compared to healthy subjects.[9-12] CKD is now recognised as an independent risk factor for coronary artery disease (CAD) in community-based studies as well as in high CV-risk populations. In community-based studies, decreased glomerular filtration rate (GFR) and proteinuria were both found to be independently associated with CAD.[13-15] Growing evidence suggests that a gradual fall in GFR is also independently associated with CV events in patients with preexisting CVD.[16-19] In addition, several studies demonstrated that systemic, persistent inflammation could be the main factor responsible for the increased risk in this population, regardless of the renal replacement therapy.[20]

The role of Rtx in terms of atherogenesis and chronic, ongoing, low-grade inflammation is still unclear. To date, in the literature, the data are scant regarding the relationship between atherosclerosis, chronic inflammation, and CV events in Rtx patients with well-functioning kidneys. This review will discuss classical and recent epidemiological, pathophysiological, and clinical aspects of atherosclerosis and inflammation in Rtx patients. Treatment of atherosclerosis and inflammation in patients with Rtx is beyond the scope of this review.

EPIDEMIOLOGY

Epidemiological studies have repeatedly shown the close relationship between CV events and CKD. However, there have been no large-scale population-based studies regarding CV events in Rtx patients. In this regard, population-based studies in CKD and ESRD patients might be fruitful to assess the CV risk of Rtx patients.

The largest population-based study demonstrated that a decline in GFR was the main independent risk factor for CV events - including hospitalisation secondary to peripheral artery disease (PAD), CAD, congestive heart failure (CHF), or stroke - even after the elimination of confounding risk factors, in more than 1.1 million adults.[21] Similar findings were also reported in a systematic review considering approximately 1.4 million adults from 42 different cohorts.[22] According to this review's results, the risk of all-cause mortality was highest in patients with lowest baseline GFR and vice versa. The gradual fall of GFR was also found to be associated with a gradual increase of death.

CV risk is increased even in the early stages of CKD, particularly in the elderly and this risk remains after several years of Rtx. In a study including approximately 30,000 older CKD patients with estimated GFR of <90 mL/min/1.7m^2, the rate of mortality at 5 years was 19.5%, 24.3%, 45.7% in those with CKD Stage 2, 3, or 4, respectively.[23]

ATHEROSCLEROSIS IN CKD AND RTX PATIENTS

Pathophysiology

Atherosclerosis is a condition characterised by formation of plaques (also referred to as atheroma) on the intima layer of vessels. According to the American Heart Association (AHA) guidelines, coronary atherosclerotic plaques constitute most of the CV diseases in the general population.[24] However, the pathophysiology of vascular disease in CKD and Rtx is poorly understood and quite different from that related to atherosclerosis in the general population.[25] Besides traditional risk factors including hypertension, diabetes, and dyslipidaemia, advanced-age novel risk factors such as ED and CKD-mineral bone disorders (CKD-MBD), abnormalities including hyperphosphataemia, hyperparathyroidism, and vascular-valvular calcification, increased oxidative stress, and chronic low-grade inflammation are highly prevalent and seem to play a more important role for vascular disease commonly seen in CKD and Rtx patients compared to healthy subjects.[9-12,26] In theory, the first step of this process is triggered by ED; however, in recent years several studies have demonstrated that systemic, persistent inflammation could be the main factor responsible for the increased risk in these patients regardless of the renal replacement therapy.[20] To prove this hypothesis, several biomarkers, including C-reactive protein (CRP), interleukin (IL)-1β, IL-6, and tumour necrosis factor-α (TNF-α), were considered in CVD and CKD populations including Rtx patients.[20,26,27] This issue will be addressed below.

Besides the factors mentioned above, the reasons why CKD patients are prone to worse

CV outcomes and why these anticipated events remain after Rtx are still unclear. In the general population, many patients with CAD develop coronary collateral circulation to overcome obstruction of the atherosclerotic coronary arteries. Charytan et al.[28] hypothesised that CKD and Rtx patients might have less collateral blood supply to an ischaemic area of the myocardium and this hypothesis might partially explain why CKD and Rtx patients have worse CV outcomes and death. However, this study has failed to prove this hypothesis because both CKD patients and subjects without CKD had similar culprit artery collateral supply (25% versus 27.2%, respectively, p=0.76).

Traditional Risk Factors

Traditional risk factors for coronary heart disease after Rtx were investigated in a report of 403 patients who received 464 kidney transplants during a 10-year period.[29] New atherosclerotic complications developed in 16% of Rtx patients. After accounting for pre-Rtx vascular disease, multivariate analysis revealed that risk factors including advanced age, diabetes mellitus, male sex, smoking, hypertension, and hypercholesterolaemia are independently associated with post-transplant atherosclerotic CVD.

Both pre-transplant diabetes and new-onset diabetes after transplant (NODAT) are closely associated with the increased risk of post-Rtx CV complications such as myocardial infarction (MI) and heart failure. Medications that contribute to NODAT include glucocorticoids, calcineurin inhibitors, and mammalian target of rapamycin (mTOR) inhibitors.[3,8]

Dyslipidaemia has been established as a classic risk factor for CVD in the general population[30] and in CKD patients receiving HD, PD, and Rtx.[31] Large-scale observational studies have confirmed that dyslipidaemia may actively participate in the pathogenesis of atherosclerosis in the general population.[32] Additionally, it has been well recognised that CKD patients (including Rtx patients) exhibit significant alterations in lipoprotein metabolism, which may result in the development of severe dyslipidaemia in this population.[33]

Previous studies demonstrated that hypertriglyceridaemia might be the earliest laboratory finding among the other lipid abnormalities even in patients who have slightly elevated creatinine levels.[33,34] In contrast, high density lipoprotein (HDL) cholesterol was found to be inversely related to the CV risk in non-CKD population.[35] HDL is not only a key player in reverse cholesterol transport but also has the ability to protect low-density lipoprotein (LDL) against oxidation. Uraemic patients usually have increased concentrations of triglyceride-rich lipoproteins and reduced serum levels of HDL-cholesterol. In addition to HDL and oxidised LDL, carbamylated LDL is proposed to cause endothelial injury and progression of atherosclerosis in patients with kidney disease.[36] However, LDL-cholesterol values were found to be within normal limits or reduced in this population.[37]

There has been a strong relation between CKD and hypertension whereby each can cause or aggravate the other. Control of blood pressure (BP) is fundamental to avoid the progression of CKD, hence several clinical practice guidelines have been published on this topic by many authorities over the last 10 years.[38,39] Additionally, in hypertensive CKD patients, inappropriate LVH may occur, which can be estimated by the ratio of observed to predicted left ventricular mass (LVM). Recently, the ratio of observed to predicted LVM was found to be independently associated with increased CV events in patients with CKD Stages [3-5.40]

Since hypertension in patients with CKD contributes to the particularly high risk of CV morbidity and mortality, ambulatory blood pressure measurement (ABPM) is one of the important diagnostic tools, especially in patients with poorly controlled hypertension.[41] Andersen et al.[42] showed that, approximately 30% of CKD patients had office BP measurements higher than ABPM, whereas 28% of the patients had office BP measurements below ABPM. ABPM showed a stronger correlation with LVM index[43] and proteinuria than single casual office BP measurements in patients with CKD[44] and in the general population.[45] A study comparing the prognostic value of office BP and home BP monitoring showed that home measurements were superior to office BP and predicted ESRD independently of other risk factors.[46]

Post-transplant hypertension is also a risk factor for CVD and chronic allograft dysfunction.[47,48] Among the causes of increased BP in Rtx patients are: reduced vascular compliance,[49] autonomic neuropathy,[50] latent over hydration, use of erythropoietin, corticosteroids, and cyclosporine

A.[51,52] ABPM may be more informative regarding the intensity of BP elevation than clinical measurements following Rtx.[53] In addition, recently, we demonstrated that prevalance of masked hypertension (MHT) is in Rtx patients.[54] According to our study results, Rtx from a deceased donor may be a predictor of MHT. The prevalence of MHT may help to explain high rate of CV events in Rtx patients. Therefore, routine application of ABPM in patients with Rtx may be plausible, particularly in patients with deceased donor type.

Recently, Kidney Disease Improving Global Outcomes (KDIGO) published a guideline regarding the management of BP in CKD.[55] According to this report they recommend that non-diabetic, adult CKD patients who have urine albumin excretion (UAE) ≤30 mg/24 hours and office BP >140/90 mmHg should be treated with antihypertensive agents, especially with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. They also suggested that BP target should be ≤130/80 mmHg in those who had UAE of 30-300 mg/24 hours and UAE ≥300 mg/24 hours.

Novel (Non-Traditional) Risk Factors

Inflammation

Inflammation seen after Rtx has complexity including innate and acquired immunity. Macrophages and neutrophils play an important role in the pathogenesis of inflammation and acute and chronic allograft rejection.[56] However, ongoing inflammation in Rtx patients is much less intense compared to CKD and ESRD patients. In recent years, researchers analysed a large panel of biomarkers to fully characterise the relationship between inflammation and CVD, including CRP, IL-1β, IL-6, and TNF-α.[20,26,27,57] In addition, several interesting new biomarkers were considered to better describe inflammation in Rtx patients, a CKD population with a particular profile, taking into account the allograft and the immunosuppressive therapy role. In this regard, neutrophil-to-lymphocyte ratio (NLR) is a potential marker for inflammation in cardiac and non-cardiac disorders[58-60] that was also shown to be a predictor of long-term mortality in patients who underwent percutaneous coronary intervention.[61] Our group demonstrated that NLR could predict inflammation in ESRD patients and in Rtx patients.[57,62] However, NLR in transplant recipients may be affected by immunosuppressive medications regardless of the kidney graft function because this relationship might be biased. In the following years, like NLR before it, platelet to lymphocyte ratio (PLR) was found to be closely related to CV events in both general and CKD population.[63-65]

Recently, a novel marker - the soluble TNF-like weak inducer of apoptosis (sTWEAK, TNFSF12) - was introduced as a TNF-related cytokine in various inflammatory and non-inflammatory disorders.[66] To date, a transmembrane protein (fibroblast growth factor-inducible 14 [Fn14]) and a scavenger receptor (CD163) were discovered as receptors of sTWEAK.[67,68] The first description of sTWEAK in the kidney was reported by Justo et al.[69] in a mouse model of folate-induced acute kidney injury. Binding of sTWEAK to Fn14 mediates multiple effects including: cellular growth, proliferation, migration, differentiation, apoptosis, angiogenesis, fibrogenesis, and inflammation.[70] In the following years, Yilmaz et al.[71] demonstrated that a decline in eGFR was accompanied by a gradual reduction in sTWEAK in CKD patients. The same group also showed that ED and decreased sTWEAK were independently associated with CV outcomes in pre-dialytic CKD patients.[72] Moreover, treatment of type 1 hypertensive diabetic CKD with amlodipin and/or valsartan was found to be effective in terms of ED and normalisation of sTWEAK.[73] A study by Turkmen et al.[74] demonstrated that Rtx patients had lower sTWEAK levels compared to healthy subjects. In this study, median values of sTWEAK levels of Rtx patients were found to be higher compared to CKD patients in the cohorts of Yilmaz et al.[72] and Carrero et al.[75] (388.97 pg/mL versus 245.5 pg/mL and 208 pg/mL, respectively). Turkmen et al.[74] also tested the relation between sTWEAK and kidney function in Rtx patients. After the classification of Rtx patients according to their eGFR, they found that sTWEAK levels were significantly decreased when eGFR values were decreased. These findings were similar to those obtained from the study by Yilmaz et al.[71] and Gungor et al.[76] We hypothesised that the decrement of sTWEAK among eGFR groups in Rtx patients might be associated with ongoing inflammation in this population. For a better understanding, we illustrated this relationship in Figure 1.

VC IN CKD AND RTX PATIENTS

VC is very common and is becoming increasingly prevalent with the worsening of kidney function

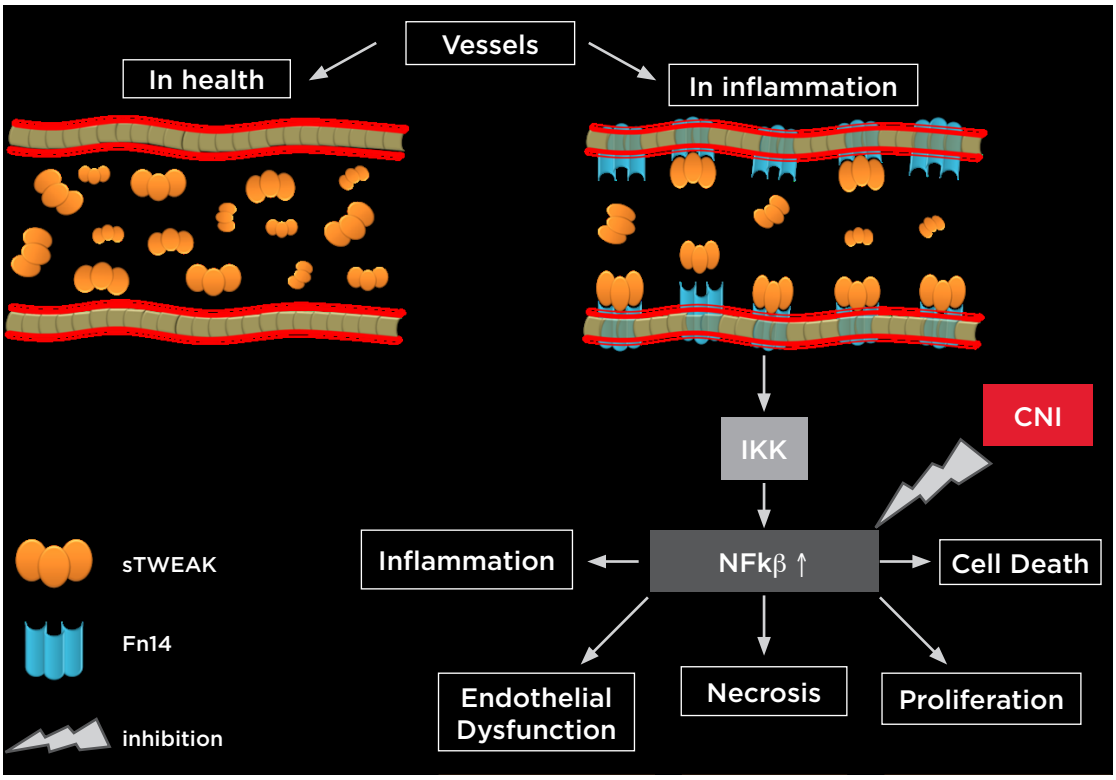

Figure 1: The relationship between sTWEAK and inflammation in renal transplant patients.
Fn14: fibroblast growth factor-inducible 14; IKK: I kappa kinase; CNI: calcineurin inhibitor; NFKβ: nuclear factor kappa-light-chain-enhancer of activated B cells.

in patients with CKD and Rtx. The importance of this process has been demonstrated by the tight relationship between VC and increased cardiac mortality in these populations.[77] The haemodynamic consequences of VC include a decrease in coronary microcirculation and arterial elasticity, an increase in pulse wave velocity, and increased LVH.[24,25] VC may develop in the intimal or the medial layer of the vessel wall. The latter is also referred to as 'Monckeberg's sclerosis' and is much more common in patients with CKD compared to the general population.[78] The main differences between these two types of VC are as follows: i) intimal calcification is highly associated with inflammation and focal occlusion secondary to the plaque formation; however, medial calcification is characterised by diffuse pipe type calcification of muscular arteries; ii) intimal calcification is commonly seen in coronary, carotid arteries, and aorta, whereas medial calcification is commonly observed in tibial and femoral arteries.[79-81]

Longitudinal studies of VC in Rtx patients are few and small, with short follow-up. Recently, Maréchal et al.[82] assessed the evolution of coronary artery and thoracic aorta calcification and their determinants in a cohort of 281 prevalent Rtx patients. They found that VC progression was substantial within 4 years in prevalent Rtx patients and was associated with several traditional and non-traditional CV risk factors. According to the study results, higher baseline coronary artery calcification score (CACS), history of CV event, usage of statins, and lower 25-hydroxyvitamin D(3) level were independent determinants of CAC progression; higher baseline aorta calcification score, higher pulse pressure, use of a statin, older age, higher serum phosphate level, use of aspirin, and male sex were independent determinants of aorta calcification progression. They also concluded that significant regression of CAC or aorta calcification was not observed in Rtx patients.

Relation of VC with Malnutrition, Inflammation, and Atherosclerosis

Despite beneficial effects of Rtx, this procedure could not reverse increased CV morbidity and mortality in ESRD patients. The question of why there are worse outcomes in this population might be answered by the association with a vicious cycle named malnutrition–inflammation–atheroscleosis/

calcification (MIAC) syndrome. MIAC syndrome has been defined as the interaction between increased levels of proinflammatory cytokines, malnutrition, and atherosclerosis/calcification in ESRD patients.[83,84] Stenvinkel et al.[85] hypothesised that malnutrition, inflammation, and atherosclerosis cause a vicious cycle, and that proinflammatory cytokines play a central part in this process. The presence of MIAC components was found to be associated with increased mortality and morbidity in ESRD patients receiving PD[85] or HD.[86] The CAC is a part of the extended state of VC, which can be detected even in the early decades of patients with ESRD,[27,80] and reflects the severity of atherosclerotic vascular disease and predicts CV events.[87,88] Wang et al.[84] showed an important association between MIAC syndrome and valvular and vascular calcification in PD patients. In a recent study, the correlation of CACS with coronary flow velocity reserve (CFVR) was investigated in HD patients.[89] According to the results of this study, HD patients with CACS >10 had a significantly lower CFVR, and the functional deterioration of coronary arteries started from low levels of CACS.

Taken together, these traditional and non-traditional risk factors, including chronic low-grade inflammation, vascular calcification, and malnutrition, might contribute to ongoing CVD and the markedly increased mortality in patients with Rtx.

CLINICAL STUDIES OF ATHEROSCLEROTIC CVD

Baber et al.[90] aimed to determine the impact of CKD on atherosclerotic plaque composition, morphology, and outcomes in patients with CAD. The authors demonstrated that CKD patients had more extensive and severe atherosclerotic plaques composed of greater necrotic core and less fibrotic tissue. They also concluded that in the following 3-years, CKD patients had a significantly higher rate of acute MI, cardiac arrest, and death compared to patients without CKD, although there was no significant difference in the rates of events adjudicated to nonculprit lesions. Similarly, Kawai et al.[91] demonstrated that the prevalance of severe coronary artery stenosis (≥70% of luminal diameter), defined by 320-row area computed tomography, was significantly higher in 131 patients with mild CKD (eGFR≥60 mL/min) compared with patients without CKD (35.1% versus 19.4%, p=0.0003, respectively), although there were no significant differences in the prevalance of high-risk plaque (13.0% versus 9.8%, p=0.3189, respectively).

In a substudy of the Acute Catheterisation and Urgent Intervention Triage strategy (ACUITY) trial, Acharji et al.[92] aimed to show the prognostic value of baseline troponin levels of 2,179 CKD patients with moderate and high-risk of ACS. Of 2,179 CKD patients, 1,291 had elevated baseline troponin (59.2%). CKD patients with higher baseline serum troponin levels had significantly higher rates of death, MI or unplanned revascularisation at 30 days and 1 year compared with CKD patients without baseline troponin elevation. Another important result of this study confers that baseline elevation of troponin independently predicts death or MI at 30 days and 1 year (HR=2.05 [1.48-2.83], p<0.0001 and HR=1.72 [1.36-2.17], p<0.0001, respectively). However, diagnosis of ACS in the patients with CKD based on troponin levels should be interpreted cautiously.

Among all dialysis patients, a cardiac mortality has been estimated as 40%. Additionally, this high rate reaches up to 50% in diabetic ESRD patients without any ACS symptoms. Accurate diagnosis of ACS is quite different in this population. In a study of 274,777 subjects (CKD, non-CKD, and patients receiving dialysis) enrolled from the US Renal Data System (USRDS) and the Third National Registry of Myocardial Infarction (NRMI 3), outcomes were reported for several subgroups, including patients with advanced CKD (baseline serum creatinine ≥2.5 mg/dL), ESRD patients receiving dialysis, and patients without CKD.[93] On admission, chest pain, ST elevation, and diagnosis other than ACS were seen in 40.4%, 15.9%, and 44% of patients with advanced CKD; 41.1%, 17.6%, and 47.7% of ESRD patients receiving dialysis; and 61.6%, 32.5%, and 25.8% of patients without CKD, respectively. In addition, mortality rates, unexpected cardiac arrest, and CHF were seen in 23%, 8.9%, and 41% of patients with advanced CKD; 21.7%, 12.3%, and 25.8% of ESRD patients receiving dialysis; and 12.6%, 6%, and 21.1% of patients without CKD, respectively (p<0.0001 for all comparisons).

Despite many studies on CKD patients, there has been limited clinical data on Rtx patients regarding CV morbidity and mortality. A retrospective study based upon the United States Renal Data System (USRDS) evaluated the clinical correlates of post-transplant MI. Among nearly 36,000 patients, the incidence of MI at 6, 12, and 36 months was

4.3%, 5.2%, and 11.1%, respectively. The principal risk factors were increased age, recipient of kidneys from older and deceased donors, delayed allograft function, and the presence of pre-transplant disease including diabetes mellitus, angina pectoris, peripheral vascular disease, and MI. The diagnosis of post-transplant diabetes and the development of allograft failure were also significantly associated with the development of a MI.[3] In a study of 53,297 patients, a markedly increased risk of acute MI was observed early after Rtx, <3 months post-surgery.[94] Compared with waitlist patients, the risk also varied by recipients of a deceased donor kidney (RR 3.57, 95% CI 3.21-3.96) and living donor kidney (RR 2.81, 95% CI 2.31-3.42).

Circulating fibroblast growth factor 23 (FGF23) was found to be closely associated with adverse CV outcomes in CKD.[95] Whether FGF23 predicts CV mortality after Rtx, independent of measures of mineral metabolism and CV risk factors, was unknown. Baia et al.[96] demonstrated that plasma FGF23 was independently associated with CV and all-cause mortality after Rtx. The association remained significant after adjustment for measures of mineral metabolism and CV risk factors.

CONCLUSION

The risk of atherosclerosis is unexpectedly high in patients with CKD and Rtx. To date, we know more about the pathogenesis of CAD in these populations; however, much remains unknown. Further experimental and randomised controlled clinical studies are needed to define the exact pathophysiological and clinical aspects of atherosclerosis especially in the Rtx population.

REFERENCES

1. Morris ST et al. Endothelial dysfunction in renal transplant recipients maintained on cyclosporine. Kidney Int. 2000;57(3):1100-6.

2. Vanholder R et al. Chronic kidney disease as cause of cardiovascular morbidity and mortality. Nephrol Dial Transplant. 2005;20(6):1048-56.

3. Lentine KL et al. Incidence and predictors of myocardial infarction after kidney transplantation. J Am Soc Nephrol. 2005;16(2):496-506.

4. Meier-Kriesche HU et al. Kidney transplantation halts cardiovascular disease progression in patients with end-stage renal disease. Am J Transplant. 2004;4(10):1662-8.

5. Jardine AG et al. Prevention of cardiovascular disease in adult recipients of kidney transplants. Lancet. 2011;378(9800):1419-27.

6. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. Transplantation. 2006;82(5):603-11.

7. US Renal Data System. USRDS 2008 Annual Data Report: atlas of chronic kidney disease and end-stage renal disease in the united states. national institutes of health nio. 2008.

8. Lentine KL et al. Cardiovascular risk assessment among potential kidney transplant candidates: approaches and controversies. Am J Kidney Dis. 2010;55(1):152-67.

9. Parfrey PS et al. Outcome and risk factors for left ventricular disorders in chronic uraemia. Nephrol Dial Transplant. 1996;11(7):1277-85.

10. Cheung AK et al. Atherosclerotic cardiovascular disease risks in chronic hemodialysis patients. Kidney Int. 2000;58(1):353-62.

11. Muntner P et al. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. J Am Soc Nephrol. 2005;16(2):529-38.

12. Himmelfarb J et al. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney Int. 2002;62(5):1524-38.

13. Sarnak MJ et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation. 2003;108(17):2154-69.

14. Muntner P et al. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol. 2002;13(3):745-53.

15. Foley RN et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol. 2005;16(2):489-95.

16. Rahman M et al. Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate. Ann Intern Med. 2006;144(3):172-80.

17. van der Velde M et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011;79(12):1341-52.

