EMJ EUROPEAN MEDICAL JOURNAL

UROLOGY

ISSN 2053-4213 Vol 3.1 • January 2015 • emjreviews.com

CONTENTS

UROLOGY

Editorial Board

Urology

EMJ GORELY NEW MEDIA

European Medical Journal
EMJ Urology Vol 3.1
January 2015

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Welcome

I would like to extend a very warm welcome to this edition of the *European Medical Journal Urology*. This year we have taken a different approach to the way we publish our journals. This first version of *EMJ Urology* will consist of high-quality peer reviewed papers, the second will review the very prestigious European Association of Urology (EAU) Congress, due to take place in March, and the third version will feature some of the top abstracts from the 11th National Endourology Congress, commencing in April.

It is estimated that in the United Kingdom alone, around 10,000 people are diagnosed with bladder cancer (BC) a year. While tobacco is suspected to be the main cause, genetic factors also play a role in its development. As a result of this there has been a vast amount of literature discussing the associations between genetic variation and BC risk. '*Bladder cancer and genetic polymorphisms: a review*' written by Erol et al. explores the idea that a pathway-based genotyping approach could possibly highlight the various effects of individual polymorphisms, and may be more beneficial to an association study.

The field of urology is a diverse and ever-changing one; it is a field which utilises the latest and best technology to achieve the best positive outcomes for patients. It is a discipline that can be very challenging and one which is constantly evolving. Therefore, it is our hope that this journal will provide you with the latest updates in clinical practice and that it will have a positive influence upon your practice, it will also help you to generate new ideas, and ultimately benefit your patients.

An excellent example of evolution in urology is minimally invasive surgery (MIS), more specifically used in radical prostatectomy (RP). Although robot-assisted surgery is more conventional, recent advancements in MIS aims to improve functional outcomes after RP while also decreasing invasiveness and complications. Drs Riikonen and Kaipia explain the benefits of this demanding procedure in detail in their paper '*Recent developments in minimally invasive radical prostatectomy*'.

With the help of our highly esteemed Editorial Board and our new Editor-in-Chief we have created an outstanding journal. We hope that this journal proves useful to people of all levels, whether you are just starting out in your career, or if you have been a specialist with many years' experience. We are very excited to see how this field will develop in the future and with the 2015 EAU Congress just around the corner, we will not have long to wait.

Spencer Gore

Director, European Medical Journal

European Medical Journal Urology is published three times a year.
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Front cover and contents photograph: Camila Carlow/eyeheartspleen.com

Foreword

Dr A. Erdem Canda

Associate Professor of Urology,
Yildirim Beyazit University, Turkey.

Dear Colleagues and Friends,

It is a great pleasure for me to be serving as the new Editor-in-Chief of the *European Medical Journal Urology* for the forthcoming editions. I would like to sincerely thank Dr Ali Serdar Gözen from Heilbronn, Germany, who has put in great efforts as the Editor-in-Chief and made *EMJ Urology* a success under his term. I would like to follow in his footsteps in the continuation of producing high-quality journals which can be beneficial to the urological community and beyond. I would also like to thank the esteemed members of the editorial board whose continued support and cooperation have made this publication possible.

> "Urology might be one of the leading surgical specialities in the world as it has made a significant development parallel to its technological developments."

EMJ Urology has made major improvements since it was first published and continues to attract the attention of many healthcare professionals with significant contributions to the field of urology. This recent publication includes many interesting papers covering the numerous sub-specialities of urology, such as urologic oncology, endourology, reconstructive urology, benign prostatic hyperplasia management, and basic clinical and scientific research. Additionally, there is a challenging case report concerning a rare case of echinococcosis, which will pique the interest of both experienced urologists as well as those starting their careers.

Urology might be one of the leading surgical specialities in the world as it has made a significant development parallel to its technological developments. Urology utilises advanced technology in almost all surgical approaches and applications, such as robotic urology, endourology, and laparoscopic urology, which particularly attract the interest and attention of the younger generation. We will see more applications of these technological developments during this year's upcoming congresses, such as the European Association of Urology (EAU) Congress, which we all look forward to participating in. The EAU 2015 Congress will be held in Madrid, Spain, from 20th-24th March 2015, and will be the main feature in the next issue of *EMJ Urology*.

I would like to take this opportunity to invite you all to submit your articles to *EMJ Urology* and visit the website!

With kind regards,

A. Erdem Canda

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

Exclusive Interviews from the European Association of Urology (EAU) Congress 2014

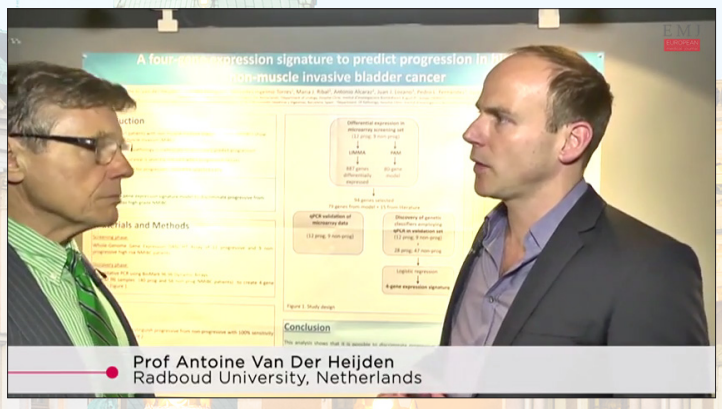
(Click on video clip to view)

PREVAIL Study Findings: Hormone Control in Prostate Cancer

Prof Bertrand Tombal

The German Working Group in Regards to mCRPC

Prof Axel Merseburger



Bladder Cancer: Invasive or Not

Prof Antoine Van Der Heijden

Meta-Analysis on Superficial Bladder Cancer

Prof Joaquim Bellmunt

Radical Prostatectomy and the Use of Radical Therapy

Prof Ashwin Sachdeva

Adjuvant Radiotherapy with Radical Prostatectomy: Phase III Study Results

Prof Kurt Miller

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EDITOR'S PICK

The surgical robot has the advantage of enabling the console surgeon to perform complex procedures more easily, providing three-dimensional 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. Robotic radical prostatectomy can be learned and performed successfully in the hands of surgeons without previous laparoscopic radical prostatectomy experience!

Dr A. Erdem Canda

RECENT DEVELOPMENTS IN MINIMALLY INVASIVE RADICAL PROSTATECTOMY

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Disclosure: J.R. was a surgeon proctor for Intuitive Surgical Inc. in 2011. A.K. has no potential conflict of interest.
Received: 23.10.14 **Accepted:** 28.11.14
Citation: EMJ Urol. 2015;3[1]:12-18.

ABSTRACT

Minimally invasive surgery has gained a dominant status in prostate cancer surgery during the last decade. The benefits of minimally invasive prostatectomy were demonstrated by pioneers of conventional laparoscopic prostatectomy, however, the real domination of laparoscopy in radical prostatectomy (RP) started after the dissemination of robotic surgery. Robot-assisted surgery still remains the most widespread method to perform minimally invasive RP, although the recent evolution of laparoscopic technology and instruments has evoked interest in conventional laparoscopy again. The recent developments in the technique of RP are focused on decreasing invasiveness and complications. The recent methods to improve postoperative functional outcome of RP can be utilised without compromising the oncological results.

Keywords: Prostate cancer, minimally invasive surgery, surgical technique, outcome.

INTRODUCTION

Intracapsular adenocarcinoma of the prostate is most effectively cured by total surgical elimination of the prostate. Even though the first reports of perineal prostatectomy date from 1901 by Proust and radical prostatectomy (RP) from the 1940s by Millin, surgical removal of the prostate remained an unpopular treatment modality for localised prostate cancer (PrC) due to its high perioperative and postoperative morbidity. Anatomical studies of the Santorini plexus[1] and cavernous nerves[2] by Walsh formed the scientific basis for the development of contemporary RP with acceptable treatment related morbidity and quality of life (QoL) combined with excellent oncological outcome. Since its introduction in the early 1980s, radical retropubic prostatectomy (RRP) with later modifications[3] has remained the gold standard for the surgical treatment of PrC.

EVOLUTION OF MINIMALLY INVASIVE RP

Minimally invasive surgery (MIS) was initially utilised in urology in the treatment of disorders of the upper urinary tract. Since the first laparoscopic nephrectomy,[4] the benefits of MIS in urological

indications soon became obvious; low perioperative morbidity combined with equal functional and oncologic outcomes made MIS a potential technique that could replace conventional surgery in several urological indications. RP, however, is a demanding procedure that requires great skill and dexterity when performed conventionally let alone by means of MIS. The first laparoscopic radical prostatectomies (LRPs) were reported by Schlusser et al.[5] and Guillonneau et al.[6] After initial enthusiasm, several early adopters discontinued performing LRPs due to the long operating time and slow learning curve. In expert hands LRP remained a viable technique[7] and its benefits in terms of low morbidity combined with good oncologic outcome were demonstrated.[8] However, global dissemination of endoscopic prostatectomy was long hindered by the long learning curve and lack of instrumentation that would ease the reconstructive phase of the procedure.

Robotic telesurgery was initially developed for the needs of military forces. In the beginning, commercially available robotic devices were utilised in thoracic surgery, but it was soon discovered that the 3D vision and superior dexterity enabled by the EndoWrist® make RP a particularly well-suited indication for robot-assisted laparoscopic surgery. Robot-assisted laparoscopic radical prostatectomy (RALRP) was first performed by Binder and Kramer[9] and reported by Abbou and associates.[10] Since its introduction, robot-assisted surgery has been criticised for the high economic burden that it causes to the healthcare system. However, this drawback is much outweighed by its benefits: low morbidity of MIS, short learning curve, and a superior potential of technical refinements of the surgical procedure. RALRP was popularised after the pioneer work of early adopters, who described the surgical procedure in detail and reported superior results.[11] Nowadays RALRP is the most common method used to perform RP in the United States, as well as in many European countries. For example in Finland, where robotic surgery landed in late 2008, around 80% of RPs were RALRPs in 2014 (unpublished data). The proportion of RALRP increased rapidly even though high-quality evidence of its superiority is lacking.[12] RALRP is dominant in affluent countries but cost is prohibitive for its universal application at present. Reduction of the cost of robotics may, in future, allow universal dissemination of minimally invasive RP. Compared to RRP, laparoscopic or robot-assisted radical prostatectomies have been shown to decrease blood loss and hospitalisation time.[8] It also seems that the complication rate after MIS is decreased.[8,13] However, no superiority in terms of oncological outcome nor postoperative urinary continence and potency has been demonstrated.[8] This review focuses on the recent developments in this field.

RECENT ADVANCES OF MINIMALLY INVASIVE PROSTATECTOMY

Although there are reports of several surgical robots that are under development worldwide, more than a decade after its introduction, the da Vinci robot by Intuitive Surgical (Intuitive Surgical, Sunnyvale, CA, USA) still remains the only commercially available robotic device. The fourth generation da Vinci Surgical System, da Vinci Xi, was only introduced recently. Da Vinci Xi features new advanced EndoWrist® instruments, free placement of the camera at any of the robotic arms, and a wider operation field. The new patient cart architecture with overhead arms facilitates preoperative arrangement by allowing easier docking of the patient cart (Intuitive Surgical, Inc., Press release, 1st April, 2014). In theory, the new da Vinci Xi may help in decreasing the operation room time, but there are no clinical studies yet to confirm this.

In contrast to open and laparoscopic surgery, in robotic surgery there is no physical contact between the surgeon and the patient. Distance between the surgeon and the surgical site is a challenge for the teaching and learning of robotic surgery. The European robotic urologic society has started a pilot study for European robotic curriculum.[14] This includes theoretical sessions, skills training, real-case observation, bedside assistance, and mentored training at the console. In the study, RALRP is divided into modules, which are categorised to levels of difficulty. As expertise grows, the trainee will start learning more difficult modules. Finally, the trainee is able to perform the whole procedure independently.[14] In laparoscopy, new generation 3D technology by Olympus (ENDOEYE FLEX 3D), Karl Storz (3D TIPCAM), Braun (Einstein Vision), and Richard Wolf (Endocam Epic 3DHD) have made 3D vision available also in conventional laparoscopic surgery. 3D display enhances the depth perception, spatial location, and surgical performance, for instance, in helping the surgeon to tie a knot.[15] In RP, 3D vision has been shown to decrease operative time (particularly that of performing the urethrovesical anastomosis),

lowers the operative blood loss and may help in improving the early continence rate.[16] Even after the recent developments of the technique of conventional laparoscopic prostatectomy, it seems that its outcomes (operative time, blood loss, hospital stay, potency recovery, and marginal status in organ-confined disease) remain slightly inferior to RALRP.[17]

The principle of minimising invasiveness has led to development of laparo-endoscopic single-site surgery (LESS). LESS has been shown to be feasible in several urological indications,[18] and it may be superior in terms of cosmetic results. Surgery via a single entry point is, however, technically challenging. Crossing instruments at the abdominal wall, lack of triangulation and instrument collision are the main difficulties of LESS surgery. Curved and angulated instruments and endoscopes have been developed to ease or overcome these challenges. Triangulation can be achieved by adding a needlescopic instrument in the configuration (hybrid LESS). Robotic manipulator decreases the trouble caused by crossing instruments at the abdominal wall and facilitates suturing. Furthermore, curved instrument cannulae and semi-rigid robotic LESS instrument have been developed. Even though robotic LESS RP is feasible and safe,[18] more developments and studies are needed before its universal clinical implementation is reasonable.

ONCOLOGICAL ASPECTS

RP is first and foremost an oncologic operation. Therefore, good oncological results must remain the main goal. Because the prognosis of localised PrC is good, great attention has to be paid also to satisfactory functional outcomes: nerve sparing is recommended if it is deemed oncologically safe. Preoperative evaluation including clinical examination, prostate specific antigen (PSA) determination, Gleason score, and the number of biopsy cores positive for cancer are used in this evaluation. Recently, preoperative magnetic resonance imaging (MRI) has also been utilised in the preoperative staging. Despite best efforts, unnecessary nerve sacrificing and incorrect nerve sparing still remain a common issue. Intraoperative neurovascular structure-adjacent frozen section examination (NeuroSAFE) of the prostate has been developed to minimise this problem.[19] The NeuroSAFE method has been shown to increase the nerve sparing rates from 81% to 97%, while decreasing positive surgical margin rates from 24% to 16%.[20]

Pelvic lymph node dissection is the most effective method to detect metastatic lymph nodes (MLNs) in PrC. Its significance to prognosis, however, is still controversial. While lymphadenectomy is safe during RALRP, it does increase the operative time and is associated with postoperative incidence of lymphoceles.[21] Despite the shown effectiveness of extended pelvic lymphadenectomy in nodal staging, isolated MLNs can also be found outside the common lymphadenectomy template.[22] The need to avoid unnecessary lymph node removal and to increase the sensitivity and specificity of the procedure, have been the main goals in the development of sentinel node (SN) mapping. Indocyanine green has been injected directly into the prostate and used as a tracer to detect lymphatic drainage.[23] Percutaneous robot guided injection of the tracer was shown to be the fastest, cheapest, and also the most aseptic method. Sentinel lymphatic drainage could be identified in the majority of patients by using this tracer. Fluorescence positivity was visualised subsequently by using Firefly® technology during robotic surgery. The method was shown to be highly sensitive but relatively nonspecific for the detection of nodal metastasis.[23] Indocyanine green technology was improved by van der Poel and co-workers[24] by using indocyanine green combined with technetium-99m tracer. Sentinel lymph nodes were detected by single-photon emission computed tomography computer tomography preoperatively and by fluorescence imaging intraoperatively.[24] Fluorescence-based SN visualisation was further optimised by increasing particle concentration, decreasing injection volume and by upgrading laparoscopic fluorescence imaging system (Image 1 HUB HD with D-Light P system). These improved the sensitivity of SN identification up to 93.5%.[25]

METHODS TO IMPROVE CONTINENCE

Incontinence is the most QoL decreasing side-effect of RP. Recent systematic review and meta-analysis has shown the incontinence rate after RALRP to be 0-11% at 1 year postoperatively.[26] Several methods have been developed to decrease and shorten the duration of postoperative incontinence. Rocco et al.[27] introduced posterior rhabdosphincter reconstruction (Rocco stitch) in RRP and showed improved postoperative continence rates. This technique was rapidly adapted to RALRP as well.

Modified Rocco stitch posterior reconstruction has been shown to decrease the urinary incontinence at 1 and 3 months after RALRP, but it has little effect on long-term continence rates.[28,29] However, in other studies, posterior rhabdosphincter reconstruction had no effect on urinary continence rates.[30-33] The putative effect of Rocco stitch was later analysed in a systematic review and meta-analysis. The cumulative analysis showed that posterior reconstruction caused small but significant improvement of urinary continence within 1 week (RR=1.79, p=0.03) and at 30-45 days (RR=1.57, p=0.004), but had no effect at 90 days postoperatively.[34] In summary, posterior rhabdosphincter reconstruction may improve short-term continence, but has no effect on long-term continence rates. Similarly Patel's method[35] to perform anterior periurethral suspension stitch has been shown to improve urinary continence at 3 months after RALRP without an effect on continence at 1, 6, and 12 months postoperatively. Our opinion is that the most important effect of posterior reconstruction is its positive effect on haemostasis, and that it permits construction of a tension-free urethrovesical anastomosis.

The concepts of either anterior or posterior reconstruction were further refined and a total pelvic floor reconstruction (posterior and anterior) technique was introduced. The total pelvic floor reconstruction showed significantly improved continence rates compared to posterior reconstruction only. The mean interval to achieve continence was also significantly shorter in the total pelvic floor reconstruction group (mean 7.7 months) than in the non-total pelvic floor reconstruction group (mean 9.8 months).[36] Later, other methods to perform periurethral reconstruction during RP have been reported. For instance Complete Reconstruction of the Posterior Urethral Support[37] is a recent method showing excellent immediate after catheter removal and 30 day postoperative continence results. Most likely these reconstructive methods have a positive effect on postoperative continence and they may shorten the time to reach continence, but their superiority is not yet thoroughly studied.