18. Segura J et al. Development of chronic kidney disease and cardiovascular prognosis in essential hypertensive patients. J Am Soc Nephrol. 2004;15(6):1616-22.

19. Knobler H et al. Reduced glomerular filtration rate in asymptomatic diabetic patients: predictor of increased risk for cardiac events independent of albuminuria. J Am Coll Cardiol. 2004;44(11):2142-8.

20. Stenvinkel P et al. Emerging biomarkers for evaluating cardiovascular risk in the chronic kidney disease patient: how do new pieces fit into the uremic puzzle? Clin J Am Soc Nephrol. 2008;3(2):505-21.

21. Go AS et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.

22. Tonelli M et al. Chronic kidney disease and mortality risk: a systematic review. J Am Soc Nephrol. 2006;17(7):2034-47.

23. Keith DS et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med. 2004;164(6):659-63.

24. Antman EM et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/

American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). J Am Coll Cardiol. 2004;44(3):E1-211.

25. Kalantar-Zadeh K et al. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. Kidney Int. 2003;63(3):793-808.

26. Turkmen K et al. Relationship between plasma pentraxin-3, neutrophil-to-lymphocyte ratio, and atherosclerosis in renal transplant patients. Cardiorenal Med. 2012;2(4):298-307.

27. Turkmen K et al. Fetuin-A, inflammation, and coronary artery calcification in hemodialysis patients. Indian J Nephrol. 2011;21(2):90-4.

28. Charytan DM et al. CKD and coronary collateral supply in individuals undergoing coronary angiography after myocardial infarction. Clin J Am Soc Nephrol. 2012;7(7):1079–86.

29. Kasiske BL. Risk factors for accelerated atherosclerosis in renal transplant recipients. Am J Med. 1988;84(6):985-92.

30. Magnus P, Beaglehole R. The real contribution of the major risk factors to the coronary epidemics: time to end the "only-50%" myth. Arch Intern Med. 2001;161(22):2657-60.

31. Sarnak MJ et al. Cardiovascular disease risk factors in chronic renal insufficiency. Clin Nephrol. 2002;57(5):327-35.

32. Lewington S et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370(9602):1829-39.

33. Tsimihodimos V et al. Dyslipidemia in chronic kidney disease: an approach to pathogenesis and treatment. Am J Nephrol. 2008;28(6):958-73.

34. Sechi LA et al. Abnormalities of glucose metabolism in patients with early renal failure. Diabetes. 2002;51(4): 1226-32.

35. Despres JP et al. HDL-cholesterol as a marker of coronary heart disease risk: the Quebec cardiovascular study. Atherosclerosis. 2000;153(2):263-72.

36. Ok E et al. Carbamylated low-density lipoprotein induces death of endothelial cells: a link to atherosclerosis in patients with kidney disease. Kidney Int. 2005;68(1):173-8.

37. Attman PO et al. Lipoprotein metabolism and renal failure. Am J Kidney Dis. 1993;21(6):573-92.

38. KDOQI Clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. http://www.kidney.org/professionals/KDOQI/guidelines_bp/index.htm.

39. Wheeler DC, Becker GJ. Summary of KDIGO guideline. What do we really know about management of blood pressure in patients with chronic kidney disease? Kidney Int. 2013;83:377-83.

40. Chen SC et al. The ratio of observed to predicted left ventricular mass is independently associated with increased cardiovascular events in patients with chronic kidney disease. Hypertens Res. 2012;35:832-8.

41. Prakash S et al. Assessment of hypertension control in chronic kidney disease patients by ambulatory blood pressure monitoring. J Assoc Physicians India. 2005;53:769-74.

42. Andersen MJ et al. Home blood pressure monitoring in CKD. Am J Kidney Dis. 2005;45(6):994-1001.

43. Tucker B et al. Left ventricular hypertrophy and ambulatory blood pressure monitoring in chronic renal failure. Nephrol Dial Transplant. 1997;12(4):724-8.

44. Agarwal R, Andersen MJ. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. Kidney Int. 2006;69(7):1175-80.

45. Hansson L, Zanchetti A. The Hypertension Optimal Treatment (HOT) Study--patient characteristics: randomization, risk profiles, and early blood pressure results. Blood Press. 1994;3(5):322-7.

46. Agarwal R, Andersen MJ. Prognostic importance of clinic and home blood pressure recordings in patients with chronic kidney disease. Kidney Int. 2006;69(2):406-11.

47. Sanders CE Jr., Curtis JJ. Role of hypertension in chronic renal allograft dysfunction. Kidney Int Suppl. 1995;52:S43-7.

48. Halloran PF et al. Rethinking chronic allograft nephropathy: the concept of accelerated senescence. J Am Soc Nephrol. 1999;10(1):167-81.

49. London GM et al. Cardiac and arterial interactions in end-stage renal disease. Kidney Int. 1996;50(2):600-8.

50. Takahashi H et al. Autonomic dysfunction in hemodialysis patients with persistent hypotension. Nephron. 1996;72(3):418-23.

51. Jones MA et al. Changes in diurnal blood pressure variation and red cell and plasma volumes in patients with renal failure who develop erythropoietin-induced hypertension. Clin Nephrol. 1995;44(3):193-200.

52. van den Dorpel MA et al. Cyclosporin A impairs the nocturnal blood pressure fall in renal transplant recipients. Hypertension. 1996;28(2):304-7.

53. Lipkin GW et al. Ambulatory blood pressure and left ventricular mass in cyclosporin- and non-cyclosporin-treated renal transplant recipients. J Hypertens. 1993;11(4):439-42.

54. Kayrak M et al. Masked hypertension in renal transplant recipients. Blood Press. 2013. [Epub ahead of print].

55. Agarwal R. Hypertension: KDIGO BP guidelines-more individualized, less prescriptive. Nat Rev Nephrol. 2013;9: 131-3.

56. Wood KJ, Goto R. Mechanisms of rejection: current perspectives. Transplantation. 2012;93(1):1-10.

57. Turkmen K et al. The relationship between oxidative stress, inflammation, and atherosclerosis in renal transplant and end-stage renal disease patients. Ren Fail. 2012;34(10):1229-37.

58. Tamhane UU et al. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol. 2008;102(6):653-7.

59. Nunez J et al. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. Am J Cardiol. 2008;101(6):747-52.

60. Walsh SR et al. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol. 2005;91(3):181-4.

61. Duffy BK et al. Usefulness of an elevated neutrophil to lymphocyte ratio in predicting long-term mortality after percutaneous coronary intervention. Am J Cardiol. 2006;97(7):993-6.

62. Turkmen K et al. The relationship between neutrophil-to-lymphocyte ratio and inflammation in end-stage renal disease patients. Ren Fail. 2012;34:155-9.

63. Acar G et al. The relation of platelet-lymphocyte ratio and coronary collateral circulation in patients with stable angina pectoris and chronic total occlusion. Clin Appl Thromb Hemost. 2013. [Epub ahead of print].

64. Turkmen K et al. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int. 2013;17(3):391-6.

65. Turkmen K. Platelet-to-lymphocyte ratio: one of the novel and valuable platelet indices in hemodialysis patients. Hemodial Int. 2013;17(4):670.

66. Burkly LC et al. TWEAK/Fn14 pathway: an immunological switch for shaping tissue responses. Immunol Rev. 2011;244(1):99-114.

67. Wiley SR, Winkles JA. TWEAK, a member of the TNF superfamily, is a multifunctional cytokine that binds the TweakR/Fn14 receptor. Cytokine Growth Factor Rev. 2003;14(3-4):241-9.

68. Polek TC et al. TWEAK mediates signal transduction and differentiation

of RAW264.7 cells in the absence of Fn14/TweakR. Evidence for a second TWEAK receptor. J Biol Chem. 2003;278(34):32317-23.

69. Justo P et al. Cytokine cooperation in renal tubular cell injury: the role of TWEAK. Kidney Int. 2006;70(10):1750-8.

70. Ortiz A et al. Considering TWEAK as a target for therapy in renal and vascular injury. Cytokine Growth Factor Rev. 2009;20(3):251-8.

71. Yilmaz MI et al. Soluble TWEAK plasma levels as a novel biomarker of endothelial function in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2009;4(11):1716-23.

72. Yilmaz MI et al. Soluble TWEAK and PTX3 in nondialysis CKD patients: impact on endothelial dysfunction and cardiovascular outcomes. Clin J Am Soc Nephrol. 2011;6(4):785-92.

73. Yilmaz MI et al. Predictors of carotid artery intima-media thickness in chronic kidney disease and kidney transplant patients without overt cardiovascular disease. Am J Nephrol. 2010;31(3):214-21.

74. Turkmen K et al. Soluble TWEAK independently predicts atherosclerosis in renal transplant patients. BMC Nephrol. 2013;14:144.

75. Carrero JJ et al. Additive effects of soluble TWEAK and inflammation on mortality in hemodialysis patients. Clin J Am Soc Nephrol. 2009;4(1):110-8.

76. Gungor O et al. The relationships between serum sTWEAK, FGF-23 levels, and carotid atherosclerosis in renal transplant patients. Ren Fail. 2013;35(1):77-81.

77. Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. J Am Soc Nephrol. 2008;19(2):213-6.

78. Shioi A et al. Mönckeberg's medial sclerosis and inorganic phosphate in uremia. Am J Kidney Dis. 2001;38(4 Suppl 1):S47-9.

79. Guerin AP et al. Arterial stiffening and vascular calcifications in end-stage renal disease. Nephrol Dial Transplant. 2000;15(7):1014-21.

80. London GM et al. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant. 2003;18(9):1731-40.

81. Shanahan CM et al. Medial localization of mineralization-regulating proteins in association with Monckeberg's sclerosis: evidence for smooth muscle cell-mediated vascular calcification. Circulation. 1999;100(21):2168-76.

82. Maréchal C et al. Progression of coronary artery calcification and thoracic aorta calcification in kidney transplant recipients. Am J Kidney Dis. 2012;59(2):258-69.

83. Stenvinkel P et al. Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant. 2000;15(7):953-60.

84. Wang AY et al. Associations of serum fetuin-A with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients. Nephrol Dial Transplant. 2005;20(8):1676-85.

85. Stenvinkel P et al. Malnutrition, inflammation, and atherosclerosis in peritoneal dialysis patients. Perit Dial Int. 2001;21 Suppl 3:S157-62.

86. Tonbul HZ et al. Malnutrition-inflammation-atherosclerosis (MIA) syndrome components in hemodialysis and peritoneal dialysis patients. Ren Fail. 2006;28(4):287-94.

87. Haydar AA et al. Coronary artery calcification is related to coronary atherosclerosis in chronic renal disease patients: a study comparing EBCT-generated coronary artery calcium scores and coronary angiography. Nephrol Dial Transplant. 2004;19(9):2307-12.

88. Raggi P et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol. 2002;39(4):695-701.

89. Caliskan Y et al. Coronary artery calcification and coronary flow velocity in haemodialysis patients. Nephrol Dial Transplant. 2010;25(8):2685-90.

90. Baber U et al. Coronary plaque composition, morphology, and outcomes in patients with and without chronic kidney disease presenting with acute coronary syndromes. JACC Cardiovasc Imaging. 2012;5(3 Suppl):S53-61.

91. Kawai H et al. Coronary plaque characteristics in patients with mild chronic kidney disease. Circ J. 2012;76:1436-41.

92. Acharji S et al. Prognostic significance of elevated baseline troponin in patients with acute coronary syndromes and chronic kidney disease treated with different antithrombotic regimens: a substudy from the ACUITY Trial. Circ Cardiovasc Interv. 2012;5(2):157-65.

93. Shroff GR et al. Renal failure and acute myocardial infarction: clinical characteristics in patients with advanced chronic kidney disease, on dialysis, and without chronic kidney disease. A collaborative project of the United States Renal Data System/National Institutes of Health and the National Registry of Myocardial Infarction. Am Heart J. 2012;163(3):399-406.

94. Kasiske BL et al. Acute myocardial infarction and kidney transplantation. J Am Soc Nephrol. 2006;17(3):900-7.

95. Wolf M. FGF23: fashion or physiology? Clin J Am Soc Nephrol. 2010;5(10):1727-9.

96. Baia LC et al. Fibroblast growth factor 23 and cardiovascular mortality after kidney transplantation. Clin J Am Soc Nephrol. 2013;8(11):1968-78.

RECENT ADVANCES IN PERCUTANEOUS NEPHROLITHOTOMY

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Disclosure: No potential conflict of interest.
Received: 16.01.14 **Accepted:** 03.03.14
Citation: EMJ Urol. 2014;1:83-89.

ABSTRACT

The continuous innovations in technology, instrumentations, and techniques allow urologists to perform percutaneous nephrolithotomy (PCNL) with increasing efficacy. Although recent advances have facilitated the procedure, some steps are still challenging. A thorough review of the recent urologic literature was performed to identify these improvements in PCNL technique. The newer developments mainly focused on multimodal imaging techniques, miniaturisation of instruments, tracking and navigation systems during access to the stone, and robotic systems. Further studies are necessary to better define the benefits of these new fruitful developments which remain an active research field.

Keywords: PCNL, imaging, access, microperc, robotic, augmented reality, navigation, and tracking.

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is a well set, well known, and widely accepted minimally invasive surgical procedure for stone removal within the urological procedures. As with many minimally invasive procedures, the main purpose of PCNL is the complete removal of the renal calculi, reducing mortality and morbidity without deteriorating quality of life. However, this technique is directly competing with other minimally invasive techniques such as retrograde intrarenal surgery (RIRS) and laparoscopic procedures. The indications for RIRS have expanded, and it became a viable alternative to PCNL in select cases. However, PCNL is still the gold standard for high-volume renal calculi (>2 cm), and data demonstrating utilisation of RIRS for >1 cm renal stones are still underwhelming. Nevertheless, excessive efforts have been made to reduce the morbidity and improve the efficiency of PCNL so as to make it more competitive.

In accordance with the developing technology, PCNL requires better instruments for complete stone removal, more precise stone targeting, and access to the kidney and relevant calices. The newer developments have mainly focused on imaging techniques, as well as the fusion of multiple imaging procedures, tracking and navigation systems during access to the stone, miniaturisation of the instruments, and robotic systems.[1-7] Furthermore, the debate continues over the use of the prone or supine position, tube or tubeless PCNL, and the efficiency of 'microperc'. Herein, the recent advances, primarily in imaging, instrumentation, and access techniques related to PCNL, are reviewed.

A recent internet survey among active Endourological Society members has shown that the majority of urologists would choose prone position for PCNL (prone: 86%, supine: 10%, and lateral decubitus: 4%). Additionally, more than 76% of respondents prefer a nephrostomy tube post-operatively, rather than a tubeless approach (2%).[8]

IMAGING

Computed tomography (CT) is mandatory for preoperative planning and appropriate percutaneous access. It shows the anatomy of kidney calices and the relation of the stone to the pelvicalyceal system, the kidney position, and its relation to other abdominal structures.[1,4,9] Angiographic CT can also be used for detailed images of blood vessels and calyceal anatomy.[1] Technological advances have also enabled the acquisition of three-dimensional (3D) images through ultrasound (US), providing volumetric measurements and 360-degree analyses of anatomic structures.[10]

After using the benefits of cone beam CT (CBCT) in neurosurgical operations, the application has been extended to percutaneous surgery. CBCT is a novel imaging modality that combines the versatility of conventional C-arm with the functionality of cross-sectional imaging to provide high-resolution, 3D, CT-like images.[9] As a result of a recent study, the authors concluded that CBCT could help for better percutaneous access using the advantages of improved imaging, which allows surgeons to have similar real-time access via high quality CT images.[11] The intraoperative availability of images may reduce the need for postoperative imaging and subsequent adjunctive procedures for clearance of residual fragments.

Multimodal Imaging

Several studies presented the combination of different imaging techniques. Among these, Li et al.[3] combined preoperative magnetic resonance imaging (MRI) with augmented intraoperative USG images, and found valuable results due to the additional advantages of high resolution, multi-planar, and 3D images. The Interactive Closest Points algorithm was used as a rigid registry process through the manual selection of pairs of points in both images from the cranial pole, caudal pole, and kidney hilum. A respiratory gating method was also used to minimise the impact of kidney deformation by using US to obtain only images at the same stages of the respiration cycles.

In another study, an automatic rigid registration method was used to combine CT and US images. Image contours were highlighted by using processing algorithms to improve cross-correlation of image intensity.[12] Wein et al.[13] presented a fully automatic image-based algorithm for registering 3D freehand USG sweeps with CT images. Target distance error ranged between 3.5-8.1 mm in these studies.[4]

Imaging is not only necessary to plan pelvicalyceal access, but also to evaluate treatment success and complications after PCNL. Previous studies aimed to identify possible preoperative radiological findings that predict prognostic factors. Several authors mentioned the necessity of reliable prediction models.[14] Thomas et al.[15] developed the Guy's stone score to grade PCNL complexity based on radiological findings. Lately staghorn morphometry, S.T.O.N.E. nephrolithometry, and a nephrolithometric nomogram have been developed to estimate PCNL success prior to surgery.

Staghorn Morphometry

Staghorn calculi sometimes require several renal access procedures to obtain complete clearance. Staghorn morphometry is a new prognostic tool to predict the position of access and stages for PCNL, which requires 3D CT urography assessment with volume-rendering software. Recently, a new classification of staghorn stones into three types has been proposed based on the volume of distribution of stone and the surface area. Type 1 staghorn stones have a total stone volume of <5,000 mm^3 with <5% of unfavourable calyceal stone percentile volume, whereas type 3 staghorn stones have a total volume of >20,000 mm^3 with >10% of unfavourable calyceal stone percentile volume. The type 2 staghorn stone is in between. Based on statistical models, they found that a type 1 staghorn stone would require one access in one stage, type 2 stones would require one access in more than one stage, or multiple accesses in one stage, and type 3 stones would require multiple accesses and stages.[9,16]

Nephrolithometric Nomogram

A nomogram was constituted to predict the stone-free rate using preoperative parameters, including case volume, prior treatment, stone burden and location, staghorn stones, and number of stones.[17] A high total score was significant for a higher chance of stone-free rate, while low score had a lower chance of stone-free rate. Stone burden was the best predictor of treatment outcome. In addition, nephrolithometric nomogram showed consistent but lower performance in the lower stone-free rate ranges.

The ROC AUC for predictions based on this nomogram was 0.76.

S.T.O.N.E. Nephrolithometry

In this scoring method, five variables from preoperative non-contrast enhanced CT were included; stone size, tract length, obstruction, number of involved calices, and essence or stone density. Stone-free patients had statistically significant lower scores than the patients with residual stones (p=0.002). Additionally, the score was correlated with the estimated blood loss (p=0.005), operative time (p=0.001), and length of hospital stay (p=0.001).[18]

PATIENT POSITIONING

The prone position in PCNL is frequently associated with discomfort, especially for obese patients, severe musculoskeletal deformities, and cardiovascular and respiratory problems.[19] However, it has the advantages of reduced risk of colonic injury without limitation of instrument movement and multiple posterior accesses. Recently, several reports have described various alternative positions such as the Valdivia, modified Valdivia, a flank position, prone split-leg position, and a completely supine position.[20-24]

According to Di Grazia and La Rosa,[25] prone position with split-leg is advantageous over supine position. The split-leg technique provides some benefits, especially in challenging cases, in cases with anatomical abnormalities and in multi-tract accesses. Cracco et al.[26] emphasised that the Galdakao-modified supine Valdivia position is safe, effective, and provides more advantages than the others. An easy puncture of the kidney, a reduced risk of colonic injury, and simultaneous antero-retrograde approach to the renal cavities without any requirements of intraoperative repositioning are just a few of the advantages of this position.

The main advantages of supine position are as follows: there is no need to change the position of the patient, simultaneous ureteroscopies can be performed, there is better airway control for the anaesthetist, and it facilitates easier evacuation of fragmented stones.[21] A randomised comparative study of the prone, supine, and flank positions in 150 patients showed that the supine and flank positions were as efficient as the prone position with experienced hands. They also concluded that the preference of the surgeon and proper case selection are the main factors for successful PCNL.[24] Although the supine position has been described as more attractive, there is still an argument for upper pole calyceal access, due to its medial, posterior, and concealed position in the rib cage. Recent meta-analysis showed that PCNL in the supine position was associated with a significantly shorter operative time, but lower stone-free rate than PCNL in the prone position. There was no difference between the two positions regarding hospital stay and complication rate.[27,28]

INSTRUMENTS

The evolution of devices from their prototypes has increased the instrumentation options for urologists. Improved lithotripsy devices (Gyrus ACMI CyberWand®, Swiss LithoClast Select with Vario® and LithoPUMP®, Cook LMA StoneBreaker®), digital nephroscopes, stone retrieval and occlusion devices (PercSys Accordion®, Cook Perc N-Circle®, etc.), and haemostatic or adhesive agents for tubeless procedure can be valuable tools for successful PCNL.[29,30] New lithotripsy devices, including a combination of ultrasonic-pneumatic device, dual ultrasonic lithotripter, and pneumatic stone breaker, have the potential to enhance the efficiency of stone fragmentation.[31]

Micro PCNL (Microperc)

Endoscopic access technique has been introduced in recent years using micro-optics, which are inserted either within the needle or the working sheath. 'Microperc' is a recently described technique in which percutaneous renal access and lithotripsy are performed in a single step using a 16 gauge micro-puncture needle. The main aim of this innovation is to reduce the tract size with the intention of less morbidity. Bader et al.[32] reported a modified needle of 1.6 mm in diameter that integrates 0.9 and 0.6 mm micro-optical system. The authors concluded that the micro-optical needle appears to be helpful for confirming percutaneous access before dilatation of the tract, thus decreasing tract size, need for imaging, and multiple accesses. Desai et al.[33] further modified this concept and completed PCNL through the 'all seeing needle'. Ten patients, two of whom were children, and each having an ectopic pelvic kidney, chronic kidney disease, and obesity, were enrolled to this study. The mean stone size was 14.3 mm.