Bladder neck preservation leads to at least partial internal sphincter sparing. It is shown to improve urinary continence at 4 months from 26.5% to 65.6%,[38] leading to earlier recovery of urinary continence.[39,40] Furthermore, bladder neck preservation did not compromise cancer control, i.e. positive surgical margins[38] nor PSA recurrence during 5-year follow-up.[39] Similarly, maximal urethral length preservation improves postoperative continence rates and shortens time to achieve continence among patients undergoing RALRP without increasing the risk of positive margins.[41] The effect of urethral length and volume and proximity of levator muscle to membranous urethra on postoperative continence rates were studied by preoperative MRI-based measurements among 967 men. Urethral length and volume and close relationship between the levator muscle and membranous urethra were associated with recovery of urinary continence at 6 and 12 months after open RP.[42] The patients who had longer membranous urethral length measured by intra operative transrectal ultrasound had better continence rates at 1, 3, and 6 months after LRP.[43] It has been suggested that urethral length preservation may actually have more effect on continence than posterior rhabdosphincter reconstruction and anterior bladder suspension.[41]

Nerve sparing is naturally associated with better postoperative erectile results, but it may also improve urinary continence.[44] Therefore, nerve sparing should not be excluded from men with impaired preoperative erectile function. Also lateral prostatic fascia (endopelvic fascia) preservation during RALRP may have a positive effect on return of continence. When the effect of lateral prostatic fascia preservation during RALRP was studied in 151 men, the return of continence was significantly improved at 6 and 12 months postoperatively.[45] Similarly the preservation of puboprostatic ligaments improves continence rates at 2 weeks and at 3 months following surgery.[46] The complete method to spare a pubovesical complex maximises preservation of the pelvic supporting system. During this technically demanding procedure the prostate must be the shelled out underneath pubovesical complex, which may enhance immediate continence results.[47]

High quality of the anastomosis is an important factor to decrease catheterisation time and to prevent anastomotic strictures. Delayed healing of the anastomosis may also be associated with delayed urinary continence.[48,49] Prevention of urethrovesical anastomosis (UVA) leakages seems to be the most important factor to ensure undisturbed healing of the anastomosis. We performed a prospective randomised study in order to examine if a catheter with a side-fenestration at the site of the anastomosis could minimise leakages after RALRP. The extra fenestration of the

catheter prevents formation of pressure at the site of the anastomosis, which may occur if the ureteral orifices are located near the bladder neck under the catheter balloon. We showed that a side-fenestrated catheter decreases UVA leakage rates after RALRP from 12.3 % to 4.6 %.[50] Urinary catheter is a major factor causing discomfort after RALRP. Attempts have been made to avoid catheterisation altogether by using a suprapubic cystostomy as drainage. This method was shown to decrease pain after RALRP in about 50% and resulted in a 2.5-fold faster recovery of continence.[51,52] However, a randomised clinical trial could demonstrate no significant difference in postoperative pain among patients having either a suprapubic cystostomy or a urethral catheter.[53]

In its introduction, the most common method to reconstruct UVA during minimally invasive prostatectomy is the van Velthoven technique.[54] However, recently uni or bidirectional barbed sutures have increased in their popularity. Prospective randomised trials have shown that the use of barbed suture (V-Loc 180, Covidien, Mansfield, MA, USA) may shorten anastomotic time and improve the primary water tightness of the anastomosis.[55-57] On the other hand, when using barbed sutures, one has to pay attention to avoid over tightening, because it may lead to the postoperative anastomotic leakage.[55]

RECOVERY OF SEXUAL FUNCTION

Prediction of postoperative incontinence after RALRP is rather complex and an uncertain issue, whereas, erectile function is more straightforward to evaluate. Postoperative continence is important to all patients, but the need of postoperative sexual function varies; if the patient is sexually active, postoperative impotence may significantly worsen his QoL. The possibility to preserve sexual function after RP became obvious when Walsh et al.[2] introduced nerve sparing RRP in 1982. Initially it was described that neurovascular bundles are located in dorsolateral aspects of the prostate.[2] Later studies have demonstrated a whole network of periprostatic nerve fibres, some of which are also located on the anterior surface of the prostate. This finding has led to new improved methods of performing nerve sparing: e.g. 'The Veil of Aphrodite'.[11] Another important technique to improve erectile function postoperatively is to use a cautery-free technique.[58] Cavernous nerves are also sensitive to traction-induced neuropraxia. Studies have shown that countertraction on neurovascular bundle can delay recovery of sexual function and potency.[59,60]

Improved vision of surgical field during laparoscopy enable more precise visualisation and dissection of the prostatic fascia. Prostate can be released from surrounding tissue intra, inter, or extrafascially. Intra and interfascial planes enable nerve sparing but increase the risk of positive surgical margins. Extrafascial dissection improves cancer control but sacrifices erectile nerves. Therefore it is essential to make careful preoperative evaluation of the dissection plane in agreement with the patient.

CONCLUSION

RP is the treatment of choice for localised PrC. RRP has set the standard of anatomical dissection and resection. Laparoscopic and robotic surgeries have successfully adopted these principles without compromising cancer control and functional outcomes while delivering the advantages of MIS. Recently the main developments in PrC surgery are aimed to further decrease the incidence of complications related to RP, i.e. incontinence and impotence. Several surgical modifications have been developed as an attempt to reach this goal. However, it seems that the most significant factors to improve both oncologic and functional outcomes of prostate surgery are excellent anatomical knowledge and meticulous surgical technique.

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BLADDER CANCER AND GENETIC POLYMORPHISMS: A REVIEW

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Disclosure: No potential conflict of interest.
Received: 13.10.14 **Accepted:** 19.11.14
Citation: EMJ Urol. 2015;3[1]:20-25.

ABSTRACT

The aetiology of bladder cancer (BC) is still not fully understood. Genetic factors and many different pathways could be involved in the formation and progression of the BC. Some investigators have reported genetic polymorphisms (GPMs) in various genes which might be associated with BC. As summarised below, we have seen an explosion of literature reporting an association between genetic variation and BC risk, as well as between GPM and clinical outcome. In this review GPMs are categorised based on their primary cellular functions: genes in carcinogen metabolism, DNA repair, cell cycle control, inflammation, apoptosis, methylation, genes functioning as G proteins, and cell adhesion molecules. A pathway-based genotyping approach, which assesses the combined effects of a panel of polymorphisms that act in the same pathway, may amplify the effects of individual polymorphisms and should be more advantageous to association study than the candidate gene approach.

Keywords: Bladder cancer, gene, polymorphism.

INTRODUCTION

Bladder cancer (BC) is the most common malignancy of the urinary tract, the fourth most common cancer in men, and seventeenth most common cancer in women. 74,690 total cases were diagnosed in the United States in 2014, accounting for 4% of all cancers.[1] Tobacco is the main known cause for urothelial cancer (UC) formation. In addition, following the skin and lungs, the bladder is the main internal organ affected by occupational carcinogens. In general, there is a long latency period of 10-20 years between the industrial exposure and the formation of the BC, thus proving a definitive causative relationship is difficult. However, there are a variety of occupations statistically associated with BC formation, and all are industrial in nature. 20-27% of all BCs are associated with industrial exposure of some type, primarily in areas with a heavy concentration of chemical industries.[2]

It is increasingly clear that genetic factors play a critical role in determining the risk of BC. First-degree relatives of patients with BC have a 2-fold increased risk of developing UC themselves, but high-risk of UC families are relatively rare. The inherited risk of BC formation appears to affect all stages of urothelial carcinoma and is not associated with BC formation at an earlier age. Unfortunately, there are no clear Mendelian inheritance patterns, making classic linkage studies impossible.

GENETIC POLYMORPHISM (GPM)

GPM is the occurrence in the same population of two or more alleles at one locus, each with appreciable frequency.[3] Geneticists use the term GPMs to describe the inter-individual, functionally silent differences in DNA sequence that make each human genome unique. There are several polymorphisms that seem to be related to the formation of BC, in particular the susceptibility to environmental carcinogens. Many different mechanisms such as, metabolism of carcinogens, DNA repair, cell cycle checkpoint control, apoptosis, and other interconnected cellular processes constitute a network that mediates the toxicologic response of the bladder micro ecosystem. In the following sections, the association between GPMs

of these key cellular mechanisms, BC risk, and disease progression is described.

Carcinogen Metabolism

Individual differences in cancer susceptibility may be explained to a certain extent by genetic differences in metabolic activation and detoxification of carcinogens. The dynamic equilibrium between carcinogen-activating enzymes and detoxifying enzymes might be fundamental to determine the cell fate after exposure. Cytochromes P-450 (CYPs) is the key metabolic enzyme family capable of metabolising drugs and chemicals. The metabolism of a toxicant consists of two phases: Phase I enzymes, mainly CYPs, typically involved in the activation of carcinogens, whereas multiple Phase II enzymes generally function to detoxify carcinogens. The balance between Phase I and II enzymes often determines the accumulation of reactive intermediates, which may cause oxidative stress and toxicity.

CYP1A1 is an important Phase I xenobiotic metabolising enzyme, well known for its involvement in the metabolic activation of tobacco procarcinogens such as polycyclic aromatic hydrocarbons and aromatic amines. It is a highly polymorphic gene with more than 11 alleles thought to lead to amino acid changes. The majority of the eligible studies observed no significant association between CYP1A1 mutations and BC risk.[4,5] No significant association was found between CYP1B1 polymorphisms and BC risk in previous published studies.[5,6] Hepatic CYP1A2 is believed to play an important role in the metabolic activation of arylamines. Humans exhibit considerable inter-individual variability in CYP1A2 activity. This inter-individual variation is most likely caused by both environmentally and genetically determined factors. Studies failed to show direct association between CYP1A2 polymorphisms and BC risk, however we have findings that the carcinogenic potential of this metabolic gene may depend upon the presence of its major inducer, cigarette smoking, and it is associated with increased risk of BC in subjects who are exposed to tobacco smoke.[7-10]

CYP2D6 encodes debrisoquine hydroxylase, whose substrates include aromatic amines, tobacco nitrosamines, and a wide range of commonly prescribed drugs such as antiarrhythmics, antihypertensives, alpha-blockers, monoamine oxidase inhibitors, morphine derivatives, antipsychotics, and tricyclic antidepressants. Current studies show CYP2D6 did not appear to influence BC susceptibility.[10,11] CYP2E1 catalyses the metabolic activation of various tobacco-related N-nitrosamines, such as N-nitrosodimethylamine and N-nitrosonornicotine, both of which are potent bladder carcinogens in experimental animals. The current studies suggested that the CYP2E1 polymorphism may be associated with BC susceptibility, especially in Caucasians.[12-14]

NADPH quinine oxidoreductase-1 (NQO1), a chemoprotective enzyme, plays an important role in protection against endogenous and exogenous quinines by catalysing two or four-electron reductions of these substrates. Rich researches suggest that NQO1 GPM contribute to BC development, especially for NQO1 C609T polymorphism.[12,15-19]

Glutathione S-transferases (GST) comprises a major group of Phase II enzymes that play the key role in the detoxification of xenobiotics, environmental substances, and carcinogenic compounds. *GSTM1* and *GSTT1* are two extensively studied GST genes for their association with BC risk. A majority of the studies suggest that the null genotypes of *GSTM1* are significantly associated with increased risk of BC.[20-23] Also Ha et al.[24] concluded *GSTM1* tissue genotype has a predictive value for determining recurrence in non-muscle invasive BC.[24] The results from many studies, which indicate increased BC risk is associated with *GSTT1* genotypes, are controversial.[10,25,26] There are studies suggesting *GSTT1* genotype as a prognostic indicator, independent of traditional pathologic prognostic parameters, for recurrence, progression,[27,28] and Bacillus Calmette-Guérin (BCG) therapy response.[29] Studies did not find any significant association between BC and *GSTA1* and *GSTP1* polymorphisms.[30]

SULT1A1 appears to be the principle human SULT (soluble sulfotransferases) form involved in the elimination of most phenolic xenobiotics, as well as some other substrates. The Arg213His polymorphism in SULT1A1 has a strong influence on the activity and stability of the enzyme. Li et al.[31] described a statistically significant protective role of the variant His allele. UDP-glucuronosyl transferases (UGT) represents another major Phase II drug-metabolising enzyme family sharing roles in detoxification and elimination of endo and xenobiotics. Contrary to previous studies, Zimmermann et al.[32] documented that there is no relationship between UGT2B7 polymorphism and BC.

N-acetyltransferases (NAT) catalyses the metabolic activation of aromatic and heterocyclic amine carcinogens by acetylation. There are two distinct NAT isozymes existing in the human population *NAT1* and *NAT2*. The *NAT2* gene is subject to extensive polymorphism, which segregates the populations into rapid, intermediate, and slow acetylator phenotypes. Controversial results exist for the *NAT1* polymorphism and BC relationship but the majority highlight that an association is found between the *NAT1* polymorphisms investigated, and BC risk.[33,34] *NAT2* polymorphisms and their association with BC have been extensively studied. There are consistent reports on the connection of the *NAT2* slow acetylator polymorphisms with higher BC risk, both independently and in association with smoking or occupational exposures, especially arylamine. Also there are some papers demonstrating conflicting results. Selinski et al.[35] identified an 'ultra-slow' acetylator phenotype associated with BC risk, though slow acetylators in general were not associated with BC risk.[35] Also, Pesch et al.[36] found that no interaction was detected between *NAT2* and any occupational exposure. The combined effect of *NAT1* and *NAT2* genotypes were also addressed in some of the studies.[37]

Myeloperoxidase (*MPO*), catechol-O-methyltransferase (*COMT*), manganese superoxide dismutase (*MnSOD*), and glutathione peroxidase 1 (*GPX1*) are single genes that encode four critical Phase II enzymes modulating carcinogen metabolism. *MPO* produces a strong oxidant, hypochlorous acid, and also activates procarcinogens in tobacco smoke. *COMT* catalyses the methylation of various endobiotic and xenobiotic substances, preventing quinine formation and redox cycling. *MnSOD* is one of the primary enzymes that directly scavenge potential harmful oxidising species and can be induced by free radical challenge and cigarette smoke. *GPX1* is a selenium-dependent enzyme that participates in the detoxification of hydrogen peroxide and a wide range of organic peroxides with reduced glutathione. Huang et al.[38] concluded The *MPO* GPMs might modify the arsenic methylation profile and BC progression. No effect was observed for BC risk with *COMT* polymorphism.[39] *GPX1* Pro198Leu polymorphism significantly increased susceptibility to BC, while the *MnSOD* Ala-9Val polymorphism was not associated with BC risk.[40,41]

DNA Repair

DNA damage, via constant attack from numerous chemical and physical agents, can initiate cancer. About 10,000 lesions are introduced in each cell every day. Our DNA repair mechanisms prevent the accumulation of the undesirable DNA injuries. Nucleotide-excision repair (NER), base-excision repair (BER), homologous recombination, non-homologous end-joint, and mismatch repair are the main DNA repair systems. Each of these repair systems can recognise and fix an array of damage. In the meantime, these repair systems form an intertwining network that functions cooperatively. GPMs of DNA repair proteins with a suboptimal DNA repair capacity have been linked to increased cancer risk.

NER is the most versatile DNA repair pathway. It operates primarily on bulky lesions caused by environmental mutagens, such as UV light and polycyclic aromatic hydrocarbons. Xeroderma pigmentosum complementation group C (XPC) and excision repair cross-complementation group 6 are essential in the NER damage recognition step with different target specificity. Dou et al.[42] indicates that XPC Lys939Gln polymorphism may contribute to the development of BC risk. Meta-analysis of Liu et al.[43] suggested that XPG Asp1104His polymorphism was not associated with BC risk. Up to now, many polymorphisms in the *XPD* gene have been identified, and the Lys751Gln is one of the most important polymorphisms. There are meta-analyses indicating XPD Lys751Gln polymorphism might contribute to the risk of BC.[44]

BER proteins mainly work on damaged DNA bases arising from endogenous oxidative and hydrolytic decay of DNA. Apurinic/apyrimidinic endonuclease 1, a rate-limiting enzyme of BER, has endonuclease function. Its relationship with BC is stil suspicious.[45] Hundreds of single nucleotide polymorphisms (SNPs) of XRCC1 have been validated and three of them were most extensively investigated: Arg194Trp in Exon 6 (rs1799782), Arg280His in Exon 9 (rs25489), and Arg399Gln in Exon 10 (rs25487). The overall results for these investigations suggest that XRCC1 Arg399Gln polymorphism might be a moderate risk factor for BC.

Cell Cycle (CC) Control

CC controls are biochemical pathways that regulate CC progression in response to DNA damage. Losses of CC control appear to be early steps in the development of carcinogenesis and, ultimately,

cancer progression. The regulation of the CC is governed by both positive and negative CC regulatory factors. p53 is a transcription factor that acts as a fundamental regulator of CC arrest in the cell. This is supported by the fact that p53 is the most frequently inactivated in malignantly transformed cells. p53 elicits CC arrest through activation of downstream genes such as p21. Genetic variants in some of the CC regulators were studied for their associations with BC risk. p53 mutations have been described in more than 50% of human cancers. In particular, p53 loss of function has been related to the development of high-grade muscle-invasive disease. Also Piantino et al.[46] tested Prima-1 molecule as a new therapeutic agent for urothelial carcinomas of the bladder, which characteristically harbours p53 mutations.

Inflammation Genes

There has been compelling evidence supporting the hypothesis that chronic inflammation contributes to cancer development. A substantial number of cancers derive from sites of chronic inflammation. Proinflammatory cytokines, growth factors, chemokines, reactive oxygen species, and COX-2 interact in a complex manner in the development and progression of an inflammatory environment. Genetic variants of inflammatory mediators have emerged in recent years as important determinants of cancer susceptibility and prognosis. Some of these polymorphisms have been linked to BC.

Cytokine proteins have key roles in carcinogenesis. On one hand, they are involved in the activation of the immune system to limit tumour growth. On the other, they may be involved in malignant transformation and tumour growth. The interleukin-1 (IL-1), one of the most potent proinflammatory cytokines, influences nearly every cell type and functions in the inflammation, cell growth, and tissue repair. IL-4 is a key cytokine produced by T cells and has an impact on B cell differentiation and proliferation. IL-4 inhibits macrophage activation and may be involved in cancer formation. Many papers exist which propose a strong relationship between IL-1 and IL-4, and BC risk.[47]

Tumour necrosis factor-alpha (TNF-α), a multifunctional cytokine, is key in inflammation, immunity, and cellular organisation. TNF-α has paradoxical roles in cancer, inducing destruction of blood vessels and cell-mediated killing of certain tumours as well as acting as a tumour promoter. The results of several studies do not reach a certain conclusion, and the relationship between TNF-α and BC remains unclear. Additionally research exists, showing an association of tumour stage[48] and outcome after BCG immunotherapy.[49] Transforming growth factor beta is a potent inhibitor of epithelial cell proliferation and it belongs to the group of tumour-derived cytokines. Castillejo et al.[50] concluded that the genetic variants analysed were not associated with an increased risk of BC.[50]

Apoptosis

Apoptosis plays a central role in cancer development. Two separate pathways (intrinsic and extrinsic) are able to trigger the caspase cascade of the apoptotic pathway. The extrinsic pathway is activated by the ligation of cell surface death receptors by their corresponding ligands, while the intrinsic pathway is triggered by disruption of mitochondrial membrane. Mittal et al.[51] and Wang et al.[52] found an association of Death Receptor 4 in BC development.