Nine patients were stone-free at the end of 1 month. A conversion to miniperc was needed due to intraoperative bleeding and obscured vision in one patient. 'Mini-microperc' is a new technical modification in which an 8 Fr sheath is used to allow insertion of ultrasonic or pneumatic lithoclast probe with suction.[34]

The advantage of the microperc is that it is a single-step renal access procedure, resulting in a shorter access time and fewer puncture attempts. The main disadvantage is the long duration of stone fragmentation. Therefore microperc is only optional for small stones less than 20 mm in size. The available evidence indicates that microperc is safe and efficient in small renal stones, especially in paediatric patients and ectopic kidneys. The high stone-free rate makes it a viable alternative to RIRS.[4,9]

ACCESS

Endoscopically Guided PCNL

Grasso et al.[35] reported first endoscopy-assisted percutaneous renal access as an alternative technique for successful access in a few patients in whom other methods failed. Later, the technique was developed as a primary access method by insertion of the needle into the collecting system under the guidance of both fluoroscopy and direct vision of flexible ureteroscope. The guidewire can be passed into the access sheath, and easily delivered via the urethral end of the access sheath. The direct visual confirmation has the advantage of a successful access in a short time with no requirement of multiple attempts. The original technique and its subsequent modifications were reported to have a success rate of 89–100%.[36-38]

Robotics

Most urological procedures are amenable for robot-assisted surgery. Different types of robotic systems are under development. These include image-guided robots that, in addition to the direct visual feedback, use medical images for guiding the intervention.[4] Recently, one centre presented three different types of medical robots. The first system (PAKY-RCM) consists of an orientation module between a needle driver and a robotic 7-degree free arm, enabling the positioning of the needle and completion of its insertion using rotational movements. Additionally, the system regulates the strength during the access. The surgeon controls all movements of the robot via a joystick under the guidance of fluoroscopic images.[6] The AcuBot robot includes previous robotic modules, but adds a bridge-like structure over the table, and a linear pre-positioning stage. This attaches to CT or fluoroscopy table of the imager. The mounted needle driver in the module is supported by a passive arm, driven by the Cartesian stage. It has 6 degrees of freedom configured for decoupled positioning, orientation, and instrument insertion.[4,6,39] The newest robot (MrBot) is introduced as a fully-actuated MRI robot for image-guided access for percutaneous interventions. The robot is customised for needle insertion and designed to be compatible with the highest field strength. It is constructed with a pneumatic stepper motor using nonmagnetic and dielectric materials. This system, with 6 degrees of freedom, has a great potential for PCNL.[4,6,40]

Lately, advances of US-guided robotic systems have been reported. The typical approach resorts to a surgical needle attached to a robotic arm that is driven automatically or controlled by the surgeon in 3D or 2D imaging volume.[41] A locator apparatus that stabilises the needle during the access was tested in a study. The authors achieved a mean access time of 225 seconds, which is much quicker than the average access time reported for traditional technique (approximately 12 minutes).[42]

Although medical robotic systems have certain benefits, supporting technology is still struggling to overcome some important problems in difficult initial setups, expensive costs, mechanical problems, absence of tactile feedback, and not fully developed motion tracking systems.[4]

Tracking and Surgery Navigation

Navigation software and augmented reality systems have recently been introduced as computer-assisted navigation systems combining imaging and tracking systems. Most of them work by obtaining the target anatomic area from preoperative data, using image segmentation algorithms or computer graphics (direct volume or surface rendering). Then, the image processed data are superimposed and registered onto a real-time intraoperative video (augmented reality) or static preoperative volume data (navigation software). The surgical tools are commonly updated using a motion tracking system.[4,43]

The use of augmented reality during surgery is challenging because of tissue deformation and respiratory movements. Therefore, many improvements are still needed for both mathematical algorithms and equipment, especially for motion tracking systems.[4,44]

Huber et al.[45] tested a navigated renal access in an *ex vivo* model. The surgical needle is guided to the renal calix according to the information retrieved by a catheter that integrates electromagnetic motion tracking sensors. The reported access time was 14 seconds with a precision of 1.7 mm. Rodrigues at al.[46] evaluated the efficiency of a new real-time electromagnetic tracking system for kidney puncture in pigs. A catheter with an electromagnetic tracking sensor was placed by ureterorenoscopy into the desired puncture site. A tracked needle with a similar electromagnetic tracking sensor was subsequently navigated into the sensor in the catheter. They described the method as highly accurate, simple, and quick.

Recently, Rassweiler et al.[47] reported iPad-assisted percutaneous access. All anatomic structures were identified and marked in preoperative CT images. Augmented virtual reality of preoperative CT 3D images could display all anatomical details of the kidney. There was no limitation of USG such as shadows caused by ribs, and the advantage of freehand needle placement without holding the US probe. The iPad was used as a camera to take a picture of the operating field. Then compressed data were transferred to a server located in a control room via Wi-Fi. The server operated the algorithm to identify the position and orientation of the navigation, and to overlay it accordingly with preoperative marked CT images, which were sent back to the iPad. The exact overlays of optical markers, which must always be visible on the iPad screen, were rigidly registered for motion tracking system.[9,47]

TUBELESS PCNL

Recently, most notably modification has been a tubeless PCNL alternative to nephrostomy tube. It appears to decrease postoperative discomfort and shorten hospital stay, without increasing complication rate in selected cases.[48] Future studies are needed to evaluate the results of tubeless PCNL in paediatric and geriatric patients, complicated cases by multiple access tracts, renal anomalies, and patients with previous renal surgery.[49-51] Although it has been used for a wide range of indications, currently, there are no sufficient data supporting the superiority of tubeless PCNL over conventional technique.[52] Therefore, tubeless PCNL can be feasible in selected patients. In order to improve outcomes of tubeless PCNL, application of haemostatic agents along the percutaneous access tract was introduced. Lipkin et al.[53] researched porcine models to depict the efficacy of haemostatic agents by using fibrin sealant Evicel and haemostatic gelatin matrix (HGM). They have found HGM more preferable than fibrin sealant, because the tract closed earlier than HGM, 10-14 days in fibrin sealant versus 30 days in HGM, post-operatively. Both forms of haemostatic agents used today, either glue or HGM, have been demonstrated to be safe and effective for tubeless procedure.[54] In a prospective cohort study published in 2013, 43 patients were randomised into two groups, with or without using autologous single donor fibrin glue after tubeless PCNL. The use of fibrin glue was found safe, though no significant role in improving results or decreasing complications was seen.[55] Gudeman et al.[56] reported their study on tubeless PCNL using fibrin sealant with 107 patients showing favourable stone-free rates, shorter hospital stays, and lower complication rates without bleeding. However, further studies are warranted with regards to its safety and histological effects on the renal tissue.[57]

Various techniques were introduced to control bleeding during or post-operative PCNL,[58] such as haemostatic sandwich technique, which was described as a successful treatment for bleeding after PCNL by Millard, and an anchoring system, which was found to be a potentially useful and safe method by Tokue et al.[59]

CONCLUSION

Urologists need to make significant efforts to improve the PCNL procedure, with the aim of further increasing stone-free outcomes and reducing morbidity. Liberal use of flexible ureteroscopy in supine position can reduce the need for multiple percutaneous accesses, but supine position alone has not demonstrated a benefit over traditional prone PCNL. A trend toward the use of tubeless PCNL improves quality of life in selected cases, but further studies are

needed. The most important advancement in PCNL is the application of medical imaging modalities, smaller surgical instruments like 'microperc', robotics, and augmented reality combined with navigation and motion tracking systems. Despite all of these new developments, it remains an active and challenging research field. Future developments should focus on real-time methods supported by radiation-free imaging techniques.

REFERENCES

1. Kalogeropoulou C et al. Imaging in percutaneous nephrolithotomy. J Endourol. 2009;23(10):1571-7.

2. Ukimura O. Image-guided surgery in minimally invasive urology. Curr Opin Urol. 2010;20(2):136-40.

3. Li ZC et al. Augmenting intraoperative ultrasound with preoperative magnetic resonance planning models for percutaneous renal access. Biomed Eng Online. 2012;11:60.

4. Rodrigues PL et al. Kidney targeting and puncturing during percutaneous nephrolithotomy: recent advances and future perspectives. J Endourol. 2013;27(7):826-34.

5. Desai MM et al. Robotic flexible ureteroscopy for renal calculi: initial clinical experience. J Urol. 2011;186(2):563-8.

6. Mozer P et al. Urologic robots and future directions. Curr Opin Urol. 2009;19(1):114-9.

7. Yaniv Z et al. Electromagnetic tracking in the clinical environment. Med Phys. 2009;36(3):876-92.

8. Sivalingam S et al. Current practices in percutaneous nephrolithotomy among endourologists. J Endourol. 2013. [Epub ahead of print].

9. Arvind P. Ganpule, Mahesh R. Desai. What's new in percutaneous nephrolithotomy. Arab Journal of Urology. 2012;10(3):317–23.

10. Jessen JP et al. Percutaneous nephrolithotomy under combined sonographic/radiologic guided puncture: results of a learning curve using the modified Clavien grading system. World J Urol. 2013;31(6):1599-603.

11. Roy OP et al. Cone beam computed tomography for percutaneous nephrolithotomy: initial evaluation of a new technology. J Endourol. 2012;26(7):814–8.

12. Leroy A et al. Rigid registration of freehand 3D ultrasound and CT-scan kidney images. Proc Int Conf. 2004;3216:837–44.

13. Wein W et al. Automatic CT-ultrasound registration for diagnostic imaging and image-guided intervention. Med Image Anal. 2008;12(5):577–85.

14. Matlaga BR, Hyams ES. Stones: can the Guy's stone score predict PNL outcomes? Nat Rev Urol. 2011;8(7):363-4.

15. Thomas K et al. The Guy's stone score—grading the complexity of percutaneous nephrolithotomy procedures. Urology. 2011;78(2):277-81.

16. Mishra S et al. Percutaneous nephrolithotomy monotherapy for staghorn: paradigm shift for 'staghorn morphometry' based clinical classification. Curr Opin Urol. 2012;22(2):148–53.

17. Smith A et al. A nephrolithometric nomogram to predict treatment success of percutaneous nephrolithotomy. J Urol. 2013;190(1):149-56.

18. Okhunov Z et al. S.T.O.N.E. nephrolithometry: novel surgical classification system for kidney calculi. Urology. 2013;81(6):1154-9.

19. de la Rosette JJ et al. Training in percutaneous nephrolithotomy--a critical review. Eur Urol. 2008;54(5):994-1001.

20. Papatsoris A et al. Improving patient positioning to reduce complications in prone percutaneous nephrolithotomy. J Endourol. 2009;23(5):831–2.

21. Kumar P et al. Supine percutaneous nephrolithotomy (PCNL):'in vogue' but in which position? BJU Int. 2012;110(11 Pt C):E1018-21.

22. Falahatkar S et al. Supine percutaneous nephrolithotomy: pro. Urol J. 2011;8(4):257–64.

23. Falhatkar S et al. Complete supine percutaneous nephrolithotomy in patients with and without a history of stone surgery: safety and effectiveness of complete supine PCNL. Urol Res. 2011;39(4):295–301.

24. Karami H et al. A study on comparative outcomes of percutaneous nephrolithotomy in prone, supine and flank positions. World J Urol. 2013;31(5):1225-30.

25. Di Grazia et al. Split-leg percutaneous nephrolithotomy: a safe and versatile technique. Arch Ital Urol Androl. 2013;85(2):82-5.

26. Cracco CM et al. The patient position for PNL: does it matter? Arch Ital Urol Androl. 2010;82(1):30-1.

27. Astroza G et al; CROES PNL Study Group. Effect of supine vs prone position on outcomes of percutaneous nephrolithotomy in staghorn calculi: results from the clinical research office of the Endourology Society Study. Urology. 2013;82(6):1240-4.

28. Zhang X et al. Is the supine position superior to the prone position for percutaneous nephrolithotomy (PCNL)? Urolithiasis. 2014;42(1):87-93.

29. Chew BH et al. The Canadian StoneBreaker trial. A randomized, multicenter trial comparing the LMA StoneBreaker and the Swiss LithoClast® during percutaneous nephrolithotripsy. J Endourol. 2011;25(9):1415–9.

30. Pugh JW. New instrumentation in percutaneous nephrolithotomy. Indian J Urol. 2010;26(3):389–94.

31. Antonelli JA, Pearle MS. Advances in percutaneous nephrolithotomy. Urol Clin North Am. 2013;40(1):99-113.

32. Bader MJ et al. The 'all-seeing needle'. Initial results of an optical puncture system confirming access in percutaneous nephrolithotomy. Eur Urol. 2011;59(6):1054–9.

33. Desai MR et al. Single-step percutaneous nephrolithotomy (microperc): the initial clinical report. J Urol. 2011;186(1):140–5.

34. Sabnis RB et al. Current role of microperc in the management of small renal calculi. Indian J Urol. 2013;29(3):214-8.

35. Grasso M et al. Flexible ureteroscopically assisted percutaneous renal access. Tech Urol. 1995;1(1):39–43.

36. Sountoulides PG et al. Endoscopy-guided percutaneous nephrostolithotomy. Benefits of ureteroscopic access and therapy. J Endourol. 2009;23(10):1649–54.

37. Wynberg JB et al. Flexible ureteroscopy-directed retrograde nephrostomy for percutaneous nephrolithotomy: description of a technique. J Endourol. 2012;26(10):1268-74.

38. Kawahara T et al. Ureteroscopy assisted retrograde nephrostomy: a new technique for percutaneous nephrolithotomy (PCNL). BJU Int. 2012;110(4):588-90.

39. Pollock R et al. Prospects in percutaneous ablative targeting: comparison of a computer-assisted navigation system and the AcuBot Robotic System. J Endourol. 2010;24(8):1269-72.

40. Cunha JA et al. Toward adaptive stereotactic robotic brachytherapy for

prostate cancer: demonstration of an adaptive workflow incorporating inverse planning and an MR stealth robot. Minim Invasive Ther Allied Technol. 2010;19(4):189-202.

41. Cinquin P. How today's robots work and perspectives for the future. J Visc Surg. 2011;148(5 Suppl):e12–8.

42. Lazarus J, Williams J. The Locator: Novel percutaneous nephrolithotomy apparatus to aid collecting system puncture: a preliminary report. J Endourol. 2011;25(5):747–50.

43. Nicolau S et al. Augmented reality in laparoscopic surgical oncology. Surg Oncol. 2011;20(3):189–201.

44. Teber D et al. Augmented reality: a new tool to improve surgical accuracy during laparoscopic partial nephrectomy? Preliminary in vitro and in vivo results. Eur Urol. 2009;56(2):332-8.

45. Huber J et al. Navigated renal access using electromagnetic tracking: An initial experience. Surg Endosc. 2011;25(4):1307–12.

46. Rodrigues PL et al. Collecting system percutaneous access using real-time tracking sensors: first pig model in vivo experience. J Urol. 2013;190(5):1932-7.

47. Rassweiller J et al. iPad-assisted percutaneous access to the kidney using marker-based navigation: initial clinical experience. Eur Urol. 2012;61(3):628-31.

48. de Cógáin MR, Krambeck AE. Advances in tubeless percutaneous nephrolithotomy and patient selection: an update. Curr Urol Rep. 2013;14(2):130-7.

49. Pillai S et al. Tubeless simultaneous bilateral percutaneous nephrolithotomy: Safety, feasibility and efficacy in an Indian setting. Int J Urol. 2013;doi:10.1111/iju.12352. [Epub ahead of print].

50. Nouralizadeh A et al. Delayed postpercutaneous nephrolithotomy hemorrhage: Prevalence, predictive factors and management. Scand J Urol. 2014;48(1):110-5.

51. Akin Y et al. Is tubeless percutaneous nephrolithotomy really less injurious than standard in the midterm? J Endourol. 2013;27(10):1192-6.

52. Agrawal MS, Agarwal M. Percutaneous nephrolithotomy: Large tube, small tube, tubeless, or totally tubeless? Indian J Urol. 2013;29(3):219-24.

53. Lipkin ME et al. Pathologic evaluation of hemostatic agents in percutaneous nephrolithotomy tracts in a porcine model. J Endourol. 2011;25(8):1353-7.

54. Choe CH et al. The use of adjunctive hemostatic agents for tubeless percutaneous nephrolithotomy. J Endourol. 2009;23(10):1733-8.

55. Ziaee SA et al. Autologous fibrin sealant in tubeless percutaneous nephrolithotomy; a prospective study. Urol J. 2013;10(3):999-1003.

56. Gudeman SR et al. Percutaneous stone surgery using a tubeless technique with fibrin sealant: report of our first 107 cases. BJU Int. 2012;110(11 Pt C):E1048-52.

57. Rigopoulos C et al. Assessing the use of haemostatic sealants in tubeless percutaneous renal access and their effect on renal drainage and histology: an experimental porcine study. BJU Int. 2013;112(2):E114-21.

58. Millard WW 2nd et al. Hemostatic sandwich to control percutaneous nephrolithotomy tract bleeding. J Endourol. 2010;24(9):1415-9.

59. Tokue H et al. Anchoring system-assisted coil tract embolization: a new technique for management of arterial bleeding associated with percutaneous nephrostomy. J Vasc Interv Radiol. 2011;22(11):1625-9.

A LITERATURE-BASED ANALYSIS OF THE LEARNING CURVES OF LAPAROSCOPIC RADICAL PROSTATECTOMY

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Disclosure: No potential conflict of interest.
Received: 07.01.14 **Accepted:** 07.03.14
Citation: EMJ Urol. 2014;1:90-96.

ABSTRACT

There is a trend for the increased adoption of minimally invasive techniques of radical prostatectomy (RP) - laparoscopic (LRP) and robotic assisted (RARP) - from the traditional open radical retropubic prostatectomy (ORP), popularised by Partin et al. Recently there has been a dramatic expansion in the rates of RARP being performed, and there have been many early reports postulating that the learning curve for RARP is shorter than for LRP. The aim of this study was to review the literature and analyse the length of the LRP learning curves for the various outcome measures: perioperative, oncologic, and functional outcomes. A broad search of the literature was performed in November 2013 using the PubMed database. Only studies of real patients and those from 2004 until 2013 were included; those on simulators were excluded. In total, 239 studies were identified after which 13 were included. The learning curve is a heterogeneous entity, depending entirely on the criteria used to define it. There is evidence of multiple learning curves; however the length of these is dependent on the definitions used by the authors. Few studies use the more rigorous definition of plateauing of the curve. Perioperative learning curve takes approximately 150-200 cases to plateau, oncologic curve approximately 200 cases, and the functional learning curve up to 700 cases to plateau (700 for potency, 200 cases for continence). In this review, we have analysed the literature with respect to the learning curve for LRP. It is clear that the learning curve is long. This necessitates centralising LRP to high volume centres such that surgeons, trainees, and patients are able to utilise the benefits of LRP.

Keywords: Learning curve, laparoscopic radical prostatectomy, prostate cancer.

INTRODUCTION

Radical prostatectomy is a recognised method of curative treatment for localised prostate cancer. Since the first laparoscopic radical prostatectomy (LRP) in 1997,[1] there has been a trend towards an increase in adoption of more minimally invasive techniques of radical prostatectomy (LRP and robotic assisted radical prostatectomy, RARP) from the traditional open radical retropubic prostatectomy (ORP), popularised by Partin et al.[2] This trend has been pioneered and driven by urologists in Europe.[3-5]

The purported advantages of LRP over ORP are reduced blood loss, reduced blood transfusion, improved cosmetic outcome, shorter time to resumption of normal activities, and shorter hospital stay.[5-7] Despite these advantages, the 2011 British Association of Urological Surgeons (BAUS) radical prostatectomy audit revealed that of the cases contributed, 26% were still performed by ORP.[8] Recently there has been a dramatic expansion in the rates of RARP being performed[9] and there have been some reports postulating that the learning curve for RARP is shorter than for LRP,[10,11] however this is still open to debate.

Coinciding with a similar rise in the rate of RARP being performed in the US, there has been a dramatic decline in the rates of prostatectomy performed by the laparoscopic route. Much of the reason for this change is the presumed longer learning curve for LRP over RARP, however this still is the subject of fierce debate. Aside from the long learning curve, the marketing pressures - more severe in the US than elsewhere - have placed pressures on surgeons to offer the latest technology.[12,13]

The recent systematic review and economic modelling of benefit and cost-effectiveness of RARP and LRP showed that RARP is more expensive than nationalised healthcare services, like the NHS in the UK, compared to LRP; however, this could be offset if there were lower positive surgical margin (PSM) rates and a higher volume (100-150 cases/year).[14] These studies, however, did not take into account the length of the learning curve, which could dramatically alter the cost-effectiveness of RARP during this period.

The aeronautical industry was the first to describe the 'learning curve' (LC) effect, where the amount of hours required to produce a product decreased in a uniform manner as the experience of workers increased.[15] The same is true of surgeons, however, the exact way to define the LC, the measures to use or indeed the definition of the completion of the LC varies widely and is the subject of debate.[16]

There is clearly much interest in the LC for minimally invasive radical prostatectomy for trainees, urologists, and healthcare providers around the world. It is also of importance to patients especially with the advent of new technologies (RARP) which affect the learning curve, something which was brought to the forefront by the UK General Medical Council Enquiry into the Bristol Paediatric Surgical Unit, where concerns were raised about patient exposure to early LCs of surgeons.[17]

The aim of this study was to review the literature and analyse the length of the LRP LCs for the various outcome measures: perioperative (blood loss, operative time, complications), oncologic PSM rate, biochemical recurrence [BCR]), and functional outcomes (urinary continence and potency). Finally, we will look at the LC for pentafecta attainment.

MATERIALS AND METHODS

A broad search of the literature was performed in November 2013 using the PubMed database. The following search terms were used during the literature search: "laparoscopic radical prostatectomy" and "learning", and "curve" or "proficiency", and "gain" and "curve". Reference lists of relevant articles were also searched for additional articles. The selection was limited to English language articles only. Only studies of real patients and those from 2004 until 2013 were included; those on simulators were excluded. Article abstracts were reviewed for suitability and further reviewed in full if they had information pertaining to LCs of urological procedures. 239 studies were identified after which 13 were included.

DISCUSSION

The LC is a heterogeneous entity, depending entirely on the criteria used to define it. The literature varies widely with respect to these criteria, the first question which arises is: what variable to use?[16] For radical prostatectomy these key performance indicators are relatively easy to define and represent the pentafecta outcomes as coined by Patel et al.[18] It is important within these variables that there is consistency in the definition of these variables, allowing comparison in a wider context. Clearly it is also important that other confounding factors are taken into consideration when comparing variables during the LC as these can have significant effects on learning. This includes D'Amico risk grouping, organisational factors (equipment/facilities), the surgical team experience, case mix etc.[16,19,20]

Perhaps one of the greatest debates and the greatest variability in the literature is the definition of the completion of the learning curve. Many authors define completion of the LC as: 'the time to achieve skills necessary to satisfactorily perform a surgical procedure.'[21] Using this definition, improvements in various outcomes (such as operative time) in consecutive cases are demonstrated, where there is a statistically significant difference between the last group and first group of patients.[22,23] Various statistical methods used to demonstrate the LC include simple linear regression, CUSUM, and fitting curve methods (e.g. locally weighted scatterplot smoothing [LOESS], negative exponential curves etc).[22,24,25]

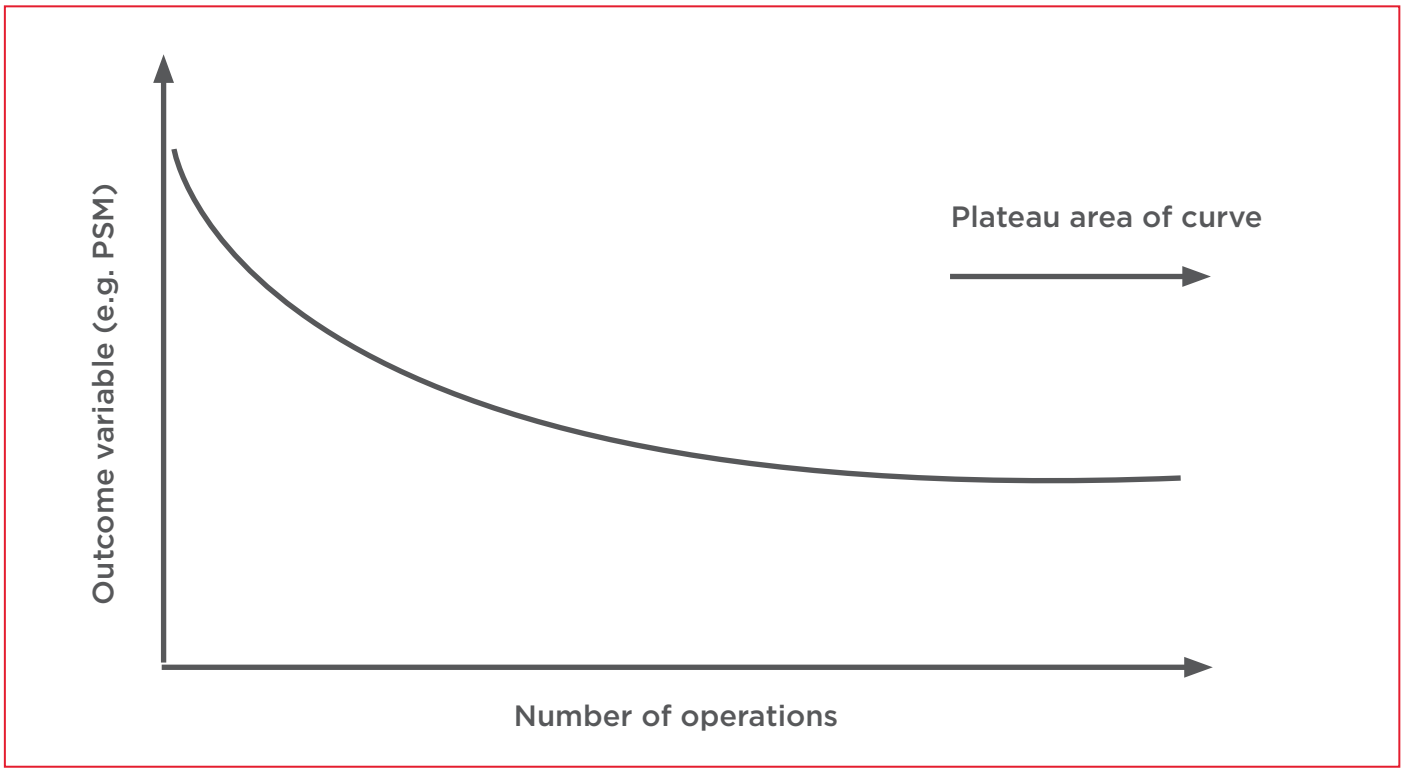

Figure 1: Graphical illustration of a learning curve, with the area of the curve showing the plateauing of the learning curve (denoted with an arrow).

These studies generally tend to use these methods of analysis as there are insufficient numbers of patients to show a plateauing of the LC.[16] This, however, does not reflect the true length of time required to complete the LC as there is no plateau (Figure 1). A better definition of completion of the LC may be: 'time to reach a level of experience after which repetition of technique yields no further improvement (LC plateau).'[21] Whilst showing a plateau in a performance indicator is taken as the best level achieved by a surgeon, it is imperative that this end plateau level is viewed within an acceptable 'expert' level, which is hard to define but is generally taken from the worldwide literature.

Due to the heterogeneity of the literature with regard to the definition used, we have used both of these definitions.

The Perioperative Learning Curve:

Table 1 summarises the evidence for the length of the perioperative LC (blood loss, operative time, and complications).

The perioperative LC is the most frequently published LC in the literature. This is the easiest for surgeons to gather and is often uploaded into databases immediately after the operation. As such, these are the most likely variables to be completely recorded in a database, and therefore, most commonly published on. That said, it is important to ensure that the definitions of when operative time is calculated from are standardised to allow comparisons between studies.

The blood loss LC is the earliest to be completed out of the variables. Most of the studies published, however, observe falling blood losses as experience increases rather than a plateauing of the LC.[23,26,27] There are, however, two studies which have shown a plateauing of the LC. The first, by Rodriguez et al.,[28] showed a plateau of blood loss that was constant over the first 200 cases; this however plateaued at 500 ml, highlighting the importance of identifying the value at which blood loss plateaus, as the systematic review of blood loss outcomes for LRP showed a much lower level.[29] Another study of the LC, by Good et al.,[25] showed a plateauing of the blood loss LC after 150 cases.

The next LC to be completed is that of the complications. This is dependent on the generation

Table 1: Studies evaluating the perioperative learning curve. Where plateau was achieved, the number of cases is indicated.

Blood loss	Blood loss	Operative Time	Operative Time	Complications	Complications
No Plateau	**Plateau**	**No Plateau**	**Plateau**	**No Plateau**	**Plateau**
Vasdev et al.[24]	Good et al.[25] – 150 cases	Ghavamian et al.[31]	Good et al.[25] – 250 cases	Ghavamian et al.[31]	Good et al.[25] – 150 cases
Hellawell et al.[23]	Rodriguez et al.[28] – 0 cases*	Poulakis et al.[32]		Hellawell et al.[23]	Hruza et al.[30] – 250 cases**
Sultan et al.[27]		Hellawel et al.[23]			
		Rodriguez et al.[28]			

* Plateau from 0 cases, but plateaued at 500 ml blood loss.
** 250 cases for third generation laparoscopic radical prostatectomy surgeons, 700 cases for first generation surgeons.

Table 2: Studies evaluating the oncologic learning curve. Where plateau was achieved, the number of cases is indicated.

PSM	PSM	BCR	BCR
No Plateau	**Plateau**	**No Plateau**	**Plateau**
Baumert et al.[33]	Good et al.[25] – pT2 200 cases, pT3 200 cases	Vickers et al.[35]	Good et al.[25] – 150 cases
Hellawell et al.[23]	Secin et al.[34] – 200 – 250 cases		
	Rodriguez et al.[28] – 200 cases		

PSM: positive surgical margin; BCR: biochemical recurrence.

of surgeon that is being investigated. A large study by Hruza et al.,[30] with over 2,200 patients, found that first generation LRP surgeons had a significantly longer LC (700 cases) to plateau than third generation surgeons, who had a much shorter learning curve of 250 cases. Another study, by Good et al.,[25] found the plateauing of the curve occurred after 150 cases. Both of these studies used the standardised Clavien-Dindo classification for grading of complications. Other studies that did not show a plateauing of the curve, but instead showed falling rates, demonstrated this after a similar numbers of cases; however, these studies did not use the standardised Clavien-Dindo classification.[23,31]

The time to complete the Operative time (Op time) LC is variable in the literature. Many studies that do not show plateauing due to lack of numbers do show a continuous falling LC throughout their series.[23,31,32] Op time, however, was found to be more lengthy to achieve by Good et al.,[25] likely due to the introduction of a nerve sparing technique after 100 cases. This, the authors concluded, was likely the reason for the curve to plateau at a later stage (after 250 cases).

The Oncologic Learning Curve:

Table 2 summarises the evidence for the length of the oncologic LC (PSM rates and BCR).

The oncologic LC consists of two variables: the PSM rate and the BCR rate. The PSM rate features more commonly in the literature with BCR rate exceedingly rare in the LC context, likely due to the difficulties in collecting PSA levels to provide meaningful follow-up data in large tertiary referral centres.

Baumert et al.[33] showed a declining PSM rate for both pT2 disease and pT3 disease after 100 cases, however, these authors did not have sufficient numbers to show a plateauing of the LC. Good et al.[25] showed a plateauing of both the pT2 and pT3 PSM LCs after 200 cases. Rodriguez et al.[28] also showed a plateauing of the pT2 LC after 200 cases. Further to this evidence, Secin et al.,[34] in an international multicentre study involving 51 different surgeons and 1,862 patients, showed a similar plateauing of the PSM LC of approximately 200-250 cases. The authors found that prior open experience or the generation of surgeon did not influence the time to achievement of the LC.

There is a paucity of data on the BCR LC, despite this being the most clinically important oncological outcome other than disease specific mortality. The study of Good et al.[25] showed a plateauing of the BCR LC after only 150 cases, however, after a plateau the BCR rate then continued to decrease. The authors postulated that this was likely due to the shorter follow-up time of the later cohort and not a lack of plateauing of the LC. Vickers et al.,[35] in another large international multicentre study involving 29 different surgeons and 4,702 patients, investigated the BCR LC. This study demonstrated a lower BCR rate as experience improves, however, it failed to plateau even after 1,000 cases. The authors demonstrated that this was slower than for ORP.

The Functional Learning Curve:

Table 3 summarises the evidence for the length of the LC associated with best functional recovery (urinary continence and potency). The functional LC is known to be the longest and most difficult to achieve, not only in achieving good outcomes consistently but also in data collection, as most studies use continence at 12 months and potency as the endpoints. These both require a length of follow-up which requires dedicated database managers to keep outcome recording updated. This is a major reason for the paucity of functional LC studies for LRP.

Huang et al.,[36] in their single surgeon series of 160 patients, showed a falling incontinence rate, which was better for the last group than the first group in the series; however, they were unable to show any plateau, likely due to the lack of patients in their series. Good et al.,[25] in their single surgeon series, were able to show a plateauing of the continence LC after 250 cases. Eden et al.,[37] in their study of their first 1,000 LRPs - whilst not specifically focusing on the functional LC - did suggest that it would take 200-250 cases to achieve it, except for potency, which continued to improve even after 700 cases.

Similarly, after 250 cases of bilateral nerve sparing endoscopic extraperitoneal radical prostatectomy (nsEERPE), the series by Good et al.[25] did not show a plateauing of the potency LC. Their series' potency rate at 12 months was 52% for bilateral nsEERPE. Both studies[25,37] commented that the potency LC is the longest and hardest to achieve.

The pentafecta attainment LC, the 'holy grail' for prostatectomists, is the least published. We were only able to find one publication on this in the literature by Good et al.[25] In this study the

Table 3: Studies evaluating the functional learning curve. Where plateau was achieved, the number of cases is indicated.

Continence	Continence	Potency	Potency
No Plateau	**Plateau**	**No Plateau**	**Plateau**
Huang et al.[36]	Good et al.[25] – 250 cases	Good et al.[25] – no plateau after 250 cases	None found
		Eden et al.[37] – still improving after 700 cases	

authors were unable to demonstrate a plateauing of the LC, despite demonstrating plateauing for all curves except the potency LC. The authors identified that the pentafecta LC in their series closely matched that of the potency LC. In their series the overall pentafecta attainment was 47%, much lower than that previously demonstrated in an RARP series by Patel et al.,[18] who quoted a pentafecta attainment at 12 months of 70.8%. It is important to note that these were on different patient cohorts.

CONCLUSION

In this review, we have analysed the literature with respect to the LC for LRP. It is clear that the LC is long, approximately 200-250 cases for non-nerve sparing proficiency, however, much longer (in excess of 700 cases) for nerve sparing procedures, which deliver the best functional outcomes. Clearly much of this evidence comes from single surgeon series, which limits it, but nevertheless it gives us real insight into the length of experience required to achieve the LCs for this complex operation.

Given the long LC required, some countries such as the US have transferred to robotic surgery with the promise that the LC is shorter,[38-40] however, recently with more rigorous studies, questions have been raised as to the true length of the LC required for RARP.[41,42] Studies comparing the plateauing of the pentafecta LCs between LRP and RARP are required as trainees and healthcare systems have made significant investments in robotics with hopes of shorter LCs and improved outcomes despite a lack of evidence.

One thing is certain from the evidence demonstrated, volume is critically important for surgeons and outcomes. A surgeon in training, performing 20–30 cases per year, may take over 10 years to achieve the LC, and may only achieve the potency LC and therefore pentafecta LC at retirement. It is critically important that both trainees and surgeons embarking on prostatectomy be situated in high-volume centres to ensure that patients do not suffer reduced quality of life whilst surgeons are on their LC. This will also help surgeons to develop quickly, as has been shown in large, pioneering centres such as Leipzig,[43,44] where institutional experience, as opposed to individual experience, provides the quality assurance sought by patients.

REFERENCES

1. Schuessler WW et al. Laparoscopic radical prostatectomy: initial short-term experience. Urology. 1997;50(6):854-7.

2. Partin AW et al. Serum PSA after anatomic radical prostatectomy. The Johns Hopkins experience after 10 years. Urol Clin North Am. 1993;20(4):713-25.

3. Guillonneau B et al. [Laparoscopic radical prostatectomy. Preliminary evaluation after 28 interventions]. Presse Med. 1998;27(31):1570-4.

4. Rassweiler J et al. Laparoscopic radical prostatectomy--the experience of the German Laparoscopic Working Group. Eur Urol. 2006;49(1):113-9.

5. Stolzenburg JU et al. Endoscopic extraperitoneal radical prostatectomy: oncological and functional results after 700 procedures. J Urol. 2005;174(4 Pt 1):1271-5; discussion 5.

6. Tooher R et al. Laparoscopic radical prostatectomy for localized prostate cancer: a systematic review of comparative studies. J Urol. 2006;175(6):2011-7.

7. Stolzenburg JU et al. Endoscopic extraperitoneal radical prostatectomy: evolution of the technique and experience with 2400 cases. J Endourol. 2009;23(9):1467-72.

8. Laird A SG et al. The UK Radical Prostatectomy Audit 2011. BJU Int. 2012;109(Supp 7):3.

9. Mirheydar HS, Parsons JK. Diffusion of robotics into clinical practice in the United States: process, patient safety, learning curves, and the public health. World J Urol. 2012.

10. Atug F et al. Positive surgical margins in robotic-assisted radical prostatectomy: impact of learning curve on oncologic outcomes. Eur Urol. 2006;49(5):866-71; discussion 71-2.

11. Ahlering TE et al. Successful transfer of open surgical skills to a laparoscopic environment using a robotic interface: initial experience with laparoscopic radical prostatectomy. J Urol. 2003;170(5):1738-41.

12. Mottrie A, Ficarra V. Can robot-assisted radical prostatectomy still be considered a new technology pushed by marketers? The IDEAL Evaluation. Eur Urol. 2010;58(4):525-7.

13. Touijer K. Marketing versus science: a fight between necessary evil and stern good over the adoption of new technology in medicine. Eur Urol. 2010;58(4):522-4.

14. Ramsay C et al. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. Health Technol Assess. 2012;16(41):1-313.

15. Wright TP. Factors affecting the cost of airplanes. J Aeronaut Sci. 1936;3(4):122-8.

16. Khan N et al. Measuring the surgical 'learning curve': methods, variables and competency. BJU Int. 2014;113(3):504-8.

17. The Bristol Royal Infirmary Inquiry. Care in the operating theatre and the learning curve. 2001. Available at: http://www.bristol-inquiry.org.uk/final_report/annex_a/chapter_14_.htm.

18. Patel VR et al. Pentafecta: a new concept for reporting outcomes of robot-assisted laparoscopic radical prostatectomy. Eur Urol. 2011;59(5):702-7.

19. Cook JA et al. Statistical evaluation of learning curve effects in surgical trials. Clin Trials. 2004;1(5):421-7.

20. Subramonian K, Muir G. The 'learning curve' in surgery: what is it, how do we

measure it and can we influence it? BJU Int. 2004;93(9):1173-4.

21. Lumen N et al. Safe introduction of robot-assisted radical prostatectomy after a training program in a high-volume robotic centre. Urol Int. 2013;91(2):145-52.

22. Ramsay CR et al. Assessment of the learning curve in health technologies. A systematic review. Int J Technol Assess Health Care. 2000;16(4):1095-108.

23. Hellawell GO, Moon DA. Laparoscopic radical prostatectomy: reducing the learning curve. Urology. 2008;72(6):1347-50.

24. McNeill AS et al. Endoscopic extraperitoneal radical prostatectomy: critical analysis of outcomes and learning curve. BJU Int. 2010;106(10):1537-43.

25. Good DW et al. Analysis of the pentafecta learning curve for laparoscopic radical prostatectomy. World J Urol. 2013 [Epub ahead of print].

26. Vasdev N et al. Developing a laparoscopic radical prostatectomy service: defining the learning curve. J Endourol. 2012;26(7):903-10.

27. Sultan MF et al. Blood loss during laparoscopic radical prostatectomy. J Endourol. 2009;23(4):635-8.

28. Rodriguez AR et al. Laparoscopic extraperitoneal radical prostatectomy: impact of the learning curve on perioperative outcomes and margin status. JSLS. 2010;14(1):6-13.

29. Ficarra V et al. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. Eur Urol. 2009;55(5):1037-63.

30. Hruza M et al. Complications in 2200 consecutive laparoscopic radical prostatectomies: standardised evaluation and analysis of learning curves. Eur Urol. 2010;58(5):733-41.

31. Ghavamian R et al. Overcoming the steep learning curve of laparoscopic radical prostatectomy: single-surgeon experience. J Endourol. 2004;18(6):567-71.

32. Poulakis V et al. Laparoscopic radical prostatectomy: prospective evaluation of the learning curve. Eur Urol. 2005;47(2):167-75.

33. Baumert H et al. Impact of learning curve in laparoscopic radical prostatectomy on margin status: prospective study of first 100 procedures performed by one surgeon. J Endourol. 2004;18(2):173-6.

34. Secin FP et al. The learning curve for laparoscopic radical prostatectomy: an international multicenter study. J Urol. 2010;184(6):2291-6.

35. Vickers AJ et al. The surgical learning curve for laparoscopic radical prostatectomy: a retrospective cohort study. Lancet Oncol. 2009;10(5):475-80.

36. Huang JL et al. [Postoperative urinary continence and learning curve after laparoscopic radical prostatectomy]. Beijing Da Xue Xue Bao. 2012;44(4):563-7.

37. Eden CG. The first 1000 cases of laparoscopic radical prostatectomy in the UK: evidence of multiple 'learning curves'. BJU Int. 2009;103(9):1224-30.

38. Gumus E et al. The learning curve of robot-assisted radical prostatectomy. J Endourol. 2011;25(10):1633-7.

39. Gyomber D et al. Robotic prostatectomy learning curves-an independent analysis of 13 unrelated surgeons over 5 years. Journal of Endourology. 2011;25:A108.

40. O'Malley PJ et al. Robotic radical prostatectomy in Australia: initial experience. World J Urol. 2006;24(2):165-70.

41. Sooriakumaran P et al. Learning curve for robotic assisted laparoscopic prostatectomy: a multi-institutional study of 3794 patients. Minerva Urol Nefrol. 2011;63(3):191-8.

42. Sharma NL et al. First 500 cases of robotic-assisted laparoscopic radical prostatectomy from a single UK centre: learning curves of two surgeons. BJU Int. 2011;108(5):739-47.

43. Wyler SF et al. Short-, intermediate-, and long-term quality of life after laparoscopic radical prostatectomy--does the learning curve of LRP have a negative impact on patients' quality of life? Eur Urol. 2007;51(4):1004-12; discussion 12-4.

44. Stolzenburg JU et al. Modular training for residents with no prior experience with open pelvic surgery in endoscopic extraperitoneal radical prostatectomy. Eur Urol. 2006;49(3):491-8; discussion 9-500.

LAPAROSCOPIC RADICAL PROSTATECTOMY IN THE ERA OF ROBOT-ASSISTED TECHNOLOGY

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Disclosure: No potential conflict of interest.
Received: 25.01.14 **Accepted:** 28.02.14
Citation: EMJ Urol. 2014;1:97-103.

ABSTRACT

In this work the outcomes of laparoscopic radical prostatectomy (LRP) with regard to perioperative morbidity, oncological effectiveness, as well as postoperative continence and potency preservation are being reviewed and compared with the gold standard open radical prostatectomy. In addition, the limitations of LRP are being presented in contrast to the advancement offered by the emerging robotic assisted radical prostatectomy in an attempt to reveal whether laparoscopic approach still has a role in the era of robot-assisted technology.

Keywords: Laparoscopic, radical, prostatectomy, prostate, cancer.

INTRODUCTION

Prostate cancer is the most frequently newly-diagnosed cancer and the third most common cause of male cancer-specific mortality in Europe.[1] Numerous different types of treatments against this neoplasia are available today, offering long-term survival in the vast majority of patients. Among them, radical prostatectomy - performed either via open surgery, laparoscopically, or under robotic assistance - is considered the mainstay in the management of localised and locally advanced prostate cancer.[2] Laparoscopic radical prostatectomy (LRP) was first introduced in 1997 by Shuessler et al.[3] but further modifications over the original technique by Guillonneau et al.[4] were deemed necessary before the acceptance of the technique worldwide. In this work, the outcomes of LRP with regard to perioperative morbidity, oncological effectiveness as well as postoperative continence, and potency preservation are being reviewed and compared with the gold-standard open radical prostatectomy (ORP). In addition, the limitations of LRP are being presented in contrast to the advancement offered by the emerging robotic-assisted radical prostatectomy (RARP) in an attempt to reveal whether laparoscopic approach still has a role in the era of robot-assisted technology.

OUTCOMES

Perioperative Outcomes

LRP is considered a minimally invasive surgical treatment option in the management of prostate cancer given that the procedure has been associated with minimum perioperative morbidity, short hospitalisation, and early recovery by the majority of reporting literature (Table 1).

Decreased intraoperative blood loss as compared with ORP is one of the fundamental benefits of the laparoscopic procedure, since CO_2 insufflation pressure diminishes venous bleeding and allows the accomplishment of the procedure in a relatively bloodless field. Touijer and colleagues,[5] in a prospective non-randomised study including 612 patients subjected to LRP and 818 subjected to ORP, documented that laparoscopy was

Table 1: Perioperative outcomes of laparoscopic radical prostatectomy.

Author	Type of Study	Comparative groups	Operative Time
Touijer[5]	Prospective non randomised	612 LRP versus 818 ORP	• Lower blood loss and transfusion rates
Coelho[6]	Meta-analysis of data from high volume centres	ORP, LRP, RARP	• Similar complications rates with ORP and RARP • Lower blood loss and transfusion rates than ORP
Tewari[7]	Meta-analysis	ORP, LRP, RARP	• Lower blood loss, transfusion rates, and hospitalisation than ORP • Low intraoperative complication rates • Similar perioperative complication rates with ORP but higher than RARP • Similar readmission rates with ORP but higher than RARP
Sugihara[8]	Propensity-score matching analysis	1627 LRP and ORP propensity-score matched pairs	• Better complication rates • Lower transfusion rates • Shorter hospitalisation • Longer operative time
Liu[9]	Retrospective review of a prospective database	4036 LRP and 1283 ORP	• Longer operative time • Lower transfusions • Lower hospitalisation • Lower perioperative complication rates and mortality
Caras[11]	Retrospective review of a nationwide database	8391 LRP versus 2278 ORP	• Lower morbidity, surgical site infections, mortality, wound disruption, urinary tract infection, bleeding, and sepsis or septic shock

ORP: open radical prostatectomy; LRP: laparoscopic radical prostatectomy; RARP: robotic assisted radical prostatectomy.

associated with less blood loss and a lower transfusion rate than ORP (315 versus 1,267 ml and 3% versus 49% accordingly). Similarly, a weighted mean of perioperative transfusion in 3.5% of LSP cases versus 20.1% after ORP was calculated in a large meta-analysis of data reported by high-volume centres.[6] Accordingly, a more recent systematic review verified the superiority of endoscopic techniques in terms of blood loss over open approach.[7]

Patients subjected to LRP can be discharged as soon as the drain has been removed and bowel function has returned, usually after the second postoperative day. However, reported LRP hospitalisation varies greatly among studies given that different departments entail different rehabilitation protocols. In general, in many institutes - especially in Europe - patients remain hospitalised until the urethrovesical anastomosis is tested by cystography and the catheter is removed (usually between the fifth and seventh postoperative day). In contrast, US patients are regularly discharged from hospital soon after surgery and return after a few days to remove the urinary catheter. Despite the abovementioned heterogeneity of LSP hospitalisation reports, the procedure has been associated with shorter hospital stay than open prostatectomy as documented by several nationwide radical prostatectomy databases reporting data from both techniques.[8,9] The latter is not only due to minimal perioperative blood loss after LRP, but also due to the minimisation of abdominal trauma that is responsible for a reduced postoperative pain and a rapid recovery. Pushing the envelope further in an attempt to decrease hospital cost, LRP has been performed even as a day case, without overnight stay, with an uneventful course.[10]

With regard to perioperative morbidity, LRP has been associated with decreased complications

compared with open prostatectomy. A recent analysis of the American College of Surgeons national, risk-adjusted surgical database (including data from 10,669 prostatectomies) revealed decreased incidence of overall and serious morbidity, mortality, surgical site complications, urinary tract infection, bleeding, and septic events for laparoscopy as compared with ORP.[11] In addition, a favourable overall complication rate for LRP was documented in an analysis based on the Japanese Diagnosis Procedure Combination database. Authors matched 1,627 LRP with a similar number of propensity-score matched ORP procedures, and found that the laparoscopic approach showed a better overall complication rate (3.4% versus 5.0%).[8]

Oncological Outcomes

Radical prostatectomy is an oncological operation performed with the intention to cure prostatic cancer. It is currently indicated only for cases of localised disease, where prostatic excision would offer complete tumour removal, and accordingly evidence of local or distal metastasis presents a contraindication for the approach. Positive surgical margins (PSM) in an excised specimen is an indicator that the radicality of tumour excision was not achieved, and indeed PSM has been clearly associated with an increased risk of future biochemical recurrence (BCR), local disease progression, and also the need for secondary cancer treatment.[12]

A significant variation of PSM rates among LRP literature is present mainly due to the fact that PSM rates in radical prostatectomy specimens are dependent on several factors, including the pathological stage of the disease, the surgeon's experience, and the quality of pathologic assessment.[13,14] A variation of PSM between 7-22% for pT2 and 26-55% for pT3 disease has been reported by high-volume centres, while no differences in overall PSM between LRP and ORP was evidenced in a cumulative analysis of comparative studies between the two techniques.[6,15]

The excellent long-term oncological effectiveness of LRP has been well documented in several studies with follow-up of more than 10 years (Table 2). Busch et al.,[16] in one of the largest LRP series (1,845 cases) with a mean follow-up of 5 years and patients followed-up to 11.3 years, reported that 5-year, 8-year, and 10-year overall BCR-free survival rates were 83.9%, 78.6%, and 75.6%, respectively. Similarly, Hruza et al.,[17] in one of the most recent reports on long-term oncological outcomes of LRP, reported that BCR-free survival rates at 10 years postoperatively for pT2, pT3a, and pT3b/4 staged patients were 80.2%, 47.4%, and 49.8%, respectively. In addition, the 10-year clinical progression-free survival rates were 97.2% (pT2), 84.4% (pT3a), and 78.1% (pT3b/4).