G Proteins

G proteins are guanine-nucleotide-binding proteins that form a super-family of signal transduction proteins. The RAS family of monomeric G proteins are small GTPases cycling between a GTP-bound active state and an inactive GDP-bound state. Three of the five human RAS genes - including *HRAS*, *KRAS*, and *NRAS* are known to be associated with human cancer through mutation and/or over expression in tumours. Studies show that *HRAS* T81C SNP moderately increases BC risk.[53-55]

Cell Adhesion Molecules

Cell adhesion is essential in all aspects of cell growth, cell migration, and cell differentiation. A growing body of evidence suggests that alterations in the adhesion properties of neoplastic cells may be pivotal in the development and progression of the malignant phenotype in a range of tumours, including BC. E-cadherin (CDH1), a member of the cadherin family, interacts with cytoskeletal proteins through the catenin complex. E-cadherin seems to function as a tumour-suppressor; loss of expression and/or abnormal function of E-cadherin leads to a loss of cell polarity and derangement of normal tissue architecture. Wang et al.[56] indicates that promoter polymorphism and methylation of CDH1 gene may be involved in the development and progression of BC. CDH1 gene promoter polymorphism and methylation might be promising biomarkers for the diagnosis and prognosis of BC.[57]

Methylation Gene

Genome-wide hypomethylation in human cancer might be a consequence of decreased S-adenosylmethionine (SAM) level. Cancer risk might be modified by polymorphisms in methyl group metabolism genes that affect intracellular concentration of SAM, such as methylenetetrahydrofolate reductase and methionine synthase. Shi et al.[58] present no evidence of an association between this polymorphism and BC risk.

PERSPECTIVE

The ultimate goals of molecular epidemiology studies are to provide a practical risk-assessment model that predicts if an individual is at a higher risk of cancer or to tailor cancer therapy (preventive or treatment) based on each individual's genetic profile. Unfortunately, we still have a long way to go. Hypothesis-driven genetic association studies, using either a candidate gene approach or a pathway-based approach, have given and will continue to provide us with very valuable information. However, our expectations should not exceed what these studies can provide. The magnitude of associations by these studies will have limited value in public health and clinical care. Continued efforts to exhaustively search and genotype all identified SNPs (single GPM) with potential functional significance in so many genes are costly and impractical. Anyone who has a predominant slow acetylation phenotype should not take up an occupation working with chemicals or dyes. Another example might be suggesting inhibition of a pathway associated with higher recurrence rates. If this is done, an oral therapy might be more attractive than catheterisation and administration of intravesical chemotherapy.

CONCLUSION

A more serious challenge to current association studies is to bypass the inherent limitation of the predominantly used candidate gene approach. Cancer is a complex multigenic and multistage disease involving the interplay of many genetic and environmental factors. It is unlikely that any single GPM would have a dramatic effect on cancer risk. The modest effect of each individual polymorphism, although providing valuable information, would have very limited value in predicting risk in the general population. Therefore, the future of risk assessment for multigenic complex diseases needs to move beyond the candidate gene approach. A pathway-based genotyping approach, which assesses the combined effects of a panel of polymorphisms that act in the same pathway, may amplify the effects of individual polymorphisms and should be more advantageous to association study than the candidate gene approach.

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AN OVERVIEW OF THE MANAGEMENT OF MALE LOWER URINARY TRACT SYMPTOMS AND BENIGN PROSTATIC OBSTRUCTION

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Disclosure: No potential conflict of interest.
Received: 22.10.14 **Accepted:** 28.11.14
Citation: EMJ Urol. 2015;3[1]:26-33.

ABSTRACT

Lower urinary tract symptoms (LUTS) in older men are common and often bothersome, resulting in a significant use of healthcare resources. Symptoms were thought to be secondary to benign prostatic obstruction (BPO) or benign prostatic enlargement (BPE). However, it should be noted that such storage symptoms are also seen in men without enlarged prostates and in women. These symptoms may be caused by detrusor overactivity, non-urological conditions, medications, or lifestyle factors. Management of BPO constitutes to a significant proportion of a urologist's workload, and will continue to do so with an increasingly ageing population. This review aims to provide an overview of the current understanding of BPE and male LUTS as well as investigations and treatment options. The primary source of data was PubMed, this was searched using Boolean strategies and by scanning a list of related articles. We also examined secondary sources from reference lists of retrieved articles.

Keywords: Alpha-blockers, benign prostatic obstruction, combination therapy, lower urinary tract symptoms, 5-alpha reductase inhibitors, phosphodiesterase-5-inhibitors, transurethral resection of the prostate, laser vapourisation.

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a histological diagnosis, the prevalence increases from 25% in men aged 40-49 years to >80% aged 70-79 years.[1] Many men with histological findings of BPH and clinical findings of benign prostatic enlargement (BPE) have no symptoms, but >50% of men in their 60's, and as many as 90% of those in their 80's, present with lower urinary tract symptoms (LUTS).[2]

Definitions

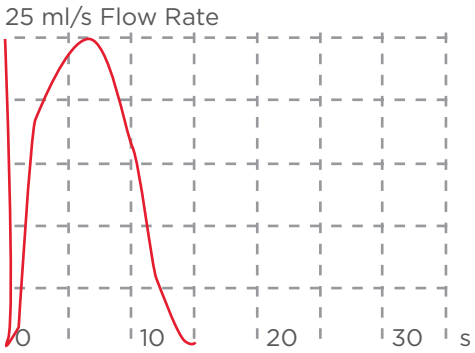
The now redundant term 'prostatism' was used to cover the clinical, pathological, and pathophysiological elements of BPH and LUTS; this wrongly suggested organ and gender specificity. In response, Abrams[3] and Chapple et al.[4] proposed a series of definitions thought to more accurately reflect the clinical, pathological, and pathophysiological components (Table 1).

Evaluation

LUTS are broadly divided into storage, voiding, and post-micturition symptoms. Although the predominant types of symptoms may aid diagnosis, one should remember that the bladder has been described as an unreliable witness and thus further investigations are required to establish a diagnosis.[5] A thorough history must determine the presence of haematuria, urinary tract infection (UTI), erectile dysfunction, diabetes, and hypertension, as well as any previous urological conditions including acute urinary retention (AUR) and any subsequent interventions.[6] Current medical therapy should be reviewed to determine current treatment and the use of anticholinergics and alpha-sympathomimetics. Clinical examination should include the abdomen, external genitalia, and a digital rectal examination to estimate prostate size.

Table 1: Definitions of benign prostatic hyperplasia (BPH) and lower urinary tract symptoms.

Term	Definition
Benign prostatic enlargement	Clinical finding of an enlarged prostate due to BPH.
Bladder outlet obstruction	Urodynamic diagnosis characterised by increased voiding detrusor pressure and reduced urine flow rate.
Benign prostatic obstruction	Obstruction of the bladder outlet secondary to benign prostatic enlargement in the absence of prostate cancer.
Benign prostatic hyperplasia	Histological diagnosis of hyperplasia i.e. a proliferation of cells within the prostate.
Storage symptoms	Symptoms experienced during the filling/storage phase i.e. daytime frequency, nocturia, urgency, incontinence.
Voiding symptoms	Symptoms experienced during the voiding/emptying phase i.e. hesitancy, poor stream, straining, a feeling of incomplete emptying, intermittency, and terminal dribbling.
Post-micturition symptoms	Symptoms experienced immediately after micturition i.e. incomplete bladder emptying, post-micturition dribble.



Results of Uroflowmetry

Voiding Time	T100	14	s
Flow Time	TQ	14	s
Time to max Flow	TQmax	6	s
Max Flow Rate	Qmax	24.8	ml/s
Average Flow Rate	Qave	15.5	ml/s
Voided Volume	Vcomp	221	ml

Figure 1: A normal flow rate.

Urinalysis, bladder diary, and uroflowmetry

Urinalysis should be performed to exclude haematuria or UTI, which necessitate further investigation. A bladder diary is an accurately completed chart over at least 3 days that can provide a useful assessment of storage symptoms such as nocturia, give information on bladder capacity, and indicate other causes of LUTS such as nocturnal polyuria or excessive fluid intake. Uroflowmetry measures the volume voided per second but is non-specific, i.e. it cannot determine if a poor flow is due to bladder outlet obstruction (BOO) or detrusor failure. Furthermore, maximum flow rate (Qmax) values on their own do not correlate well with either LUTS or bladder outlet resistance.[7] Ideally more than one flow rate should be performed and can only be considered representative if >150 ml is voided.[8] See Figure 1 for a normal flow rate.