Functional Outcomes

Lack of standardisation in continence report after radical prostatectomy (most studies use no validated institutional questionnaires) renders comparative assessment of continence between studies very difficult.[18] Still, the wide accumulative experience with LRP has clearly indicated that the laparoscopic approach demonstrates excellent continence rates, equivalent with the open approach.[15] At 12 months, following LRP, continence rates ranging between 82-95% have been reported by high-volume centres with a trend for further improvement up to 97% at >18 months postoperatively.[6] Significant incontinence, defined as patients needing more than two pads per day, is reported in 1.3-6% of patients subjected to LRP as documented by centres using validated continence questionnaires.[19,20]

Potency is considered one of the most complicated parameters to assess the surgical quality of a particular radical prostatectomy technique. Many non-surgical independent factors such as age, preoperative erectile status, presence of comorbidities, emotional status, presence of partner, and others contribute significantly to the recovery of potency. In addition, assessment of postoperative erectile function is somewhat subjective as it is based on the patient's self-assessment, while different potency definitions are regularly used between studies. Accordingly, differences in potency reported by different studies could reflect not only differences on the quality of nerve sparing technique but also variations in baseline characteristics of studied populations and potency definition.

With all the above limitations of postoperative erectile function assessment taken into consideration, studies reporting potency rates after LRP demonstrate a wide variability of 32-85%.[21] Still, accumulative evidence has rendered the procedure equivalent to ORP in patients subjected to nerve sparing surgery.

Table 2: Oncological outcomes of laparoscopic radical prostatectomy.

Author	Type of Study	Outcome of LRP
Coelho[6]	Meta-analysis of data from high volume centres	• PSMs 12.4% for pT2 and 39.2% for pT3 disease • Similar PSM with ORP but higher than RARP
Ficarra[15]	Meta-analysis of comparative studies	• Similar oncologic outcomes with ORP and RARP
Busch[16]	Retrospective cohort	• 29.2% overall PSM • 5-year, 8-year, and 10-year BCR-free survival rates were 83.9%, 78.6%, and 75.6%, respectively
Hruza[17]	Retrospective review of a prospective database	• BCR-free survival rates at 10 years were 80.2%, 47.4%, and 49.8% in patients staged pT2, pT3a, and pT3b/4, accordingly

PSM: positive surgical margins; BCR: biochemical recurrence; ORP: open radical prostatectomy; LRP: laparoscopic radical prostatectomy; RARP: robotic assisted radical prostatectomy.

Table 3: Functional outcomes of laparoscopic radical prostatectomy.

Author	Type of Study	Outcome of LRP
Coelho[6]	Meta-analysis of data from high-volume centres	• 84.8% continence at 12 months • 54% potency for BNS
Ficarra[15]	Meta-analysis of comparative studies	• LRP and ORP showed similar continence and potency rates • No significant differences with RARP
Stolzenburg[19]	Retrospective cohort	• 94.7% continence at 12 months • 84.9% potency at 12 months for BNS
Guillonneau[20]	Retrospective review of a prospective database	• 82.3% continence at 12 months • 85% of pts <70 years recovered spontaneous erections
Kilminster[22]	Meta-analysis using only data obtained from potent men before surgery	• 58-74% potency at 48 months

BNS: bilateral nerve sparing; ORP: open radical prostatectomy; LRP: laparoscopic radical prostatectomy; RARP: robotic assisted radical prostatectomy.

Kilminster et al.,[22] in a cumulative meta-analysis of studies reporting erectile function in preoperatively potent patients, calculated a similar cumulative range of potency rates after LRP versus ORP at 48 months (58-74% versus 49-74% accordingly). Selected literature reporting functional outcomes after LRP are presented in Table 3.

Pentafecta Outcome of LRP

Being a major oncological reconstructive urological operation, the three main goals of radical prostatectomy in order of importance are: to cure cancer, to maintain urinary continence, and to preserve potency. The term 'trifecta' was introduced to report the concomitant meeting of all these three parameters (a continent and potent patient with no BCR). To better address the ideal radical prostatectomy operation, two additional perioperative variables - the lack of complications and the negative surgical margins on surgical specimen - were added to the trifecta to form the 'pentafecta'. Good et al.[23] reported that, following a long learning curve of more than 250 operations, pentafecta could be achieved in up to 63% of LRP patients. Similarly, Si-Tu et al.[24] reported a 73% pentafecta outcome 60 months after LRP. In contrast, Asimakopoulos et al.[25] reported that out of 91 prospectively-followed LRP patients only

25 (27%) met the pentafecta. The majority (80%) of reported cases lost the pentafecta goal only due to missing potency recovery.

THE STIFF LEARNING CURVE OF LRP

As evidenced from above, LRP offers equivalent oncological and functional outcomes with ORP in the setting of minimally invasive surgery. Still, LRP has a major drawback which is the presence of a demanding and stiff learning curve with a significant impact on perioperative, functional, and oncological outcomes. The surgeon must perform a difficult reconstructive operation in a virtual two-dimensional environment, using instruments with restricted degrees of freedom, confronting a notable physical fatigue as a result of longer operating times and defective ergonomy. Hruza et al.,[26] analysing 2,200 consecutive patients who underwent LRP at a single institution, reported that first generation surgeons with a vast open surgical experience required 700 cases to reach a plateau in complication rates. Of notice, third generation surgeons reached the same plateau earlier, at 250 cases. In terms of PSM, Secin et al.[27] revealed that there was an apparent improvement in PSM rates up to a plateau at 200-250 surgeries. Once this plateau was reached, changes in PSM rates were relatively minimal. In contrast, Vickers et al.[28] reported a significant improvement in PSM rates even after 250 cases, demonstrating that for a patient treated by a surgeon with experience of 250 and 750 previous LRPs, the 5-year risk of BCR decreased from 16% to 9%, accordingly. Conclusively, significant training is required for a surgeon to achieve a basic level of competency to safely perform LRP and a long-lasting learning curve to provide optimum oncological outcomes.

ROBOT-ASSISTED SURGERY

The Fast and Widespread Diffusion of Robotic-Assisted Radical Prostatectomy

In contrast to laparoscopy, in the case of robotic-assisted surgery the efficient translation of human hand motion into robotic arm movement and the three-dimensional vision allows a rapid integration of open surgical experience to robotic-assisted surgery. Sejima et al.,[29] during the introduction of robotic technology to radical prostatectomy operations in their department, used a RARP termination protocol, which was applied when there was excessive bleeding or surgical time. Based on the above criteria, no conversion to open surgery was deemed necessary during the first 100 cases. In addition to improved safety, even from the initial cases, long-term oncological data of RARP became available and demonstrated that the robotic assistance does not compromise the oncological effectiveness and functional outcomes of radical prostatectomy.

According to the recent European Association of Urology (EAU) guidelines on robotic surgery, RARP offers a long BCR-free survival equivalent to the other radical prostatectomy approaches in addition to not-inferior continence and potency rates. Furthermore, a trend towards faster recovery of potency and continence becomes evident as cumulative data are maturing.[30] This explains why RARP has gained significant popularity. Obviously, being competent to safely perform a RARP does not mean that a surgeon has reached the end of the learning curve, and in accordance to the other radical prostatectomy approaches, a long-lasting learning curve exists for robotic-assisted approach as well.[31] Still, robotic surgery is considered easier to master than laparoscopy, and once mastered is definitely more comfortable for the surgeon.

Taking the above into consideration, in expert hands LRP and RARP are at least comparable in terms of oncological and functional effectiveness, however, significant differences still exist in required learning curve and surgeon's fatigue during surgery in favour of robotic approach.

Role of LRP in the Era of Robot-Assisted Technology

Currently available robotic technology is expensive and becomes cost-effective only by the centralisation of care in high-volume centres in Western countries.[32] Until robotic technology prices drop - due to industrial competition or the availability of cheaper robots - laparoscopy will remain the only minimally invasive surgical treatment option for the majority of worldwide prostate cancer patients. In addition, laparoscopic instrumentation is constantly evolving to address the limitations of laparoscopy. Three-dimensional laparoscopes are available today offering stereoscopic view in conventional laparoscopic surgery. In addition, articulating laparoscopic instruments increase the degrees of freedom, diminish instrument classing, and facilitate intracorporeal suturing. Using this novel technology the learning curve of laparoscopy

is expected to be reduced and its worldwide adaptation to increase. Finally, particular concepts reducing morbidity in laparoscopic surgery cannot be integrated by current robotic technology. Miniaturising laparoscopic instruments is a trend in laparoscopy aiming to reduce abdominal trauma and scar formation caused by laparoscopic trocar insertion. The so-called 'needlescopic' or 'mini-laparoscopic' surgery uses 3-4 mm laparoscopic instruments (solely or in combination with conventional or multiport trocar devices), providing a scarless result (given that 3-4 mm incisions do not require official suturing). Current robotic arm technology is too large to fit into the mini-laparoscopic setting, which can be utilised only via the conventional laparoscopic approach.

COST OF LRP

It is not the purpose of this work to discuss the cost of LRP given that data on the subject are of low quality (lack of randomised comparative studies) and significant variations of cost estimations exist among different studies, different countries, and different departments. Generally, the cost of LRP is considered more than ORP due to the added expenses associated with the cost of disposable laparoscopic equipment. Still, it should be mentioned that at least part of this added cost is equated by the reduced hospitalisation and morbidity of the laparoscopic approach. In contrast, LRP is considered less expensive than robotic-assisted surgery mainly due to the fixed capital and maintenance charges for the robotic system.[33]

CONCLUSION

In conclusion, a wealth of high quality data have documented that LRP is a surgical approach offering favourable oncological and functional outcomes with minimum morbidity. When compared to RARP, the conventional laparoscopic approach demonstrates equivalent safety and efficacy, yet with a longer learning curve and a restricted ergonomy during operation. Still laparoscopy is more cost-effective than RARP and available worldwide. Integration of novel laparoscopic instruments in LRP can address the majority of laparoscopic drawbacks and further increase its adaptation in the urological community.

REFERENCES

1. Ferlay J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403.

2. Heidenreich A et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol. 2011;59(1):61-71.

3. Schuessler WW et al. Laparoscopic radical prostatectomy: initial short-term experience. Urology. 1997;50(6):854-7.

4. Guillonneau B et al. Laparoscopic radical prostatectomy: technical and early oncological assessment of 40 operations. Eur Urol. 1999;36:14-20.

5. Touijer K et al. Comprehensive prospective comparative analysis of outcomes between open and laparoscopic radical prostatectomy conducted in 2003 to 2005. J Urol. 2008;179(5):1811–7.

6. Coelho RF et al. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: a critical review of outcomes reported by high-volume centers. J Endourol. 2010;24(12):2003-15.

7. Tewari A et al. Positive surgical margin and perioperative complication rates of primary surgical treatments for prostate cancer: a systematic review and meta-analysis comparing retropubic, laparoscopic, and robotic prostatectomy. Eur Urol. 2012;62(1):1-15.

8. Sugihara T et al. Comparisons of perioperative outcomes and costs between open and laparoscopic radical prostatectomy: a propensity-score matching analysis based on the Japanese Diagnosis Procedure Combination database. Int J Urol. 2013;20(3):349-53.

9. Liu JJ et al. Perioperative outcomes for laparoscopic and robotic compared with open prostatectomy using the National Surgical Quality Improvement Program (NSQIP) database. Urology. 2013;82(3):579-83.

10. Dudderidge TJ et al. Evolution of care pathway for laparoscopic radical prostatectomy. J Endourol. 2012;26(6):660-5.

11. Caras RJ et al. Laparoscopic Radical Prostatectomy Demonstrates Less Morbidity Than Open Radical Prostatectomy: An Analysis of the American College of Surgeons-National Surgical Quality Improvement Program Database with a Focus on Surgical Trainee Involvement. J Endourol. 2013. [Epub ahead of print].

12. Yossepowitch O et al. Positive surgical margins in radical prostatectomy: outlining the problem and its long-term consequences. Eur Urol. 2009;55(1):87-99.

13. Secin F et al. The Learning Curve for Laparoscopic Radical Prostatectomy: An International Multicenter Study. J Urol. 2010;184(6):2291–6.

14. Fontenot PA, Mansour AM. Reporting positive surgical margins after radical prostatectomy: time for standardization. BJU Int. 2013;111(8):E290-9.

15. Ficarra V et al. Retropubic, laparoscopic, and robot assisted radical prostatectomy: a systematic review and cumulative analysis of comparative studies. Eur Urol. 2009;55(5):1037-63.

16. Busch J et al. Long-term oncological and continence outcomes after laparoscopic radical prostatectomy: a single-centre experience. BJU Int. 2012;110(11 Pt C):E985-90.

17. Hruza M et al. Long-term oncological outcomes after laparoscopic radical prostatectomy. BJU Int. 2013;111(2):271-80.

18. Touijer K, Guillonneau B. Laparoscopic radical prostatectomy: a critical analysis of surgical quality. Eur Urol. 2006;49(4):625-32.

19. Stolzenburg JU et al. Endoscopic

extraperitoneal radical prostatectomy: evolution of the technique and experience with 2400 cases. J Endourol. 2009;23(9):1467-72.

20. Guillonneau B et al. Laparoscopic radical prostatectomy: assessment after 550 procedures. Crit Rev Oncol Hematol. 2002;43(2):123-33.

21. Ferronha F et al. Is there any evidence of superiority between retropubic, laparoscopic or robot-assisted radical prostatectomy? Int Braz J Urol. 2011;37(2):146-58.

22. Kilminster S et al. Predicting erectile function outcome in men after radical prostatectomy for prostate cancer. BJU Int. 2012;110(3):422-6.

23. Good DW et al. Analysis of the pentafecta learning curve for laparoscopic radical prostatectomy. World J Urol. 2013. [Epub ahead of print].

24. Si-Tu J et al. Prospective evaluation of pentafecta outcomes at 5 years after laparoscopic radical prostatectomy: results of 170 patients at a single center. Neoplasma. 2013;60(3):309-14.

25. Asimakopoulos AD et al. Laparoscopic versus robot-assisted bilateral nerve-sparing radical prostatectomy: comparison of pentafecta rates for a single surgeon. Surg Endosc. 2013;27(11):4297-304.

26. Hruza M et al. Complications in 2200 consecutive laparoscopic radical prostatectomies: standardised evaluation and analysis of learning curves. Eur Urol. 2010;58(5):733-41.

27. Secin FP et al. The learning curve for laparoscopic radical prostatectomy: an international multicenter study. J Urol. 2010;184(6):2291-6.

28. Vickers AJ et al. The surgical learning curve for laparoscopic radical prostatectomy: a retrospective cohort study. Lancet Oncol. 2009;10(5):475-80.

29. Sejima T et al. Robot-assisted radical prostatectomy: a case series of the first 100 patients constitutional introduction and implementation on the basis of comprehensive department of minimal invasive surgery center. BMC Res Notes. 2013;6:436.

30. Merseburger AS et al. EAU guidelines on robotic and single-site surgery in urology. Eur Urol. 2013;64(2):277-91.

31. Mirheydar HS, Parsons JK. Diffusion of robotics into clinical practice in the United States: process, patient safety, learning curves, and the public health. World J Urol. 2013;31(3):455-61.

32. Stitzenberg KB et al. Trends in radical prostatectomy: centralization, robotics, and access to urologic cancer care. Cancer. 2012;118(1):54-62.

33. Ramsay et al. Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer. Health Technol Assess. 2012;16(41):1-313.

ROBOTIC RADICAL CYSTECTOMY FOR BLADDER CANCER: CURRENT PERSPECTIVES

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Disclosure: No potential conflict of interest.
Received: 30.11.13 **Accepted:** 02.03.14
Citation: EMJ Urol. 2014;1:104-110.

ABSTRACT

The most effective local treatment of muscle invasive bladder cancer and non-invasive, high-grade bladder tumours that recur or progress despite intravesical therapies, is open radical cystectomy (RC), extended pelvic lymph node (LN) dissection with urinary diversion. Performing these complex procedures using pure laparoscopy is extremely difficult. On the other hand, the surgical robot has the advantage of enabling the console surgeon to perform complex procedures more easily, providing three-dimensional (3D) and magnified views, higher grades of wristed hand movements, and decreased hand tremor, while the fourth robotic arm offers additional assistance and tissue retraction which facilitates the learning curve. The number of centres performing robot-assisted radical cystectomy (RARC) is increasing. Although most of the centres perform extracorporeal urinary diversion following RARC, very few centres - including ours - have reported their outcomes on RARC with total intracorporeal urinary diversion. Some of the articles, comparing open RC versus RARC, have suggested similar outcomes in terms of operative time, mean LN yield, positive surgical margin (PSM) rates, and complication rates, whereas others have suggested decreased estimated blood loss, transfusion rate, complications, length of hospital stay, wound problems, time to flatus, and time to regular diet in the postoperative period in RARC patients. The surgical technique of total intracorporeal RARC with urinary diversions is still evolving, and these complex robotic procedures seem to be technically feasible with good intermediate-term oncologic results, acceptable morbidities, excellent short-term surgical and pathological outcomes, and satisfactory functional results.

Keywords: Robotic radical cystectomy, bladder cancer, minimally invasive surgery, intracorporeal urinary diversion.

INTRODUCTION

Open radical cystectomy (RC), bilateral extended pelvic lymph node (LN) dissection, and urinary diversion is the gold standard surgical approach in the management of muscle invasive bladder cancer in addition to high-grade, recurrent, non-invasive tumours.[1] However, minimally invasive surgical approaches have attracted great interest, particularly following the introduction of the da Vinci-S four-arm surgical robot (Intuitive Surgical, Sunnyvale, CA). Thus, robot-assisted radical cystectomy (RARC) is increasingly being performed worldwide. Herein, we summarised the current literature on RARC.

RARC PROCEDURE

Briefly, the whole procedure consists of three main steps including neurovascular bundle (NVB)-sparing RARC, robotic bilateral extended pelvic LN dissection, and extracorporeal or intracorporeal urinary diversion.

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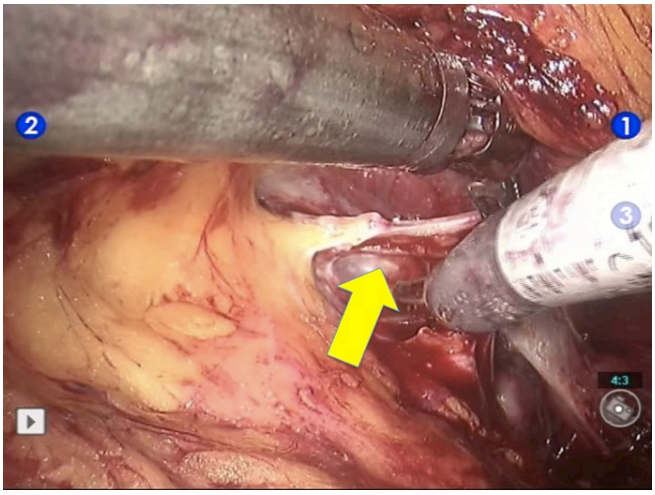

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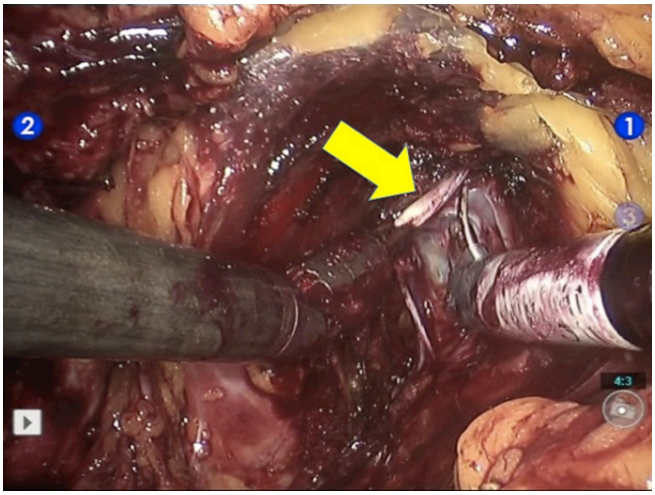

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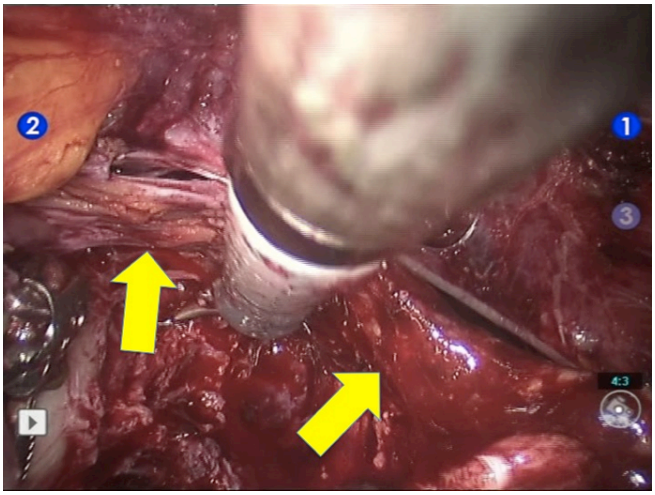

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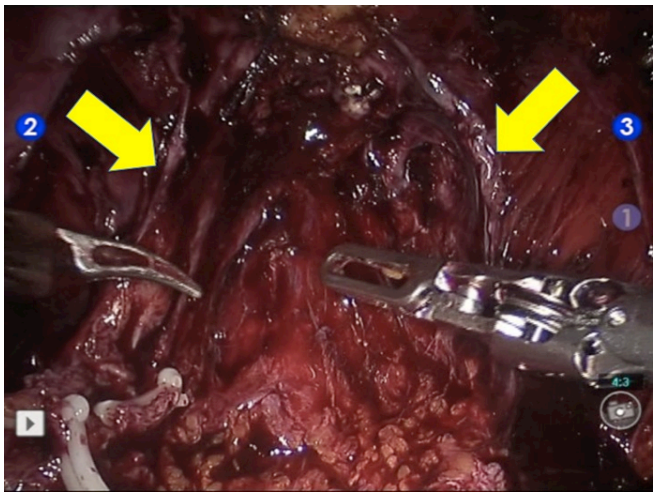

Figure 1A: High anterior release neurovascular bundle preservation (right side, arrow).
Figure 1B: High anterior release neurovascular bundle preservation (left side, arrow).
Figure 1C: Preserved neurovascular bundle (left side, arrows).
Figure 1D: Preserved bilateral neurovascular bundles in the pelvis (arrows).
Obtained from Prof Balbay and Dr Canda's own robotic surgical procedure.

Step 1: NVB-Sparing RARC

The surgical robot has the advantage of three-dimensional (3D) and magnified image capability, higher grades of wristed hand movements, and decreased hand tremor.[2] In addition, the fourth robotic arm facilitates this complex surgery by means of additional assistance and tissue retraction in the abdomen and pelvis.[2] In our experience, these technological details give significant advantages to the operating console surgeon that facilitates dissection of tissues and particularly the NVBs (Figure 1A-D), which is expected to have an impact on the postoperative functional outcomes and quality of life, namely urinary continence and penile erection.[2,3] Menon et al.[4] stated that NVB-sparing RARC combines the oncological principles of open surgery with the technical advantages of the surgical robot, allowing a precise, gentle, quick, and safe surgery. Of note, the presence of anatomic anomalies such as ureteric duplication could easily be surgically managed by using the surgical robot.[5]

A positive surgical margin (PSM) rate of <10% was suggested as surgical oncological sufficiency in open RC.[6,7] Due to the published RARC literature including the International Robotic Cystectomy

Consortium (IRCC) series, a PSM rate of 0-8.9% was reported, which is in line with this requirement.[8-12] Most of the published literature comparing open versus robotic RC is retrospective and non-randomised, therefore a selection bias is inevitable in most of these studies. There are only two articles that prospectively compare open versus robotic approaches.[13,14] Estimated blood loss, quicker return of bowel function, and the lower use of inpatient narcotics were detected as the main advantages of the robotic approach.[13,14] A decreased complication rate seems to be another advantage of robotic surgery when compared to open approach. A number of comparative studies have reported decreased complication rates in the robotic groups due to modified Clavien classification,[15,16] whereas some others have reported similar complication rates.[14,17]

Step 2: Robotic Bilateral Extended Pelvic LN Dissection

A LN yield of >15 LNs was suggested for surgical oncological sufficiency in open RC.[18,19] RARC seems to maintain sufficient LN yield due to the published literature.[3,10,12,20] In our experience, the advantages gained from the use of the robotic surgical instruments with magnified 3D vision, used during robotic extended pelvic LN dissection, lead to delicate dissection of the lymphatic tissues (Figures 2 and 3). In order to acquire a sufficient amount of LNs following completion of RARC, we suggest initially performing at least 50 cases of robot-assisted radical prostatectomy (RARP) with pelvic LN dissection to gain sufficient experience and confidence with extended pelvic LN dissection.

We use a total of six trocars for this type of robotic surgery. A 12 mm camera port is placed 2 cm above the umbilicus in the midline. Regarding the robotic arms, two 8 mm robotic trocars are placed at the level of umbilicus, 8 cm apart from the camera port. The fourth arm robotic trocar is placed 3 cm above the iliac crest, as lateral as possible, on the right side of the patient. Two assistant trocars are placed on the left abdomen of the patient. A 15 mm trocar for inserting bowel staplers and endobags is placed 3 cm above the iliac crest laterally, and the remaining 12 mm assistant trocar is placed between the camera and the second arm of the robot. Although the whole surgery can be performed with a 0° lens, we prefer to switch to a 30° lens when we start the intracorporeal Studer pouch reconstruction.

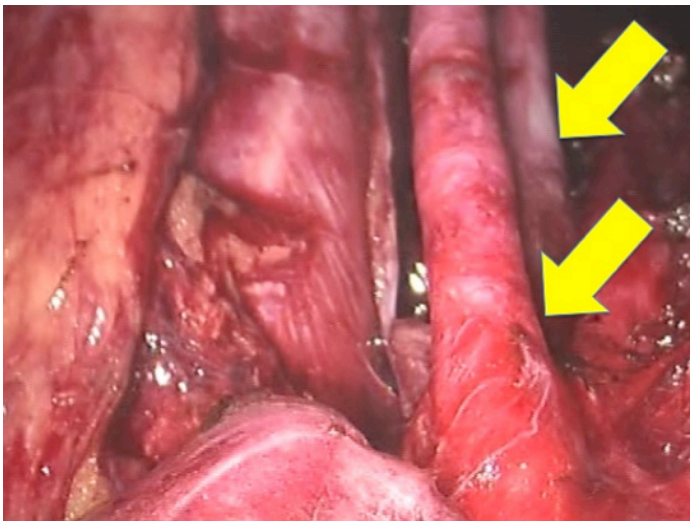

Figure 2: Extended lymph node dissection and appearance of skeletonised major pelvic vasculature (arrows).
Obtained from Prof Balbay and Dr Canda's own robotic surgical procedure.

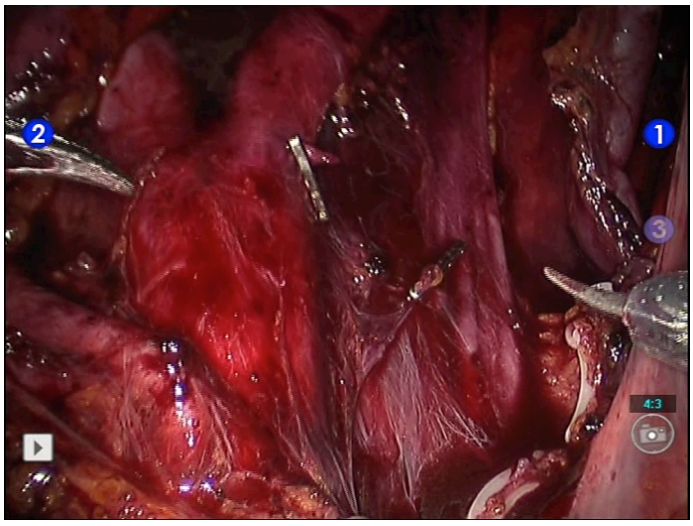

Figure 3: Skeletonised abdominal aorta and vena cava inferior are seen. Please note titanium endoclips on the vasculature used for haemostasis.
Obtained from Prof Balbay and Dr Canda's own robotic surgical procedure.

The patient is placed in a deep (30°) Trendelenburg position until the completion of robotic bilateral extended LN dissections and transposition of the left ureter. Thereafter, the patient is taken to a mild (5°) Trendelenburg position for intracorporeal Studer pouch reconstruction. LNs including external, internal, and common iliac, obturator, presacral, interbifurcation, preaortic, paracaval LNs within the boundaries between the genitofemoral nerves, psoas muscles, and ureters laterally, cut

the edge of the endopelvic fascia over the NVBs and internal iliac vessels medially, inferior mesenteric artery (IMA) and accompanying vena cava superiorly are removed. Thereafter, the left ureter is transposed to the right gutter under the sigmoid colon. We use an endowrist 8 mm monopolar Maryland curved scissors (Intuitive Surgical, Sunnyvale, CA) on the right hand and an endowrist Maryland bipolar forceps (Intuitive Surgical, Sunnyvale, CA) on the left hand. For the fourth arm, we use a Cadiere forceps (Intuitive Surgical, Sunnyvale, CA).[21]

Due to the published literature oncologic outcomes of the RARC series including the IRCC outcomes, the mean LN yield has been reported to range between 15-21 LNs and PSM rate ranges between 1.4-7%.[3,22-26]

Step 3: Extracorporeal or Intracorporeal Urinary Diversion

Urinary diversion is performed extracorporeally in most of the published literature relating to RARC. Including ours, only a few centres have reported their experience on intracorporeal urinary diversion including ileal conduit and Studer pouch reconstruction. Very recently, Tyritzis et al.[22] reported The Karolinska Institute's experience of 70 patients with RARC and totally intracorporeal modified Studer ileal neobladder formation, which is the largest published single institution series of this particular robotic technique. The median follow-up was 30.3 months in their series. The surgical margins were negative in all but one patient (98.6%). Perioperative complications (Clavien 3-5) occurred in 22 of 70 patients (31.4%) between postoperative 0-30 days. Comparatively, Clavien 3-5 complications occurred in 13 of 70 patients (18.6%) in postoperative 31-90 days. The overall complication rate was calculated as 58.5% within postoperative 90 days. Recurrence-free, cancer-specific, and overall survival rates at 24 months were 80.7%, 88.9%, and 88.9%, respectively. They also reported functional outcomes in their series. Of the patients, daytime continence rates were 70-90% and satisfactory sexual function or potency was reported both in men and women at 12 months. They concluded that totally intracorporeal neobladder diversion has satisfactory and comparable outcomes when compared to open series.

In our experience with 27 cases, the mean operation time was 9.9±1.4 hours (range, 7.1-12.4) and estimated blood loss was 429±257 mL (100-1,200). Regarding surgical oncologic parameters including SMs mean LN yield, SMs were negative in all-but-one patient who had pT4b disease and whose mean LN yield was 24.8 (9.2, 8-46). Postoperative pathological stages were as follows: pT0 (n=5), pTis (n=1), pT1 (n=1), pT2a (n=5), pT2b (n=3), pT3a (n=6), pT3b (n=2), pT4a (n=3), and pT4b (n=1). Positive LNs were detected in six patients. Incidental prostate cancer was detected in nine patients. The mean length of hospital stay was 10.5±6.8 days (range, 7-36) and the mean follow-up time was 6.3±2.9 months (range, 1.8-11.3). In the perioperative (0-30 days) period, nine minor (Grade 1 and 2) and four major (Grade 3-5) complications were detected as described in modified Clavien classification. On the other hand, there were four minor and three major complications in the postoperative (31-90 days) period. Regarding our functional outcomes, of the available 18 patients: 11 were fully continent, 4 had mild day-time incontinence, and 2 had severe day-time incontinence.[3]

Our technique of robotic intracorporeal Studer pouch formation was described before and follows in more detail.[3] The first step is to suture the urethral remnant to the assigned 1 cm opening on the antimesenteric border of the wall of the ileal segment to be segregated. An estimated 10 cm segment on the right and a 40 cm segment on the left side of urethro-ileal anastomosis were assigned. The distal 20 cm ileal segment is left attached to the caecum. Laparoscopic intestinal staplers are introduced from the 15 mm trocar on the left abdomen and are placed perpendicular across the intestinal wall, with inclusion of the adjacent 2 cm of mesointestinum. The proximal and distal ends of the ileum are put together and a side-to-side ileoileostomy is accomplished with the use of two more laparoscopic intestinal staplers. The proximal 10 cm segment of the afferent loop is spared. The antimesenteric border of the remaining ileal segment is incised. Asymmetric closure of the posterior wall is performed. To facilitate and reinforce this closure, the medial aspects of the opened ileal segments are sutured together. A completed posterior wall anastomosis - running from the upper-right to the lower-left and leaving 10 cm segments on each side of the urethra located in the middle - is accomplished. Thereafter, anterior wall anastomosis is performed, leaving the proximal redundant wall that will be closed at the very end of the

surgery, following the insertion of ureteral stents. A Wallace-type uretero-ureteral anastomosis is made. Then, we excise the stapler line at the proximal end of the afferent loop. The posterior wall is anastomosed halfway between the ileal wall and the medial edge of the uretero-ureteral anastomosis. A feeding tube is inserted through the urethra, advanced within the lumen of the ileal segment, and held close to the anastomosed ends of the ureters. Then, JJ stents are passed through the feeding tube over a guidewire to the uretero-intestinal anastomosis site and fed up to the ureters and renal pelves. The guidewires are then removed and both ends of the JJ stents are allowed to coil. For a Studer pouch, the distal tips of the stents are tied to the tip of a 22°F urethral catheter outside the body that will then be passed through the urethra into the pouch over a guidewire. With this manoeuvre the urethral catheter and JJ stents tied to it are removed together 21 days after surgery following cystography. Lastly, the redundant ileal wall of the pouch is closed on itself.[3] Figures 4 and 5 show robotic construction of an intracorporeal Studer pouch. In our initial 27 cases, there were 25 males and 2 females. Mean patient age was 61.4 years (range 43–80) and mean body mass index (BMI) was 25.5 kg/m^2 (range 19.3–32.8). Overall, eight patients (29.6%) received neoadjuvant chemotherapy.

Schumacher et al.[27] reported the mean operative time and the mean blood loss as 476±96 minutes (325-760) and 677±477 mL (200-2,200) in RARC and intracorporeal Studer pouch reconstruction (n=36) and ileum conduit formation (n=9) patients, respectively. Goh et al.[28] performed RARC and intracorporeal Studer pouch reconstruction (n=8) and ileal conduit formation (n=7) overall in 15 patients. The mean operation time was 7.5 hours in both groups. The mean estimated blood loss was 225 mL and 200 mL in Studer pouch and ileal conduit group, respectively.

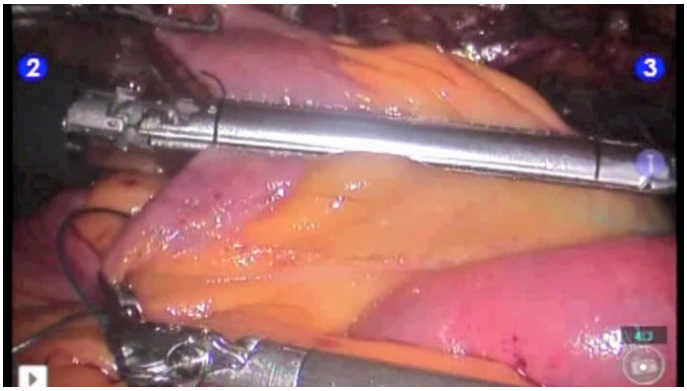

Figure 4: Laparoscopic bowel stapler is seen introduced from the 15 mm port located on the left abdomen approximately 2 cm above the anterior superior iliac spine to divide the ileum for Studer pouch reconstruction.
Obtained from Prof Balbay and Dr Canda's own robotic surgical procedure.

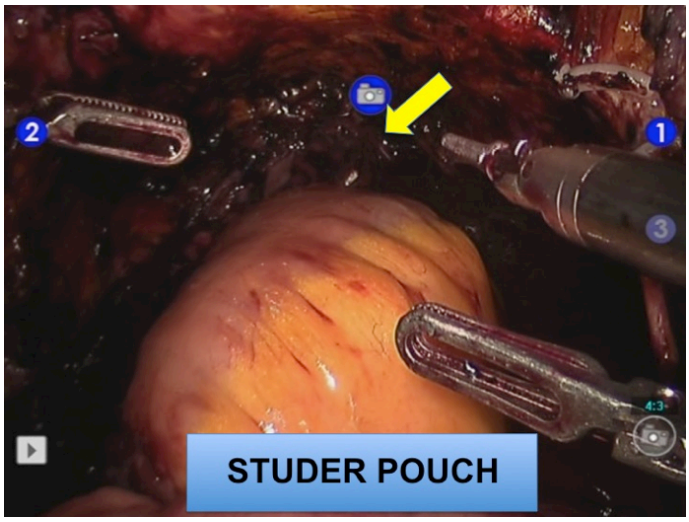

Figure 5: Completed intracorporeal Studer pouch with internalised bilateral DJ stents. Arrow points out the anastomosis between the urethra and the pouch.
Obtained from Prof Balbay and Dr Canda's own robotic surgical procedure.

OPEN VERSUS ROBOTIC APPROACH

A number of studies have compared open versus robotic RC. Most of the published studies are retrospective series, therefore, a selection bias is inevitable that precludes drawing strict conclusions on this issue. Two prospective and randomised clinical trials compared open versus robotic RC procedures.[13,14] In both of these studies, around 20 patients were included in the study arms. The estimated blood loss was detected to be significantly lower in the robotic group in both studies.[13,14] Additionally, quicker return of bowel functions and lower use of inpatient narcotics were detected in the robotic arm in one of the studies.[14]

Wang et al.[29] conducted a prospective but non-randomised study in order to compare open (n=21) versus robotic (n=33) approaches. Significantly decreased blood loss, transfusion requirement,

hospital stay, and time to resumption of regular diet were detected in the robotic group.[25] Complications and perioperative oncologic outcomes of open versus robotic RC in 200 patients with extracorporeal urinary diversion were compared retrospectively in another study.[16] The robotic group was found to have the advantages of a significantly shorter mean operative time, significantly lower mean estimated blood loss and mean hospital stay, and significantly fewer overall and major complications.[16]

Styn et al.[17] reviewed a total of 50 RARC and 100 open RC cases with similar demographic parameters. The robotic group was found to be associated with a significantly decreased median estimated blood loss and 30-day transfusion rate. However, the operative time was longer in the robotic group. RARC was found to be an independent predictor of fewer overall and major complications at postoperative 30 and 90 days by Ng et al.[15] On the other hand, other studies also did not find any significant differences between open and robotic approaches in terms of complications.[13,14,16,17,29] Schumacher et al.,[27] from The Karolinska Institute, published surgery-related complications of RARC with intracorporeal urinary diversion in 45 patients. Overall, fewer complications were observed between the groups over time, with a significant decrease in late versus early complications.[27]

Very recently, the IRCC reported an analysis of intracorporeal versus extracorporeal urinary diversion following RARC for bladder cancer. Overall, 18 international centres, with 935 patients, were included. Of those patients, 167 underwent intracorporeal urinary diversion (ileal conduit: 106; neobladder: 61) and 768 underwent extracorporeal urinary diversion (ileal conduit: 570; neobladder: 198). No significant differences were detected in terms of patient age, gender, BMI, American Society of Anesthesiologists (ASA) scores, and the rate of prior abdominal surgery between the groups. The mean operation time was detected to be similar in both groups. Although not significant, the duration of hospital stay was longer in the intracorporeal urinary diversion group (9 days versus 8 days, p=0.086). Reoperation rates during the perioperative period (0-30 days) were similar. No significant difference was detected during the 90-day complication rates between the groups. However, a better trend in favour of intracorporeal urinary diversion groups was detected (41% versus 49%, p=0.05). An important finding of this study was that gastrointestinal complications were significantly lower in the intracorporeal group (p≤0.001). In addition, patients who underwent intracorporeal urinary diversion were regarded as having a lower risk of experiencing postoperative complications at 90 days of surgery (p=0.02).[30]

CONCLUSIONS

Currently, the most effective local treatment of muscle-invasive bladder cancer and non-invasive, high-grade bladder tumours that recur or progress despite intravesical therapies is open RC, extended pelvic LN dissection with urinary diversion. Performing these complex procedures utilising pure laparoscopy is very difficult. However, a surgical robot enables the surgeon to perform complex procedures much more easily due to having the advantages of 3D and magnified image capability, higher grades of wristed hand movements, and decreased hand tremor, and also due to the fourth robotic arm, which enables additional assistance and tissue retraction, leading to a shorter learning curve.

According to the published literature comparing open and robotic RC, some authors have published similar outcomes in terms of operative time, mean LN yield, PSM rate, and complication rates between the groups, whereas some others have reported decreased estimated blood loss, transfusion rate, complications, length of hospital stay, wound problems, time to flatus, and time to regular diet in the postoperative period in robotic group.

Totally intracorporeal RARC with urinary diversions are technically feasible procedures with good intermediate-term oncologic results, acceptable morbidities, excellent short-term surgical and pathological outcomes, and satisfactory functional results.

REFERENCES

1. Huang GJ, Stein JP. Open radical cystectomy with lympha- denectomy remains the treatment of choice for invasive bladder cancer. Curr Opin Urol. 2007;17(5):369–75.
2. Canda AE et al. 'Robotic-assisted laparoscopic radical cystoprostatectomy and intracorporeal urinary diversion (Studer pouch or ileal conduit) for bladder

cancer'. Canda AE (eds), Bladder Cancer: From Basic Science to Robotic Surgery (2012), Croatia: InTech, pp. 321-44.

3. Canda AE et al. Robot assisted laparoscopic nerve sparing radical cystectomy with bilateral extended lymph node dissection and intracorporeal urinary diversion for bladder cancer: Initial experience in 27 cases. BJU Int. 2012;110(3):434-44.

4. Menon M et al. Nerve-sparing robot-assisted radical cystoprostatectomy and urinary diversion. BJU Int. 2003;92(3):232-6.

5. Canda AE et al. Ureteric duplication is not a contrandication for robot assisted laparoscopic radical cystoprostatectomy and intracorporeal Studer pouch formation. JSLS. 2011;15(4):575-9.

6. Herr H et al. Bladder Cancer Collaborative Group. Standardization of radical cystectomy and pelvic lymph node dissection for bladder cancer: a collaborative group report. J Urol. 2004;171(5):1823-8.

7. Skinner EC et al. Surgical benchmarks for the treatment of invasive bladder cancer. Urol Oncol. 2007;25(1):66-71.

8. De Nunzio C et al. Analysis of radical cystectomy and urinary diversion complications with the Clavien classification system in an Italian real life cohort. Eur J Surg Oncol. 2013;39(7):792-8.

9. Hellenthal NJ et al. Surgical margin status after robot assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. J Urol. 2010;184(1):87-91.

10. Pruthi RS et al. Robotic radical cystectomy for bladder cancer: surgical and pathological outcomes in 100 consecutive cases. J Urol. 2010;183(2):510-4.

11. Khan MS et al. Analysis of early complications of robotic-assisted radical cystectomy using a standardized reporting system. Urology. 2011;77(2):357-62.

12. Guru KA et al. The lymph node yield during robot-assisted radical cystectomy. BJU Int. 2008;102(2):231-4.

13. Parekh DJ et al. Perioperative outcomes and oncologic efficacy from a pilot prospective randomized clinical trial of open versus robotic assisted radical cystectomy. J Urol. 2013;189(2):474-9.

14. Nix J et al. Prospective randomized controlled trial of robotic versus open radical cystectomy for bladder cancer: perioperative and pathologic results. Eur Urol. 2010;57(2):196-201.

15. Ng CK et al. A comparison of postoperative complications in open versus robotic cystectomy. Eur Urol. 2010;57(2):274-81.

16. Kader AK et al. Robot-assisted laparoscopic vs open radical cystectomy: comparison of complications and perioperative oncological outcomes in 200 patients. BJU Int. 2013;112(4):E290-4.

17. Styn NR et al. Matched comparison of robotic-assisted and open radical cystectomy. Urology. 2012;79(6):1303-8.

18. Stein JP et al. Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. J Urol. 2003;170(1):35-41.

19. Herr HW et al. Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol. 2004;22(14):2781-9.

20. Murphy DG et al. Robotic-assisted laparoscopic radical cystectomy with extracorporeal urinary diversion: initial experience. Eur Urol. 2008;54(3):570-80.

21. Akbulut Z et al. Robot-assisted laparoscopic nerve-sparing radical cystoprostatectomy with bilateral extended lymph node dissection and intracorporeal Studer pouch construction: outcomes of first 12 cases. J Endourol. 2011;25(9):1469-79.

22. Tyritzis SI, et al. Oncologic, Functional, and Complications Outcomes of Robot-assisted Radical Cystectomy with Totally Intracorporeal Neobladder Diversion. Eur Urol. 2013;64(5):734-41.

23. Xylinas E et al. Robotic-assisted radical cystectomy with extracorporeal urinary diversion for urothelial carcinoma of the bladder: analysis of complications and oncologic outcomes in 175 patients with a median follow-up of 3 years. Urology. 2013;82(6):1323-9.

24. Treiyer A et al. Robotic-assisted laparoscopic radical cystectomy: surgical and oncological outcomes. Int Braz J Urol. 2012;38(3):324-9.

25. Hellenthal NJ et al. Lymphadenectomy at the time of robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. BJU Int. 2011;107(4):642-6.

26. Hayn MH et al. Does previous robot-assisted radical prostatectomy experience affect outcomes at robot-assisted radical cystectomy? Results from the International Robotic Cystectomy Consortium. Urology. 2010;76(5):1111-6.

27. Schumacher MC et al. Surgery-related complications of robot-assisted radical cystectomy with intracorporeal urinary diversion. Urology. 2011;77(4):871-6.

28. Goh AC et al. Robotic intracorporeal orthotopic ileal neobladder: replicating open surgical principles. Eur Urol. 2012;62(5):891-901.

29. Wang GJ et al. Robotic vs open radical cystectomy: prospective comparison of perioperative outcomes and pathological measures of early oncological efficacy. BJU Int. 2008;101(1):89–93.

30. Ahmed K et al. Analysis of intracorporeal compared with extracorporeal urinary diversion after robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. Eur Urol. 2014;65(2):340-7.

NEOADJUVANT CHEMOTHERAPY IN MUSCLE-INVASIVE BLADDER CANCER

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Disclosure: No potential conflict of interest.
Received: 29.01.14 **Accepted:** 06.03.14
Citation: EMJ Urol. 2014;1:111-117.

ABSTRACT

Neoadjuvant chemotherapy (NAC) in muscle-invasive bladder cancer was introduced several years ago. Despite the evidence supporting its use in clinical practice, only a minority of patients who undergo radical cystectomy receive preoperative chemotherapy. In addition, recommendations and methods to detect patients who would benefit the most from NAC are still unclear. The European Association of Urology (EAU) guidelines panel on muscle-invasive and metastatic bladder cancer recommends the use of cisplatin-based NAC for T2-T4a, cN0 M0 bladder cancer if the patient has a performance status ≥2 and if the renal function is not impaired, but the American Urological Association, for example, does not have any guideline recommendations on this topic at all. In this review we describe the current literature supporting NAC in association with radical cystectomy in muscle-invasive urothelial carcinoma of the bladder. Evidence acquisition was made searching the Medline database for original articles published before 1st February 2014, with search terms: "neoadjuvant chemotherapy", "radical cystectomy", and "invasive bladder cancer".