Residual volume and prostate-specific antigen (PSA)

Residual volume can either be estimated by ultrasound scan or by catheterising after voiding. Measurements should be assessed as a series rather than as a single reading as there may be considerable variation between repeated measurements.[9] Persistently high residual volumes may be due to detrusor dysfunction or BOO. PSA may be used in the detection of prostate cancer (PrC); the potential benefits and disadvantages of using serum PSA to detect PrC should be discussed with the patient. However, PSA seems to correlate directly with prostate volume, as well as

the risk of symptom progression. Patients with a PSA of >1.6 at baseline were at an increased risk of progression.[10]

Scoring systems

Symptom score questionnaires have become a standard part of the assessment of male LUTS, the most widely used being the International Prostate Symptom Score (IPSS) also known as the American Urological Association Symptom Index. It consists of seven questions (three based on storage and four based on voiding symptoms). Each question is scored from 0-5 (0 being never affected and 5 being constantly affected). The sum of all 7 questions gives an overall score out of 35. Patients are classified as suffering from mild (0-7), moderate (8-19), and severe (20-35) LUTS. IPSS also includes a quality of life score (QoL) which has been shown to be consistent, and has been validated in a wide range of languages. The main problem with IPSS is that it does not assess for urinary incontinence. International Consultation on Incontinence Questionnaire Male Lower Urinary Tract Symptoms has been derived from the International Continence Society (ICS) male questionnaire, which resulted from an outcome of the ICS 'Benign Prostatic Hyperplasia' Study.[11] It is a widely used and validated patient-completed questionnaire for evaluating MLUTS.[11] Scoring systems are a useful tool in follow-up to see if medical or surgical therapies have effected symptoms.

Urodynamics

The information obtained from invasive urodynamics can be extremely useful. Storage LUTS may be caused by detrusor overactivity and voiding LUTS by detrusor underactivity or by outflow obstruction. Various nomograms are available, such as the ICS nomogram (also called the Abrams-Griffiths nomogram) to determine whether a patient is obstructed based on the information obtained from the pressure flow studies. This is calculated during the voiding phase of urodynamics by using the formula PdetQmax-2Qmax, a value of >40 suggests obstruction, 20-40 equivocal, and <20 unobstructed.[12] The bladder contractility index can be calculated by PdetQmax+5Qmax. If <100, it suggests that the bladder is underactive.[13] Due to the invasive nature of urodynamics, they are usually reserved for patients in whom conservative and medical therapies have failed and intervention is planned.

Table 2: European Association of Urology (EAU) guidelines for specialist assessment in BPE.

Investigation	EAU recommendations	Level of evidence	Grade of recommendation
Medical history and examination	Recommended	4	A
Symptom score	Recommended	3	B
Urinalysis	Recommended	3	A
Uroflowmetry and post void residual	Recommended	3	B
Pressure flow studies	Optional	3	B/C
Cystoscopy	Optional	3	B
Upper tract imaging	Optional	3	B
Voiding chart	Optional	3	B
PSA and creatinine	Recommended	1b	A
Excretory urography	Not routinely recommended	-	-
Filling cystometry	Not routinely recommended	-	-
Retrograde urethrography	Not routinely recommended	-	-
CT/MRI	Not routinely recommended	-	-

BPE: benign prostatic enlargement; PSA: prostate-specific antigen; CT: computed tomography; MRI: magnetic resonance imaging.

The indications for urodynamics in BPE can be seen in the European Association of Urology (EAU) guidelines.[14] The EAU has produced guidelines[14] that suggest relevant investigations for LUTS/BPO (Table 2).

Natural History

The progression of BPH in untreated patients can only be inferred because of the nature of the disease and the infeasibility of a longitudinal study. Therefore, conclusions are derived from placebo arms of long-term interventional studies. A sub-analysis of the Olmstead County Data demonstrated a mean increase in prostatic volume of 1.6% per year and a mean increase in IPSS score of 0.18 symptom units per year.[15,16] Jacobsen et al.,[17] using the Olmstead County data, identified the following risk factors for AUR: age (men in their 70's are 8 times more likely to have AUR than men in their 40's), prostate volume >30 ml, IPSS >7, Qmax <12 ml/s, and post-void residual >50 ml. The annual incidence was 0.7% over the 4 year study interval.

MANAGEMENT

Lifestyle Advice

There are a number of conservative strategies for patients with mild-to-moderate LUTS. These involve patient education, reassurance, and periodic monitoring. Specific lifestyle advice includes: reduction of fluid intake at specific times, avoidance of bladder stimulants such as coffee, use of double voiding techniques, urethral milking, and bladder retraining along with a review of current medications. When lifestyle measures are adhered to they may have a significant improvement on IPSS as an alpha blockade.

Alpha-Adrenergic-Receptor Blockers (ARBs)

Alfuzosin, doxazosin, tamsulosin, terazosin, and the most recently developed ARB, silodosin have all been approved by the FDA for the treatment of male LUTS. A meta-analysis, published in 2004, suggests that there is no significant difference in the efficacy between different ARBs (not including silodosin) in terms of IPSS reduction 35-40% and increased Qmax 15-30%, although tolerability was variable.[18] Improvements in LUTS are usually seen within 2 weeks and evidence exists to show that effects can be seen within hours to days, and last up to 4 years.[19] The side-effects of ARBs include asthenia, postural hypotension, and an ejaculation. It is recommended that men with LUTS secondary to BPE should be asked about any planned cataract surgery to avoid the risk of intraoperative floppy iris syndrome. Those with planned cataract surgery should not start ARBs until their surgery has been completed.

5-Alpha Reductase Inhibitors (5ARIs)

The effect of testosterone and dihydrotestosterone (DHT) in the development of BPH are well described. The 5-alpha reductase enzyme converts testosterone to the more potent DHT, this is competitively inhibited by the 5ARIs. This effectively shrinks the prostate by 25-30% and reduces further prostatic growth. There are two approved 5ARIs: finasteride, which blocks the Type 2 5α-reductase isoenzyme, leading to a fall in serum DHT levels by 70-90%, and dutasteride blocks, both Type 1 and Type 2 5α-reductase isoenzymes, reducing DHT to levels that approach zero.[20] Both have demonstrated an improvement in LUTS over a period of 2-6 months with a corresponding improvement in IPSS by four to five points.[21] In a direct comparison between the two agents the effects of finasteride and dutasteride were similar.[22] The PLESS study[23] demonstrated a 55% and 57% relative risk reduction in those requiring surgery and those having an episode of AUR respectively in the finasteride arm. However, this translates to a 4% relative risk reduction over 4 years, so although finasteride does reduce the risk of retention, it is reducing the risk of something which is already quite rare. Side-effects of 5ARIs included decreased libido, erectile dysfunction (ED), and ejaculatory dysfunction and gynaecomastia. Trials have also been conducted to try to ascertain if finasteride or dutasteride could prevent PrC. Treatment with finasteride resulted in an absolute risk reduction of 6% when compared to placebo, but was also associated with an increased risk of moderate-to-high grade PrC (Gleason >7).[24] The REDUCE study,[25] which looked at dutasteride, showed similar results. In a more recent study men treated with a 5ARI for LUTS had a decreased risk of low-grade PrC (Gleason 2-7) and showed no evidence of increased risk of high-grade cancer (8-10) after up to 4 years treatment.[26] It should also be noted that patients on 5ARIs should be aware that their PSA will fall by 50%, this needs to be considered in any eventual PSA directed cancer strategy.

Combination Therapy

A number of studies have looked at the potential benefit of combination therapies in the

management of BPO. Short-term studies, such as the Veterans Affairs Co-operative and the PREDICT trial, demonstrated that patients on both ARB monotherapy and ARB + 5ARI combination therapy show a significant improvement in outcomes (Qmax and IPSS). However, there is no significant difference between monotherapy or combination therapy in the short term.[27,28] Long-term data from the MTOPS trial[19] demonstrated that combination therapy significantly reduced the risk of clinical progression when compared with placebo and monotherapy over a mean 4.5 year follow-up. The COMBAT trial[29] (dutasteride and tamsulosin) looked at the management of LUTS in men with larger prostates. It suggested that combination therapy had a significantly greater improvement in symptom score as well as Qmax from baseline than either tamsulosin or dutasteride alone. Combination therapy also reduced the relative risk of AUR or BPO surgery over 4 years by 66% compared with tamsulosin monotherapy. However, those on combination therapy suffered from a higher frequency of adverse effects.[29]

Antimuscarinics

In some cases a degree of bladder overactivity may co-exist or be the results of BOO. In this case standard treatment for BOO may fail and may not be sufficient to control the storage symptoms. Kaplan et al.[30] compared the combination of ARB and antimuscarinics to individual therapy. It demonstrated that as monotherapy, the therapies performed less well compared with placebo, but in combination showed good efficacy in improving QoL scores. The risk of AUR in the antimuscarinic group was not significant.

Phosphodiesterase-5 Inhibitors (PDE5-I)

PDE5-I were initially approved for use in the management of ED but they also seem to improve LUTS. PDE5 is present in prostatic tissue, particularly the transition zone as well as the detrusor and the smooth-muscle cells relating to the urinary tract. Inhibition of PDE5 leads to smooth muscle relaxation. This may alsohave anti-proliferative effects in prostatic and bladder smooth-muscle cells. Thus far only tadalafil has received FDA approval for the treatment of LUTS. In a randomised, placebo-controlled trial involving men with LUTS for at least 6 months, a 5 mg dose of tadalafil resulted in an average decrease in the IPSS by 2.8 points at 6 weeks and 3.8 points at 12 weeks.[31] Efficacy was shown as early as 4 weeks.[32] Interestingly, none of the studies looking at PDE5I use for LUTS have shown a significant effect on urinary flow rate (Qmax). This may be explained by PDE5-Is primarily affecting detrusor activity rather than BOO itself.