Keywords: Neoadjuvant chemotherapy, muscle-invasive bladder cancer.

INTRODUCTION

Muscle-invasive urothelial carcinoma of the bladder (MIBC) is an aggressive malignant disease exhibiting a high rate of early systemic spread. Radical cystectomy with extended lymphadenectomy is currently the gold standard of treatment for patients with MIBC. The prognosis of these patients is, however, highly dependent on the possible nodal metastases and on the local pathological stage of the disease. To improve the prognosis of these patients, neoadjuvant and adjuvant chemotherapy have been used. The European Association of Urology (EAU) guidelines panel on muscle-invasive bladder cancer gives a recommendation to use neoadjuvant chemotherapy (NAC) in T2-T4a bladder cancer if the patient is fit and no impairment in the renal function is detected.[1] Without neoadjuvant or adjuvant chemotherapy, MIBC patients undergoing radical cystectomy have a 10-year disease-specific survival (DSS) of 90.5% if pT0/a/is/1 pN0 disease is detected in a cystectomy specimen, whereas in muscle invasive disease without nodal metastases (pT2a/b pN0), the 10-year DSS drops to 67%.[2] In locally advanced disease the prognosis is even worse with 60% 10-year DSS in Stage pT3a/b pN0 and 37% in Stage pT4a/b pN0. A patient with nodal metastases has the worst prognosis, i.e. 10-year DSS is only 17% irrespective of the pathological stage of the disease.

However, until today, optimal timing of the therapy (neoadjuvant or adjuvant) and drugs used in the regimen, as well as their dose and the schedule, are still under debate. In this review we aim to present relevant literature regarding the use of NAC in the treatment of MIBC.

FROM MVAC TOWARDS BETTER-TOLERATED REGIMENS

In 2003, Grossman et al.[3] reported the efficacy of neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) therapy in a randomised SWOG/US intergroup trial of patients with Stage T2-T4a bladder cancer. The patients in the trial were treated either with radical cystectomy alone or with three cycles of MVAC followed by radical surgery. After an 11-year trial period, the median survival was 46 months in patients with surgery alone and 77 months among patients who received combination therapy. 5-year overall survival was 57% in the NAC group and 43% in patients with upfront cystectomy. However, it should be mentioned that although this result was not statistically significant with a two-sided t-test ($p=0.06$), it is widely considered to demonstrate the benefit of NAC since the original endpoint of a statistically significant difference (defined as a one-sided t-test of $p<0.05$) was received. The study also showed that in both groups the improved survival was associated with the absence of residual cancer in the cystectomy specimen. In addition, the amount of stage pT0 disease was significantly higher among the patients who received NAC.

Although MVAC therapy is very effective, its use in clinical practice is limited due to its toxicity. The morbidity and mortality with this regimen is acceptable, but not yet substantial, and it should be administered after proper patient selection.[4] The most common toxicities of MVAC therapy are granulocytopaenia, in up to 56% of patients (33% classified severe), and Grade 3 gastrointestinal toxicity, which is detected in 17% of the patients.[3] These toxicities are, however, self-limiting in most of the cases and have not been shown to decrease the patients´ chances to undergo radical cystectomy. In addition, doxorubicin has a relatively high rate of cardiovascular toxicity and the therapy without it (cisplatin, methotrexate, and vinblastine [CMV]) has been better tolerated; it is also effective as shown in a randomised prospective trial by International Collaboration of Trialists.[5] CMV combination gives a statistically significant survival advantage and reduces the risk of death by 16%.

Other agents combined with cisplatin have also been studied. In a study by Dash et al.,[6] gemcitabine-cisplatin (GC) regimen gave similar complete response rates and disease-free survival in the neoadjuvant setting as MVAC therapy. However, this study was retrospective in nature and only 42 patients received cisplatin and gemcitabine. Since this primary study, several other retrospective series have supported the use of this regimen in a neoadjuvant setting as well, but we still do not have prospective comparisons.[7-11] These studies also showed a decreased time between NAC and radical cystectomy compared with MVAC regimen.

Figure 1 illustrates our own patient with cT3, high-grade bladder cancer who was treated with three cycles of NAC using GC combination followed by cystoprostatectomy and lymphadenectomy. Stage pT0N0M0 was detected postoperatively, and during 5-year follow-up the patient has remained disease-free.

In the European Organisation for Research and Treatment of Cancer (EORTC) Intergroup Study,[12] 30,987 GC combinations were compared with paclitaxel-GC in patients with locally-advanced or metastatic urothelial cancer. The addition of paclitaxel provided higher response rate to chemotherapy and 3 months survival benefit. This regimen was well tolerated, supporting its role also in the neoadjuvant setting.

In elderly patients with a high prevalence of cardiovascular disease and renal dysfunction, even GC regimen can be problematic. To develop more tolerable treatment regimens, carboplatin has been used instead of cisplatin.[13,14] This combination seems to be safe even for cisplatin-unfit patients, and provides a favourable pathological cancer-free state within a short follow-up.[15] However, there are no randomised trials demonstrating improvement in the outcomes and, therefore, carboplatin-based regimens still remain investigational.

Despite the previously introduced studies showing a clear advantage of using NAC in MIBC, there are two randomised prospective trials where no benefit of administering preoperative chemotherapy could be found. The first was published in 1996 and is known as Nordic

Cystectomy Trial I, and the second, Nordic Cystectomy Trial II, was published in 2002.[16,17] In Nordic Cystectomy Trial I, 311 patients with cT1G3-T4NxM0 disease were randomised to receive either two cycles of cisplatin and doxorubicin or no chemotherapy at all. All patients also had 20 Gy of neoadjuvant radiotherapy. After 5-year follow-up there were no significant differences in overall survival or DSS using NAC. However, in a subgroup analysis, patients with pT3-T4 disease gained a 15% absolute survival benefit after NAC. In Nordic Cystectomy Trial II, the regimen used was three cycles of neoadjuvant cisplatin and methotrexate. This combination was tested against radical cystectomy alone. Again, no differences in 5-year overall survival could be seen. The limitation of these studies is that they both used unconventional regimens and, in fact, a combined analysis of both of the studies revealed better overall survival after 5 years in the NAC group (5-year survival 56% versus 48%; p=0.049).[18] Key randomised prospective trials of radical surgery alone or with NAC are summarised in Table 1.

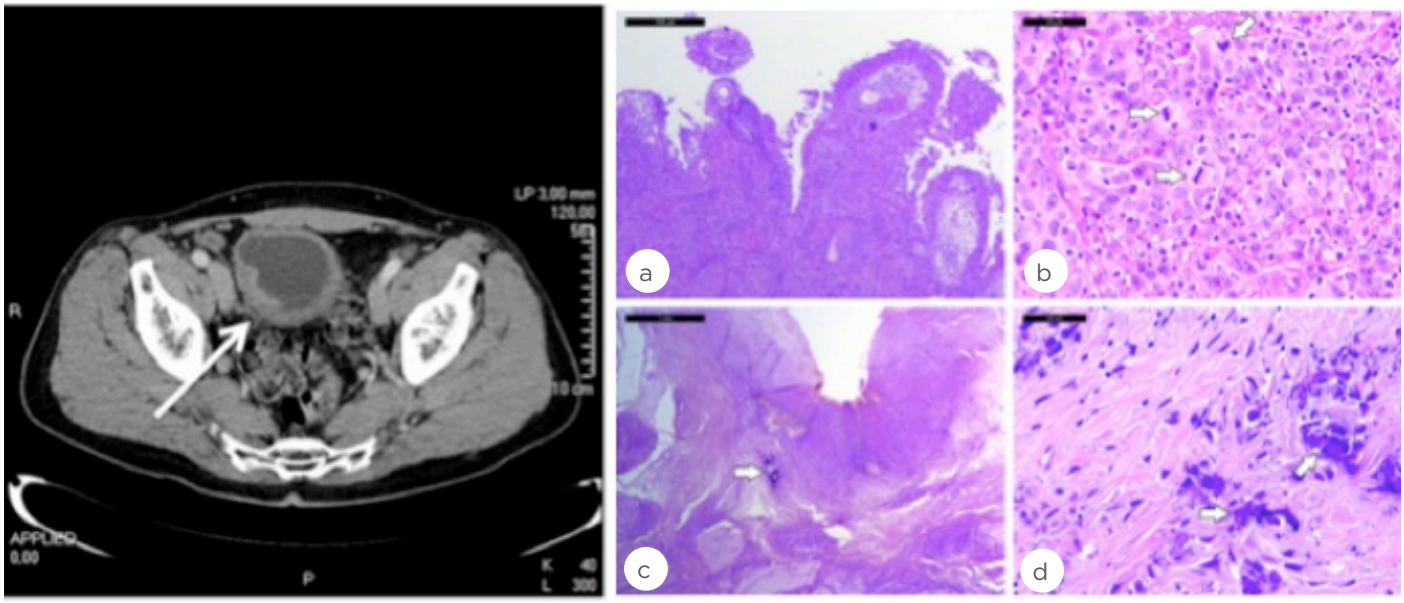

Figure 1: Computed tomography (CT) scan and histological images from a patient with cT3 high grade urothelial carcinoma of the bladder.

The white arrow in the CT scan points to the region with suspected extravesical involvement. Primary tumour after transurethral resection (a) shows invasive tumour with severe nuclear atypia and frequent mitosis (b; arrows indicate the mitotic cells). After neoadjuvant chemotherapy with three cycles of cisplatin-gemcitabine combination and cystoprostatectomy (c and d), large postoperative area containing necrotic tissue, fibrosis, and calcification (arrows) is observed, while no residual tumour is detected.

Table 1: Key randomised prospective trials of radical surgery alone or with neoadjuvant chemotherapy.

Trial	Patients (n)	Regimen Used	Survival Benefit
SWOG/US Intergroup[3]	317	MVAC x 3	Yes
International Collaboration of Trialists[5]	976	CMV x 3	Yes
Nordic Cystectomy Trial 1[16]	325	CA	No
Nordic Cystectomy Trial 2[17]	317	CM	No

SWOG: Southwest Oncology Group; MVAC: methotrexate, vinblastine, doxorubicin, cisplatin; CMV: cisplatin, methotrexate, vinblastine; CA: cisplatin, doxorubicin; CM: cisplatin, methotrexate.

WHO SHOULD RECEIVE NAC?

As discussed above, MIBC is a systemic disease and if the patient with MIBC undergoes relapse after radical cystectomy, the situation is often attributable to micrometastatic disease at the time of the surgery. Therefore, it is important to administer systemic therapy early enough to eradicate possible systemic disease which could not be cured with the surgery alone. If chemotherapy could be applied to patients with Stage ≥pT3 or pT2 with lymphovascular invasion only (high-risk patients), the risk of overtreatment for those with non-invasive or superficially-invasive disease could be reduced. However, despite the fact that the effect of NAC seems to be greater within the higher stages of the disease, patients with T2 tumours actually do extremely well and gain 2.5-year survival benefit with this treatment.[3]

Clinical staging is very demanding being reliant on physical examination, transurethral resection of the tumour with bimanual palpation, and radiological examination of the bladder and the upper urinary tract. Bimanual palpation, for example, is highly inaccurate and only 57% of patients can be correctly staged with this method.[19] Computed tomography, at its best, is 50% accurate in predicting local disease; however, significant inter-observer variability exists.[20,21] If we look at the patients with clinical T2 disease, there is a high risk of understaging the disease before the cystectomy. Furthermore, it has been shown in another study that 43-73% of patients who have clinical T2 disease before the cystectomy are upstaged in final pathological reports.[22] These patients also have a 16-22% risk of microscopic lymph node metastases at the time of radical surgery.[23-25]

Another reason to favour the use of NAC is that it does not seem to adversely affect a patient´s chance to undergo radical cystectomy and the drug delivery is excellent, with only 20% of patients receiving less than the intended number of treatment cycles.[5,26] In contrast, it is very demanding to plan postoperative chemotherapy after major surgery for these patients (usually with advanced age and co-morbidities) because of the long recovery period and possible perioperative complications. This often delays the induction of adjuvant chemotherapy compromising optimal results. In a study by Donat et al.,[27] these complications - after radical surgery and extended pelvic lymph node dissection - affected the induction of adjuvant chemotherapy in up to 30% of patients. Eldefrawy et al.[28] compared the likelihood of the initiation and completion of neoadjuvant and adjuvant chemotherapy regimens in a total of 363 patients.[28] Their finding showed that 88.6% of patients who were offered NAC initiated the treatment, whereas only 68.0% of patients considered for adjuvant chemotherapy were able to start planned regimen ($p<0.001$). 83.5% of the NAC group and 35.5% of the adjuvant group completed the planned number of cycles, and the difference was again statistically significant ($p<0.001$).

To better identify high-risk patients, a standardised system was recently put in place.[29] In that system, patients were considered to be high-risk if they had hydronephrosis, cT3b-T4a disease, and/or histological evidence of lymph-vascular invasion in transurethral resection specimen. If these features were not present, 5-year DSS was greater than 80% with surgery only, and NAC-associated toxicity could be avoided. This kind of advanced staging - with novel imaging techniques combined with biomarkers and gene expression profiles of the tumour - could possibly help to identify patients who would receive the greatest benefit from NAC.[30-32]

DO WE DELAY RADICAL SURGERY WITH NAC?

Several studies have suggested that delaying radical cystectomy over 3 months from the initial diagnosis is associated with progressive disease and decreased disease-specific and overall survival.[33-35] A theoretical possibility of adverse outcomes exists for patients who develop complications from NAC and their operation is postponed.[36] In the study by Alva et al.,[37] cystectomy delivery within 10 weeks after NAC did not significantly alter the risk of patient survival. In addition, the most common reason for the operation after 10 weeks was procedural scheduling.

Another concern is the possible disease progression during NAC since there are some patients who do not respond to this treatment. Therefore, identifying the patients who are not likely to respond would allow for better selection of those who do benefit from the upfront cystectomy. In the study by Mossanen et al.,[38] approximately one in five patients did not respond to NAC.

However, the study was retrospective in nature, and different regimens (MVAC, GC, and carboplatin-gemcitabine) were used. Non-response was more likely with carboplatin-gemcitabine combination. This finding corresponds to the fact that cisplatin-based treatment is superior to carboplatin and should be used as the first-line chemotherapy in MIBC.[39-41] In addition, elderly patients were more likely to be non-responders because they were less likely to tolerate full doses of chemotherapy due to co-morbidities and renal insufficiency. Personalising the treatment and the selection of patients to different treatment arms may be aided in the future by biomarkers and pharmacogenomics.[42,43] With these new tools, patients who are likely to be non-responders to conventional NAC could be operated on without any delay, or alternatively, neoadjuvant treatment using different regimens and possible novel agents may be offered.

NAC AND PERIOPERATIVE MORBIDITY

Current data on this topic are largely based on studies that are not specifically designed to evaluate complications.[3,44] However, a reason to underuse NAC - even in the tertiary centres - may be due to the concern of increased perioperative complications. A recent study by Johnson et al.,[45] using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database, was the first to specifically address this question. Of the 878 patients evaluated, there were 457 who had at least one complication within 30 days after the radical cystectomy. NAC was administered to 78 patients, 55.1% of whom had at least one complication; among patients who did not receive NAC, the outcome was 51.8%. NAC was not a predictor of complications, reoperation, wound infections, or wound dehiscence. Furthermore, NAC did not predict increased operation time and the length of hospitalisation was in fact shorter among these patients. Another retrospective study, also from the United States, used the Surveillance Epidemiology and End Results (SEER)-Medicare linked database to assess the effect of NAC on perioperative outcomes;[46] 416 (11.1%) of 3,760 patients with MIBC received NAC. The overall complication rate was 66.0% at 30 days and 72.5% at 90 days. The corresponding mortality rates were 5.3% and 8.2%. NAC did not increase the rate of complications, readmissions, or mortality. It should be noted, that possible confounder of non-randomised studies of this type is selection bias as neoadjuvant treatment is more likely given to patients who are younger and have fewer co-morbidities compared with those undergoing cystectomy without NAC.

DO WE USE NAC AS OFTEN AS WE SHOULD?

EAU guidelines give Grade A recommendation to use NAC in MIBC.[1] However, the use of NAC seems to be very low. In US National Cancer Data Base registers, only 11% of patients with MIBC undergo chemotherapy, and the majority of them are carried out in adjuvant setting.[47,48] The number is equally low in Western and Central European sites, where roughly 12% of about 5,000 MIBC patients undergoing cystectomy annually receive NAC.[49] As discussed earlier, the utilisation of NAC may possibly be hindered by physicians' concern about increased postoperative complications after radical surgery. However, there is now data to remove those concerns.[45] Another reason for the low utilisation may be potentiated by the perception of both patients and physicians that 5-6% of absolute overall survival benefit and 16% of relative disease-specific mortality risk reduction over 10 years are not enough to warrant systemic therapy with potential complications. If we look at the data on other systemic therapies widely used in breast and colon cancers, they both confer on a 7% survival benefit, which is in-line with the results in MIBC.[50]

CONCLUSION

There are still subgroups of patients who are problematic to treat with NAC. The largest subgroup consists of patients with renal insufficiency. Data from three single-institution reports from large, tertiary cancer care centres suggest that up to 30-40% of patients undergoing radical cystectomy may be ineligible for NAC because of their impaired renal function.[51] Consistent with these reports, the study by Johnson et al.[45] showed that 30% of patients were also not eligible for NAC. However, although exclusion of these patients only partially accounts for the low utilisation of NAC, it underscores the need to develop more efficacious and more tolerated therapy options. One of such therapies might be immunotherapy against melanoma antigenic epitope A3 (MAGE-A3), which has already been studied in preclinical setting in MIBC, and it has

been previously used in metastatic melanoma and non-small cell lung cancer with a low amount of side-effects, even in patients with co-morbidities.[52-54] As it is natural, novel - but not yet widely known - therapeutic options to treat muscle-invasive forms of urothelial carcinomas in the future are in the early phase of development.[55,56] These studies are so far preclinical and no data exist in clinical settings.

REFERENCES

1. Witjes JA et al. EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2013 Guidelines. Eur Urol. 2014;65(4):778-92.

2. Hautmann R et al. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: long-term results in 1100 patients. Eur Urol. 2012;61(5):1039-47.

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

4. Sternberg C et al. ICUD-EAU International Consultation on Bladder Cancer 2012: Chemotherapy for urothelial carcinoma-neoadjuvant and adjuvant settings. Eur Urol. 2013;63(1):58-66.

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

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

7. Matsubara N et al. Comparison between neoadjuvant and adjuvant gemcitabine plus cisplatin chemotherapy for muscle-invasive bladder cancer. Asia Pac J Clin Oncol. 2013;9(4):310-7.

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

9. Fairey A et al. Neoadjuvant chemotherapy with gemcitabine/cisplatin vs. methotrexate/vinblastine/doxorubicin/cisplatin for muscle-invasive urothelial carcinoma of the bladder: A retrospective analysis from the University of Southern California. Urol Oncol. 2013;31(8):1737-43.

10. Kaneko G et al. Neoadjuvant gemcitabine plus cisplatin for muscle-invasive bladder cancer. Jpn J Clin Oncol. 2011;41(7):908-14.

11. Pal S et al. Retrospective analysis of clinical outcomes with neoadjuvant cisplatin-based regimens for muscle-invasive bladder cancer. Clin Genitourin Cancer. 2012;10(4):246-50.

12. Bellmunt J et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol. 2012;30(10):1107-13.

13. Bellmunt J et al. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. Cancer. 1997;80(10):1966-72.

14. Bamias A et al. The combination of gemcitabine and carboplatin as first-line treatment in patients with advanced urothelial carcinoma. A Phase II study of the Hellenic Cooperative Oncology Group. Cancer. 2006;106(2):297-303.

15. Koie T et al. Efficacies and safety of neoadjuvant gemcitabine plus carboplatin followed by immediate cystectomy in patients with muscle-invasive bladder cancer, including those unfit for cisplatin: a prospective single-arm study. Int J Clin Oncol. 2013;18(4):724-30.

16. Malmström PU et al. Five-year followup of a prospective trial of radical cystectomy and neoadjuvant chemotherapy: Nordic Cystectomy Trial I. The Nordic Cooperative Bladder Cancer Study Group. J Urol. 1996;155(6):1903-6.

17. Sherif A et al. Neoadjuvant cisplatin-methotrexate chemotherapy for invasive bladder cancer -- Nordic cystectomy trial 2. Scand J Urol Nephrol. 2002;36(6):419-25.

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

19. Ploeg M et al. Discrepancy between clinical staging through bimanual palpation and pathological staging after cystectomy. Urol Oncol. 2012;30(3):247-51.

20. Tritschler S et al. Interobserver variability limits exact preoperative staging by computed tomography in bladder cancer. Urology. 2012;79(6):1317-21.

21. Paik ML et al. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. J Urol. 2000;163(6):1693-6.

22. Canter D et al. Clinicopathological outcomes after radical cystectomy for clinical T2 urothelial carcinoma: further evidence to support the use of neoadjuvant chemotherapy. BJU Int. 2011;107(1):58-62.

23. Ghoneim MA et al. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. J Urol. 1997;158(2):393-9.

24. Leissner J et al. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. BJU Int. 2000;85(7):817-23.

25. Stein JP. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001;19(3):666-75.

26. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. International collaboration of trialists. Lancet. 1999;354(9178):533-40.

27. Donat SM et al. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. Eur Urol. 2009;55(1):177-85.

28. Eldefrawy et al. Neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer: The likelihood of initiation and completion. Indian J Urol. 2012;28(4):424-6.

29. Culp S et al. Refining Patient Selection for Neoadjuvant Chemotherapy before Radical Cystectomy. J Urol. 2014;191(1):40-7.

30. Ozcan M et al. Low ERCC1 expression is associated with prolonged survival in patients with bladder cancer receiving platinum-based neoadjuvant chemotherapy. Urol Oncol. 2013;31(8):1709-15.

31. Kato Y et al. Predicting response of bladder cancers to gemcitabine and carboplatin neoadjuvant chemotherapy through genome-wide gene expression profiling. Exp Ther Med. 2011;2(1):47-56.

32. Font A et al. BRCA1 mRNA expression and outcome to neoadjuvant cisplatin-based chemotherapy in bladder cancer. Ann Oncol. 2011;22(1):139-44.

33. Chang S et al. Delaying radical cystectomy for muscle invasive bladder

cancer results in worse pathological stage. J Urol. 2003;170(4 Pt 1):1085-7.

34. Hara I et al. Optimal timing of radical cystectomy for patients with invasive transitional cell carcinoma of the bladder. Jpn J Clin Oncol. 2002;32(1):14-8.

35. Lee C et al. Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in decreased disease specific and overall survival. J Urol. 2006;175(4):1262-7.

36. Gallagher DJ, Bajorin DF. Neoadjuvant chemotherapy for the treatment of muscle-invasive bladder cancer: argument in favor. Nat Clin Pract Urol. 2008;5(9):484-5.

37. Alva A et al. Efficient delivery of radical cystectomy after neoadjuvant chemotherapy for muscle-invasive bladder cancer: a multidisciplinary approach. Cancer. 2012;118(1):44-53.

38. Mossanen M et al. Nonresponse to Neoadjuvant Chemotherapy for Muscle-Invasive Urothelial Cell Carcinoma of the Bladder. Clin Genitourin Cancer. 2013;doi:10.1016/j.clgc.2013.10.002. [Epub ahead of print].

39. Petrioli R et al. Comparison between a cisplatin-containing regimen and a carboplatin-containing regimen for recurrent or metastatic bladder cancer patients. A randomized phase II study. Cancer. 1996;77(2):344-51.

40. Bellmunt J et al. Phase I-II study of paclitaxel, cisplatin, and gemcitabine in advanced transitional-cell carcinoma of the urothelium. Spanish Oncology Genitourinary Group. J Clin Oncol. 2000;18(18):3247-55.

41. Dogliotti L et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. Eur Urol. 2007;52(1):134-41.

42. Mertens L et al. Biomarkers for assessing therapeutic response in bladder cancer. Arch Esp Urol. 2013;66(5):495-504.

43. Dancik GT, Theodorescu D. Pharmacogenomics in bladder cancer. Urol Oncol. 2014;32(1):16-22.

44. Meeks J et al. A systematic review of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. Eur Urol. 2012;62(3):523-33.