Phytotherapy

Saw palmetto is thought to be the active agent derived from serenoa repens. Apart from a single systematic review and meta-analysis in 1990, the general opinion from more recent randomised controlled trials (RCTs) do not support the efficacy of saw palmetto over placebo and hence it is excluded from many guidelines.[33]

SURGERY

Transurethral Resection of Prostate (TURP)

TURP continues to be the gold standard in the treatment of BPO. The basic principles are of removal of prostatic tissue from the transition zone to improve voiding symptoms. The indications for TURP can be found in the EAU guidelines.[14] The number of TURPs being performed has declined over the last two decades, primarily due to the significant benefits of medical therapy and to a lesser extent the advent and proliferation of alternative surgical techniques. In a systematic review, TURP has been shown, on average, to improve the mean IPSS score from 18.8 to 7.2 (-62%) after 12 months post-op, as well as improve Qmax by 9.7 ml/s, a mean increase of 120%.[34] Bipolar TURP is a valid alternative to monopolar TURP with equivalent outcomes and a similar side-effect profile. Transurethral resection syndrome has not been reported with bipolar TURP due to the use of physiological saline irrigation fluid and reduced fluid absorption during the procedure. While transurethral incision of prostate reduces LUTS secondary to BPO by incising the bladder outlet without tissue removal. This technique is used in in men with LUTS with prostate size <30 ml and without a middle lobe.

Open Prostatectomy

Open prostatectomy is the oldest surgical treatment for moderate to severe LUTS secondary to BPO. It is usually reserved for those with large prostates (>80-100 ml) the obstructive prostatic adenoma is enucleated either via the bladder (Freyer's transvesical prostatectomy) or through the anterior prostatic capsule (Millin's retropubic prostatectomy). Open prostatectomy results in

a reduction of LUTS by 63-86% (12.5-23.3 IPSS points). It has been described using both laparoscopic and robotic-assisted approaches.[35]

Transurethral Laser Surgery

Lasers have been used in the surgical management of BPE either by coagulating, vapourising, or enucleating the prostate. Potassium-titanyl-phosphate (KTP) lasers (Greenlight laser–KTP) has been used for photoselective vapourisation of the prostate (PVP); over time the power of these lasers has increased from 60 W to 180 W. Two RCTs comparing TURP with 80 W PVP have shown similar[36] or improved flow rates[37] at up to 1 year follow-up. KTP laser has been shown to reduce intraoperative blood loss and blood transfusion rates when compared to TURP. Urethral stricture, retrograde ejaculation, and retreatment rates are comparable with TURP.

Initially holmium lasers were used to vaporise the prostate, then to resect the prostate, and now to enucleate the prostate (HoLEP). The lobes are resected and then pushed back into the bladder and then morcellated. There have been six RCTs comparing TURP to HoLEP. Essentially there is no statistically significant difference between HoLEP and TURP in improving symptom and QoL scores at up to 7 years.[38,39] Less blood loss and transfusion rates have been observed with HoLEP but there is a significant learning curve. HoLEP has been described as an endoscopic Millin's prostatectomy – at 5 years follow-up HoLEP is comparable with open prostatectomy.[40] Transfusion rates for HoLEP are significantly lower than for open prostatectomy. NICE suggests that HoLEP be offered as an alternative to TURP or open prostatectomy. It should be performed in a centre specialising in the technique, or with mentorship arrangements in place.[41]

Thulium laser allows better tissue vaporisation than holmium - at 1 year follow-up there does not appear to be any difference between Thulium techniques and HoLEP.[42,43] A multicentre trial is being conducted in the UK funded by the National Institute for Health Research to compare Thulium vapouresection of the prostate to TURP. Laser techniques in the management of BPO appear to have equivalent results to TURP but there is limited long-term data available. They may be superior to TURP in anti-coagulated patients where risks of bleeding and the requirements for post-op blood transfusion remain low. Another advantage of laser procedures is that saline can be used as an irrigant solution avoiding the risks of development of TURP syndrome. The advantages of shorter catheterisation period and reduced length of stay need to be balanced against the increased operating costs (in terms of equipment and increased operating time) and the procedural learning curve for the holmium laser.

Injection Therapy

Injection therapy of the prostate involves administration of dehydrated ethanol at four to eight sites in the prostate. It can be administered transurethrally, transrectally, or transperineally. It results in coagulative necrosis reducing prostate volume. IPSS and Qmax do improve, but significant adverse events have been recorded including bladder neck necrosis and ureteric injury requiring reimplantation.[44,45] These techniques are rarely utilised. There have also been small studies examining the use of intraprostatic botulinum toxin use as well as NX-1207; these have shown a decrease in prostatic volume and symptom scores.[46]

MECHANICAL DEVICES

Intraprostatic stents have been used for patients who were not fit for surgery and who did not want to be managed with a long-term catheter. A variety of stents are available, however, they are rarely used due to complications such as migration and encrustation. Urethral lift is a technique that works by pulling the lateral lobes of the prostate laterally to increase the calibre of the urethral lumen. It can be performed under local anaesthesia or sedation. A non-absorbable monofilament suture with a nitinol capsular tab is inserted in an anterolateral fashion to compress the lateral prostatic lobes additional sutures are placed as required to achieve a cystoscopically open urethral channel. NICE issued procedure guidance approving the prostatic lift in 2014. Late complications are uncommon but may include UTI prostatitis and transient ED. Short-term results show a 40% reduction in IPSS scores, 40-50% improvement in QoL scores, and 30% improvement in Qmax. This improvement is seen within 2 weeks and appears to be sustained up to 2 years later.[47-49]

CONCLUSION

BPO is a complex condition which remains incompletely understood. Treatment options for BPO have become more widespread ranging

from lifestyle advice, medical therapy, minimally invasive surgery, and conventional TURP and open prostatectomy. As urologists, we now have many treatment modalities, however, only time will tell which will become the 'gold standard'.

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CONTEMPORARY ROLE OF TESTIS SPARING SURGERY: A SYSTEMATIC REVIEW

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Disclosure: No potential conflict of interest.
Received: 21.10.14 **Accepted:** 19.11.14
Citation: EMJ Urol. 2015;3[1]:34-40.

ABSTRACT

Testis-sparing surgery (TSS) represents a therapeutic choice for testicular cancer (TC). However, international guidelines are very cautious about the use of the testis-sparing technique, namely due to the lack of certain indications and long-term oncological outcomes. The aim of this systematic-review is to illustrate current trends of what may today be the uses of organ-sparing surgery in TC, to evaluate the relationship between the organ-sparing safety and oncological features such as definitive histology, tumour size, and post-surgery oncological outcomes. This analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines. An electronic search of the Medline and Embase was undertaken until September 2014. The search was limited to English-Language articles. Current indications of TSS are synchronous bilateral testicular tumours, metachronous contralateral tumours, or tumour in a solitary testis with normal preoperative testosterone levels. Moreover, histological characteristics should not be taken into account when performing a TSS approach. TSS outcomes for germ cell tumours are encouraging and we reported high rates of disease-free survival and a few cases of patients receiving neoadjuvant chemotherapy or radiotherapy. In light of the examined, TSS could be considered a viable alternative to radical surgery of the testis but it should be performed in specialised centres with competence.

Keywords: Testicular cancer, testis sparing surgery, risk factors, germ cell tumour, orchiectomy.

INTRODUCTION

Today, testicular cancer (TC) is one of the most important challenges in urology. The reasons must primarily be due to the increasing incidence of neoplasia in Caucasian patients, as reported by the statistics of the Surveillance, Epidemiology, and End Results in the USA.[1] To confirm this trend Huyghe et al.[2] showed that TC incidence is increasing throughout Europe, although there was no difference between European countries. For instance, the present incidence rate is 0.8/100,000 in Portugal and 15.4/100,000 in Denmark. Common risk factors, according to the European Association of Urology (EAU) guidelines 2014, are identified in the history of cryptorchidism or undescended testis (testicular dysgenesis syndrome), Klinefelter's syndrome, familial history of testicular tumours among first-grade relatives (father/brothers), the presence of a contralateral tumour or testicular intraepithelial neoplasia (TIN), and infertility.[3-7] Other risk factors has been also recently introduced, such as tallness[8,9] and the use of pesticides such as the p,p'-dichlorodiphenyldichloroethylene, primary metabolite of dichlorodiphenyltrichloroethane,[10] but these associations should be further confirmed Another controversy is represented by the choice of the surgical approach. EAU guidelines identify radical orchiectomy as the gold standard treatment for TC when a 'suspicious testicular mass' is found. In recent years, a new concept of surgery has emerged, the minimally invasive surgery (MIS), and not only in the urological field. To this regard, the organ-sparing surgery (OSS) represents a therapeutic

choice. However, EAU guidelines are very cautious about the use of the testis-sparing technique, due to the lack of certain indications and long-term oncological outcomes.

It is with this in mind that some reports have raised doubts about this surgical approach. The main skepticisms on this topic precisely regard the heterogeneous histological features of TCs and the lack of appropriate diagnostic techniques that can distinguish and characterise them. Furthermore, matched-paired analyses and randomised studies, comparing testis sparing versus orchiectomy, are lacking; all these controversies limit the evaluation of current data. The aim of this systematic review is to illustrate current trends of what may today be the uses of OSS in TC, to evaluate the relationship between the organ-sparing safety and oncological features such as definitive histology, tumour size, and post-surgery oncological outcomes.