45. Johnson D et al. Neoadjuvant Chemotherapy for Bladder Cancer Does Not Increase Risk of Perioperative Morbidity. BJU Int. 2013;doi:10.1111/bju.12585. [Epub ahead of print].

46. Gandaglia G et al. The effect of neoadjuvant chemotherapy on perioperative outcomes in patients who have bladder cancer treated with redical cystectomy: a population based study. Eur Urol. 2014;doi:10.1016/j.eururo.2014.01.014. [Epub ahead of print].

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

48. Fedeli U et al. Treatment of muscle invasive bladder cancer: evidence from the National Cancer Database, 2003 to 2007. J Urol. 2011;185(1):72-8.

49. Burger M et al. Use of neoadjuvant chemotherapy for muscle-invasive bladder cancer is low among major European centres: results of a feasibility questionnaire. Eur Urol. 2012;61(5):1070-1.

50. Apolo A et al. Practical use of perioperative chemotherapy for muscle-invasive bladder cancer: summary of session at the Society of Urologic Oncology annual meeting. Urol Oncol. 2012;30(6):772-80.

51. Dash A et al. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer. 2006;107(3):506-13.

52. Dyrskjøt L et al. Expression of MAGE-A3, NY-ESO-1, LAGE-1 and PRAME in urothelial carcinoma. Br J Cancer. 2012;107(1):116-22.

53. Brichard VG, Godechal Q. MAGE-A3-specific anticancer immunotherapy in the clinical practice. Oncoimmunology. 2013;2(10):e25995.

54. Declerck SV, Vansteenkiste J. Immunotherapy for lung cancer: ongoing clinical trials. Future Oncol. 2014;10(1):91-105.

55. El Behi M et al. An essential role for decorin in bladder cancer invasiveness. EMBO Mol Med. 2013;5(12):1835-51.

56. Sainio A et al. Lack of decorin expression by human bladder cancer cells offers new tools in the therapy of urothelial malignancies. PLoS ONE. 2013;8(10):e76190.

Personalising prostate cancer

A PERSONALISED tool has been developed to help predict the likelihood of prostate cancer over-diagnosis, proving to be a valuable tool for both clinicians and patients.

> "We think this is a useful tool for patients and their providers because it helps to tailor knowledge of the risks and benefits of different treatment choices to their individual situations."
>
> *Mr Roman Gulati, University of Washington, Seattle, USA*

Around 42% of prostate cancer cases are over-diagnosed, resulting in unnecessary treatments which can cause devastating side-effects.

"Men with screen-detected prostate cancer are making decisions about treatment based on limited information about the chances that their cancer has been over-diagnosed," said Mr Roman Gulati, lead study author, a statistical research associate, Fred Hutch's Public Health Sciences Division, University of Washington, Seattle, Washington, USA.

The nomogram is a graphical calculating device, which can help to determine personalised treatment options. Incorporating a patient's age, prostate-specific antigen (PSA) level, and Gleason score, it determines the likelihood of over-diagnoses in screening-detected prostate cancer.

By using a visual population, representing men aged 50-84 years of age, the researchers applied existing data, including biopsy practices and cancer diagnosis patterns, to learn about cancer progression in patients with and without screening, and overlaid this with screening and biopsy patterns, to determine when the men would have been diagnosed with and without screening, and who would have died of other causes.

From this, it was predicted that the likelihood of over-diagnosis ranges from 2.9-88.1%, depending on patient age, PSA level, and Gleason score at diagnosis. While nomograms have been used previously, this is the first tool to determine the likelihood of over-diagnosis on an individual level.

Mr Gulati said: "We think this is a useful tool for patients and their providers because it helps to tailor knowledge of the risks and benefits of different treatment choices to their individual situations."

This tool has tremendous potential to help many patients diagnosed with prostate cancer every year. The next step in the process is to develop an interface and test the nomogram in a pilot study.

One drug to cure two cancers

TRASTUZUMAB administered to micropapillary urothelial carcinoma (MPUC) patients with human epidermal growth factor receptor 2 (HER2) amplification, could improve outcomes, just as it has for breast cancer.

HER2 is a known driver of some breast cancers, occurring in approximately 20-30% of cases; the presence of HER2 amplification is associated with particularly aggressive tumours. In order to combat this amplification, trastuzumab is used. This drug has proven to be effective in HER2-positive breast cancers, and because of this it could be an effective therapy to treat MPUC, a type of bladder cancer.

"Targeted treatments for HER2-positive breast cancer have led to markedly improved survival," said Dr John Cheville, a pathologist at the Mayo Clinic, Rochester, Minnesota, USA.

Dr Cheville added: "In one sense, what we are trying to do with HER2-positive bladder cancer is a relatively simple thing. We are trying to identify prognostic and therapeutic biomarkers, and ultimately match the most effective drug to the individual patient's tumour, rather than its location in the body."

The researchers from the Mayo Clinic discovered that some bladder cancers similarly show HER2 amplification and produce too much of the HER2 protein product, which in turn results in more rapid tumour growth and expansion.

These findings are encouraging as it can help pave the way for individualised therapy in cancer care, as well as opening the door for clinical trials. It is crucial that pathologists recognise this particular type of bladder cancer and will enable providers to order the appropriate tests. Dr Cheville said: "This will be essential for any clinical trial examining the effectiveness of trastuzmab in treating MPUC."

"We are trying to identify prognostic and therapeutic biomarkers, and ultimately match the most effective drug to the individual patient's tumour, rather than its location in the body."

Dr John Cheville, Pathologist, Mayo Clinic, Rochester, USA

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Dance incontinence away

DANCING is not one of the first activities that springs to mind when aiming to help senior women combat incontinence, but virtual reality dance games can help to improve pelvic floor muscle strength.

"Dancing gives women confidence, as they have to move their legs quickly to keep up with the choreography in the video game while controlling their urine. They now know they can contract their pelvic floor muscles when they perform any daily activity to prevent urine leakage. These exercises are therefore more functional," explained Dr Chantal Dumoulin, Urogynecological Health and Aging Canadian Research Chair, Faculty of Medicine, University of Montreal, Quebec, Canada.

24 participants followed a series of dance exercises using a video game designed as a physiotherapy programme for pelvic floor muscles. The results indicated that there was an improvement in effectiveness as participants had a greater decrease in daily urine leakage, and an increase in compliance as there were higher weekly participation rates.

> "Dancing gives women confidence, as they have to move their legs quickly to keep up with the choreography in the video game while controlling their urine."
>
> *Dr Chantal Dumoulin, University of Montreal, Montreal, Canada*

Dr Dumoulin explained: "Compliance with the programme is a key success factor: the more you practise, the more you strengthen your pelvic floor muscles. Our challenge was to motivate women to show up each week. We quickly learned that the dance component was the part that the women found most fun and didn't want to miss. The socialisation aspect shouldn't be ignored either: they laughed a lot as they danced!"

While the virtual reality video is not central to the study, it is the most cost-effective technique. Although virtual reality videos have proven effective in a number of studies, this is the first time that a programme such as this has been used to treat urinary incontinence, which opens the door for randomised clinical trials.

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Increased testosterone leading to increased risk of stroke, MI, and death

TESTOSTERONE therapies, used to increase low testosterone, could increase the patient's risk of stroke, myocardial infarction (MI), or death by 29%.

Dr Rebecca Vigen, University of Texas, Southwestern Medical Center, Dallas, USA, warned: "Although physicians should continue to discuss the symptomatic benefits of testosterone therapy with patients, it is also important to inform patients that long-term risks are unknown and there is a possibility that testosterone therapy might be harmful."

This study, is the first observational study which suggests a causal link between testosterone therapy and adverse cardiovascular outcomes. Using data from the Veteran Administration's Clinical Assessment Reporting and Tracking (CART) program, the researchers analysed 8,709 men who had been diagnosed with low testosterone levels and had a high burden of comorbidities: 20% had a history of MI, half had diabetes, and more than 80% had coronary artery disease.

Of the men included in the study, 1,223 were taking testosterone therapy to address their low testosterone levels. After an average of a 28 month follow-up, there were 1,710 adverse events - 443 had MIs, 519 experienced strokes, and 748 men died.

The absolute risks of these events were significantly greater in testosterone users than in non-users, being 1.3% higher at 1 year, 3.1% higher at 2 years, and 5.8% higher at 3 years. In an adjusted analysis of the data, testosterone users were 29% more likely to experience adverse outcomes compared to non-users.

Although it is unclear as to why testosterone increases heart risks, it has been suggested that the hormone might make platelets stick together, possibly leading to blood clots. In order to clarify the safety of these therapies, randomised clinical trials are necessary.

"Although physicians should continue to discuss the symptomatic benefits of testosterone therapy with patients, it is also important to inform patients that long-term risks are unknown and there is a possibility that testosterone therapy might be harmful."

Dr Rebecca Vigen,
University of Texas,
Dallas, USA

Prostate cancer drugs not preventing relapse

"By breaking the cancer down into its component cell types, we get insights into why cancers come back after treatment."

Dr Davide Pellacani, University of York, York, UK

DRUGS which are developed to treat prostate cancer may not be as effective in targeting the root cause of the disease as previously thought, allowing the cancer to return.

Therapies aimed at reversing the process of methylation may not be effective against cancer stem cells, allowing the cancer to return. Methylation was previously thought to drive the development of cancer, but it has now been discovered that it occurs in cells which are already cancerous, making therapies insufficient.

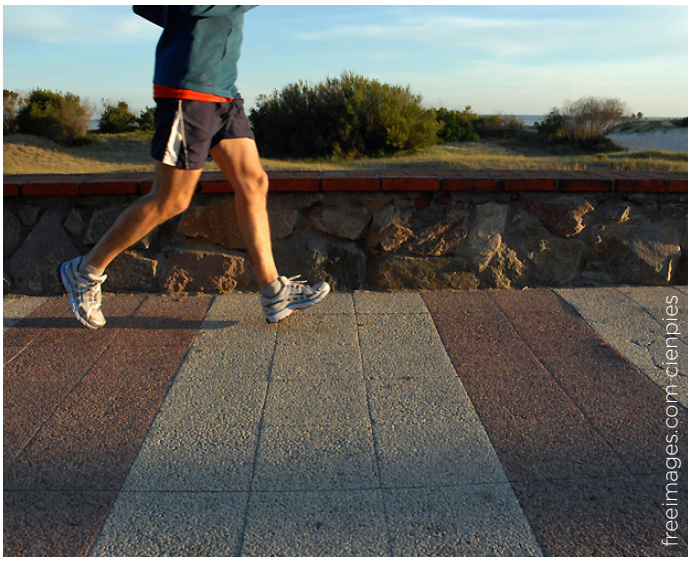
Dr Davide Pellacani, Department of Biology, University of York, United Kingdom, said: "There are obvious differences in the methylation of genes in prostate cancer cells and non-cancer cells. This previously suggested that the process could be driving the progression of cancer, and that this could be reversed by using specific drugs, but our research has suggested that this may not be the case."

However, the researchers have suggested that the methylation in prostate cancer cells is not the primary driving force for the cancer. In fact, strongly linked to the methylation difference is a change from rare basal cells, from which the tumour is formed, and luminal cells, which form the tumour mass – a process called differentiation.

Every week, 267 people die from cancer in Yorkshire; it is for this reason that this team explored the exact molecular properties which allow these cells to spread, survive, and resist aggressive treatments, such as radiation and chemotherapy.

"There are clear implications for the effectiveness of new drugs currently being developed to change the methylation pattern in cancers. At the moment we only treat a proportion of the cells. By breaking the cancer down into its component cell types, we get insights into why cancers come back after treatment. Only by treating all the cells in a cancer will we approach long term treatment or even cure."

ADT: changing men, both mentally and emotionally



CHANGES in both mental and emotional wellbeing have been reported in prostate cancer patients treated with androgen deprivation therapy (ADT).

ADT remains the gold standard for treating advanced prostate cancer, either alone or with radiation therapy. Some patients are likely to experience more adverse effects and complications from the treatment than they do from the cancer itself.

Previous studies have reported a number of cognitive and affective symptoms, but it is unclear if these are a direct effect of the treatment, or if they are in fact linked to factors such as age, comorbidities, hot flashes, fatigue, and insomnia.

Researchers at the University of California, San Francisco, California, USA, gathered data from the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) registry, and studied 3,000 men diagnosed with localised prostate cancer in 1995-2011, who had completed a pre and post-treatment quality of life assessment checklist.

Of the patients included in the study, 75% were treated with local therapy, 20% with combination therapy, and 5% with primary ADT (PADT). In the PADT group, 84% of men were treated with luteinising hormone-releasing hormone agonist monotherapy, and 16% received combined androgen blockade.

> "These results could be related to men in the ADT group adapting to their symptoms over time, thus reporting improved scores."
>
> *Dr Clint Cary, University of California, San Francisco, USA*

The results concluded that exposure to ADT was associated with significant changes in mental and emotional wellbeing; 18% of the PADT group reported poorer memory, compared to 12% in the local group, and 15% in the combination group. After 24 months however, this did not result in clinically meaningful declines.

Dr Clint Cary, lead investigator of the study, University of California, explained: "These results could be related to men in the ADT group adapting to their symptoms over time, thus reporting improved scores."

To minimise the possible ADT-related quality of life changes, Dr Cary advises that all patients should be informed of the potential adverse effects of ADT, and that exercise programmes, as well as dietary/lifestyle changes, should be implemented.

Botox: combatting wrinkles and incontinence

BOTOX, conventionally used to treat wrinkles, could be used to treat urinary incontinence. It is a treatment which has been implemented in India, and the success rate until now has been 100%.

Simple lifestyle changes are often recommended to cure incontinence; however, when these fail then other medical therapies and treatments are suggested.

"It is very helpful in cases where oral and conventional therapy have failed as first line of medical management," said Dr Sanjay Pandey, Urology-Andrology Department, Mumbai's Kokilaben Dhirubhai Ambani Hospital, Mumbai, India.

> "In this case, with one injection of Botulinum Toxin Type A, the effect lasts up to 10 months, depending on the individual's condition, providing ample relief from the debilitating ailment."
>
> *Dr N.K. Mohanty, Delhi Saket City Hospital, New Delhi, India*

Purified protein is injected into the detrusor muscle and blocks the overactive nerve impulses which trigger excessive muscle contraction in the bladder. This non-invasive procedure takes around 15 minutes, and does not affect any other part of the body.

Dr Pandey added: "Lasting up to 9-10 months, the bladder's over-activity is vastly decreased (by Botox) and thus returns to the reorganised activity of the concerted bladder contractions in response to stimuli of bladder filling at more appropriate times of complete bladder fullness."

Although only a temporary measure, Botox provides various advantages, Dr N.K. Mohanty, Head of the Urology department, Delhi Saket City Hospital, New Delhi, India, explained: "Take a condition where a person has to take medicine every day. There is the cost you bear with long intake of the medicine, plus if you forget to take the medicine, it will impact the effect.

"In this case, with one injection of Botulinum Toxin Type A, the effect lasts up to 10 months, depending on the individual's condition, providing ample relief from the debilitating ailment."

Botox is often used when other remedies fail, as a result, the US Food and Drug Administration have approved the use of Botox to treat overactive bladders in adults.

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Urology

Responsible for the development of some of the world's most important drug products in fields ranging from diabetes care to veterinary medicines, Bayer HealthCare is a giant and key innovator in the manufacturing of pharmaceutical and medical products. The Bayer subdivision's aim is to make state-of-the-art, ground-breaking products to improve the lives of patients worldwide. It aims to accomplish this through its consumer care, medical care, and pharmaceuticals divisions, with an eye on addressing some of the great challenges in the modern era. The company has bases in 5 continents, with approximately 55,300 people working for the subgroup in over 100 countries.

Ferring Pharmaceuticals Ltd has a product portfolio that demonstrates an innovative and successful track record in urology, endocrine oncology, gastroenterology, endocrinology, and reproductive health. The company has developed strong expertise through the development of technologies, which facilitate the use of peptide and protein compounds, and is thus able to capitalise on its position as one of the world's leading companies in this field of chemistry. Ferring has a powerful global presence, and its products are distributed across more than 70 countries. In-house manufacturing is carried out in Switzerland, Denmark, Germany, Czech Republic, and China, and there are research centres in Denmark and the USA.

Institut Biochimique SA (IBSA) is a privately owned pharmaceutical company based in Lugano, Switzerland, marketing its products in over 70 countries, including the USA. IBSA has developed a series of proprietary technologies for improvement of already-available and widely-used molecules and therapeutic solutions. IBSA has become established on a global scale through partnerships and local branches in Italy, France, Hungary, Slovak Republic, Poland, Turkey, and China. Their successes are due to an in-depth competence in basic research, pre-clinical and clinical development, high manufacturing quality, regulatory expertise, and direct marketing of proprietary products.

Ipsen is a Paris-based pharmaceutical firm that looks to find effective therapeutic solutions to cure disease and relieve pain in communities worldwide. The company aims to become one of the top ten global pharmaceutical powers in terms of growth and profitability. Ipsen focuses its resources heavily on three targeted specialty care areas, which have been organised into specific franchises: neurology, endocrinology, and uro-oncology. Ipsen is also present in primary care in the symptomatic treatment of certain forms of cognitive disorders in the elderly (Tanakan®), as well as in gastroenterology (Smecta®, Forlax®), and rheumatology.

Lenus Pharma is an Austrian pharmaceutical company that specialises in fertility medicines, aiming to become one of the main global players in the healthcare industry, and it is always striving to develop and market innovative products. Lenus is constantly working to deliver novel compounds of the highest quality, and has an impressive track record including PROfertil®, PROpregna®, and PROglanat®. Lenus handles the entire manufacturing process for these drugs, from the raw materials to the finished packaging stages. The company delivers these life-changing treatments internationally.

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- COOK MEDICAL
- CRYOLIFE EUROPA, LTD.
- CURAN MEDICAL BV
- DIREX GMBH
- DORNIER MEDTECH EUROPE GMBH
- DYNAMESH BY FEG
- EDAP TMS
- EIGEN
- ELEKTA
- ELI LILLY AND CO.
- ELMED LITHOTRIPSY SYSTEMS
- ELMEDICAL LTD.
- EMS ELECTRO MEDICAL SYSTEMS
- ENDOCARE, INC.
- ENDOCONTROL
- ERASMUS S.A.
- ERBE ELEKTROMEDIZIN GMBH
- ESSM
- EUROMEDICAL GMBH
- EUROPA UOMO
- FERRING INTERNATIONAL CENTER S.A.
- GALIL MEDICAL
- GE HEALTHCARE
- GENOMIC HEALTH
- GLAXOSMITHKLINE
- GRENA LTD.
- HISTOSCANNING™ by AMD
- HITACHI MEDICAL SYSTEMS EUROPE HOLDING AG
- HOLOGIC, INC.
- IBSA INSTITUT BIOCHIMIQUE SA
- IDL BIOTECH AB
- INCONTROL MEDICAL, LLC
- INTUITIVE SURGICAL
- INVIVO
- IPSEN
- ISTEM MEDIKAL
- JANSSEN PHARMACEUTICAL COMPANIES
- JENA MED TECH GMBH
- KARL STORZ GMBH & CO. KG
- KITALPHA MED LTD.
- KLS MARTIN GROUP

Urology

- KOELIS
- LABORIE
- LASER PERIPHERALS
- LENUS PHARMA GESMBH
- LISA LASER PRODUCTS
- LUMENIS (GERMANY) GMBH
- LUT GMBH
- M.A.S.
- MCUBE TECHNOLOGY
- MEDA CO., LTD.
- MEDAC GMBH
- MEDCOM GMBH
- MEDICA S.P.A.
- MEDICAL MEASUREMENT SYSTEMS B.V.
- MEDISPEC LTD
- MEDKONSULT
- MEDPRO MEDICAL B.V.
- the MENARINI GROUP
- MIM SOFTWARE, INC.
- MONTAVIT GMBH
- MYRIAD GENETICS GMBH
- NEOMEDIC INTERNATIONAL S.L.
- NEOTRACT, INC.
- OLYMPUS EUROPA SE & COKG
- OPKO DIAGNOSTICS
- PAJUNK GMBH
- PHYSION
- PIERRE FABRE MÉDICAMENT
- PROFOUND MEDICAL, INC.
- PROGENICS PHARMACEUTICALS, INC.
- PROMEDON S.A.
- QUANTA SYSTEM SPA
- RECORDATI
- RICHARD WOLF GMBH
- ROCAMED
- SAMED GMBH DRESDEN
- SANDOZ & NOVARTIS
- SIEMENS AG HEALTHCARE SECTOR
- SONACARE
- SONY EUROPE LIMITED
- SPHINX MEDICAL LTD.
- STARMEDTEC GMBH
- STORZ MEDICAL AG
- SURGIQUEST, INC.
- SYNERGO-MEDICAL ENTERPRISES
- TAEWOONG MEDICAL, CO. LTD.
- TAKEDA
- T-DOC COMPANY, LLC
- TELEFLEX
- TEVA ONCOLOGY
- TRIBUTE PHARMACEUTICALS CANADA, INC.
- TRISTEL SOLUTIONS
- UROMED KURT DREWS KG
- UROTECH GMBH & UROVISION GMBH
- VIRTAMED AG
- VISION-SCIENCES, INC.
- WELLSPECT HEALTHCARE
- ZEPHYR SURGICAL IMPLANTS

Annual Meeting of the British Association of Urological Surgeons (BAUS)

23rd-26th June 2014

Liverpool, United Kingdom

The aim of the BAUS meeting is fostering education, research and clinical excellence, all within the practice of urology. The main events will focus on academic urology, andrology and genito-urethral surgery, and also female neurological and urodynamic urology, as well as an education teaching and skill course.

69th Annual Meeting of the Canadian Urological Association

28th June-1st July 2014

St John's, Canada

The educational programme aims to represent the dynamic groups within all regions of Canada and also all of the sub-specialties within urology. This event includes topics such as paediatric urology, prostate cancer, endourology and stone disease, and also female urology and pelvic floor reconstruction.

25th World Congress on Videourology and Advances in Clinical Urology

19th-22nd July 2014

Sofia, Bulgaria

You are invited to this meeting which promotes the exchange of knowledge among both researchers and clinicians in a variety of plenary sessions and presentations. All healthcare providers with an interest in urology and videourology are urged to attend this very promising and enthralling scientific event.

7th International Symposium on Focal Therapy and Imaging in Prostate and Kidney Cancer

21st-23rd August 2014

Pasadena, USA

Aimed at practicing urologists as well as urologic trainees, a world-class faculty will present hands-on sessions which will teach trainees the practical skills required in contemporary practice. The event will take a more direct and interactive approach by featuring a number of live-surgery demonstrations.

32nd World Congress of Endourology

3rd-7th September 2014

Taipei, Taiwan

Organised by the Endourology Society, this international event acts as a forum for endourologists worldwide. The topics featured include female urology, transurethral surgery, and ureteroscopy. Throughout the Congress there will be a number of interactive sessions and also live-surgery demonstrations. The main theme of the Congress this year is: 'Evolving endourology for future generations'. The most cutting-edge technology in endourology will be showcased throughout the event.

11th Meeting of the EAU Robotic Urology Section (ERUS)

17th-19th September 2014

Amsterdam, the Netherlands

This meeting is specifically designed for urologists interested in the latest technical developments, and the continuous progress of urological science and practice. Specialists who attend will be educated in robotic surgical techniques, with the ultimate goal of improving the level of patient care.

Urology Update 2014: New Ideas, Approaches and Techniques

31st October-1st November 2014

Toronto, Canada

Participants with an interest in clinical urology are invited to attend this event, which focuses on updates within the field, including new developments and their various alternatives. These lectures will consist of discussions, case presentations, and audience participation, all presented by world-renowned experts. Participants will increase their knowledge within the field of clinical urology, facilitating the management of clinical problems.

6th European Multidisciplinary Meeting on Urological Cancers (EMUC)

14th-16th November 2014

Lisbon, Portugal

The world's leading experts in the management of urological cancers will join together for this renowned and truly multidisciplinary event. Participants will attend events concerned with the latest updates in treatment strategies, translational research data, and care discussions pertaining to many controversial issues.