MATERIAL AND METHODS

This analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.[11] An electronic search of the Medline and Embase was undertaken until September 2014. The search was limited to English-Language articles. The search terms included: "testis cancer", "testis sparing surgery", "risk factor", "cancer specific survival", "disease recurrence", "predictors", and "outcomes". Citation lists of retrieved articles were screened manually to ensure sensitivity of the search strategy. References of the included papers were hand searched in order to identify other potential relevant studies. Studies were reviewed by two independent reviewers (G.I.R. and G.R.); differences in opinion were discussed in consultation with the last author (G.M.) (Table 1). Figure 1 shows the flowchart of included studies.

RESULTS

Indication

Current indications of testis-sparing surgery (TSS) are synchronous bilateral testicular tumours, metachronous contralateral tumours, or tumour in a solitary testis with normal preoperative testosterone levels. However, organ preserving surgery can be performed when the tumour volume is <30% of the testicular volume, and surgical rules are respected. The need for such strict regulations suggests that TSS is still not a safe technique as opposed to an extremely definitive surgery such as orchiectomy. On the other hand, orchiectomy itself could be considered as an overtreatment of neoplastic disease in selected cases. Regarding international guidelines on TC, European urologists still refer to the EAU guidelines.[12] The latest update in TC has inserted a new section on OSS, confirming the need for support for this minimally invasive surgical approach. It also reported that some histological features for which a minimally invasive surgical approach is more suitable are Leydig cell or Sertoli cell tumours. Patients with gynaecomastia, or hormonal disorders, or typical imaging such as calcifications, or small circumscribed tumours may be suspected for Leydig cell or Sertoli cell tumours. However, a TSS is recommended in every small intraparenchymal lesion with the purpose of obtaining a histological diagnosis. The testis-sparing approach must be performed only if testicular parenchyma (TP) is sufficient for endocrine and also exocrine (in stromal tumours) functions.

Currently, the American Urological Association guidelines do not seem to agree on the choice for a MIS in TC, and therefore define it as 'controversial'. Indications given by the American Society are similar to those of the EAU: available for mass <2 cm, for simultaneous bilateral tumours, in solitary testicle with normal serum testosterone levels, biopsy performed on adjacent parenchyma (for the possibility of intratubular germ cell neoplasia presentation in 80% of cases), and eventually treatment with 20 Gy radiotherapy in the remaining TP. The National Comprehensive Cancer Network guidelines did not take into consideration TSS. Regarding the TSS technique, the ability to operate on a frozen section during the procedure appears to be of great interest. Subik et al.[13] performed frozen section in a series of 45 patients with testicular masses and found that 36 of 43 patients (83.7%) demonstrated the oncological feasibility of this technique. The utilisation of the frozen section has also been confirmed in a study by Steiner et al.[14] which performed 32 testis-sparing procedures using an initial frozen section from each sidewall and from the bottom of the tumour bed, from August 1994 to May 2002. They moved the subsequent frozen section into the adjacent parenchymal, in case of TIN in the initial frozen section. In this way they identified the presence of 10 TIN on 11 germ cell tumours (GCTs) and proceeded with appropriate treatment (i.e. radiotherapy). Another challenge of TSS seems

to be the preservation of fertility. The choice of a MIS (saving the normal TP) is obviously indicated when one would ensure the best exocrine function directed to procreation.

As reported by the EAU Guidelines, the infertility rate after OSS significantly increases in patients receiving adjuvant radiation therapy. For this reason it raises the possibility of delaying the radiological treatment or carrying out any sperm preservation after procreation. Focussing on this, Hallak et al.[15] conducted a study of five patients with TC associated with azoospermia, and treated with TSS and contemporary microdissection for excision of the best tubules in order to select them and perform cryopreservation: in 80% of patients it was seen that the extraction procedure for all patients and the levels of serum testosterone were maintained in the normal range after one year of follow-up. The question of radiotherapy therefore seems controversial in the literature: on one hand it is necessary for the control of localised disease with the simultaneous presence of TIN, on the other it is deleterious for the reproductive and endocrine functions of the testis. So what is the best approach for adjuvant radiation therapy? It seems evident that a dose of 20 Gy radiation represents a concentration sufficient to eradicate the carcinoma *in situ* (CIS), if present.[16,17] The EAU Guidelines to this regard, however, conceived the possibility of delaying radiation therapy for all those patients who wish to have a child, obviously paying them a rigorous follow-up with ultrasonography of the residual TP.[17]

Histological Features

A careful analysis of the literature confirmed that there are no limitations, in terms of histological features, for TSS. Likewise GCTs stromal tumours can be treated with MIS. Concerning GCTs, the European Germ Cell Cancer Consensus Group indicated that testis-sparing is a viable alternative for small tumour volume but it must be performed only in specialised centres that can manage technique-related complications.[18] In a report on 27 patients treated with TSS, the average size of the tumour mass detected by ultrasound was 11 mm (range 6-27 mm). Although three of these patients had a multifocal carcinoma and seven had an associated CIS, no local occurrence occurred after 5.7 years of follow-up.[19] Focus on the presence of TIN and multifocality in GCTs has been investigated in the literature.[20]

A rate of multifocality of up to 63% has been reported[13] in tumours with a size of up to 20 mm. Furthermore, multifocality could be a finding in testicular GCT cases and in those with seminomatous histology, as reported by a recent study. Anyway, the significance of this finding is not well understood.[21] However, the high percentage of multifocal tumour presence is inconsistent with the number of tumour relapses reported in the literature or with the histological tumour type, regardless of administration of adjuvant therapy following TSS. In contrast with these observations, we have recently reported a much smaller percentage of tumour multifocality. In 140 analysed tumours with a size <4 cm, the percentage of multifocality was around 26%. This pathological feature of testicular GCT did not correlate with the histological subtype, in particular seminomatous histology, as previously described,[21] neither with other adverse clinical and pathological variables. Based on these considerations and because they are different to other urological tumours, such as bladder or kidney cancer, the presence of multifocality in TC should not be considered as an adverse pathological feature at the time of orchiectomy, together with all of the others.

The presence of TIN must be also established whenever TSS is performed. The rate of TIN has been reported as ranging from 72-98%, but a recent perspective has attributed the presence of TIN in TP as adjacent to a GCT. TIN is found in 4.9% of patients with tumours on the contralateral testicles. To this regard, we have retrospectively reported data on 126 patients affected by testis cancer (76 seminomatous and 50 non-seminomatous) and treated with orchiectomy. We showed that the prevalence of multifocal TC and TIN decreased in the presence of a smaller main mass (1 cm) and increased when the index mass tumour diameter is >1.1 cm.[22] Based on these considerations, tumour volume and focality should be considered before performing a TSS.

In the literature, TSS is also described for other histological types of GCTs, such as teratoma, although pertaining to paediatric urology. Shukla et al.[23] have revised their own data from 1976-2002 and reported 77 pediatric testicular tumours: 43 were GCTs. They reported 13 testis-sparing procedures, including 8 teratomas and epidermoid cysts, with 5 confirming, as final consideration, the OSS as a safe technique with good cancer control. Furthermore, the focus of TSS has also been reported for leydigomas.

Table 1: Characteristics of included studies.

Year	Authors	Country	Number of Cases	Number Treated with TSS	Mean Size Tumour mass US D_{max} (range)	Histological Findings (% on TSS procedures)	Outcome after TSS
2014	Favilla et al.[22]	Italy	126	nv	19.4 mm (6-50 mm)	Seminomatous: 76 (60.31%) Nonseminomatous: 50 (39.69%)	nv
2014	Leonhartsberger et al.[31]	Austria	65	33 in 30	14.8 mm (2-30 mm)	Stromal cell tumour: 19 (57.57%) Metachronous bilateral: GCT: 6 (18.18%) Bilateral Synchronous: Seminoma: 2 (6.06%) Benign lesions: 6 (18.18%)	- Disease-free survival: 100%
2014	Favilla et al.[22]	Italy	254	nv	35 mm (5–120 mm)	Seminomatous: 148 (58.26%) Nonseminomatous: 106 (41.74%)	nv
2014	Bojanic et al.[32]	Serbia	44	26	>20 mm	Seminoma: 16 (61.53%) Nonseminoma: 9 (34.61%) Leydigoma: 1 (3.84%)	- Local recurrence: 7 (26.92%) - Radical orchiectomy: 5 (19.23%) - Overall survival: 100%
2013	Bozzini et al.[25]	Italy	22	22	11.4 mm (5-31 mm)	Leydig cell tumour: 20 (90.90%) Non-malignant stromal: Tumour: 1 (4.54%) B cell lymphoma: 1 (4.54%)	- Local recurrence or distant: 0 (0%) - Disease-free survival: 100%
2010	Lawrentschuk et al.[19]	Canada	30	27	Benign 10 mm (5–28 mm) Malignant 11 mm (6–27mm)	Benign Seminoma: 8 (36.3%) Nonseminomatous GCT: 2 (7.4%) Malignant Seminoma: 11 (40.7%) Nonseminomatous GCT: 3 (13.6%) Mixed: 1 (4.54%) Teratoma: 2 (7.4%)	- No perioperative complications - Observation in 12 of 17 cases (70.59%) - Local recurrence: 2 (11.76%) - Retroperitoneal lymph node dissection: 1 (5.88%)
2009	Suardi et al.[24]	Italy	610	28	13.3 mm	Leydig cell tumour: 28 (100%)	- Patient died from the disease during the follow-up: 0 (0%) - Local or distant recurrence: 0 (0%)
2004	Shukla et al.[23]	USA	77	13	nv	Mature teratomas: 8 (61.53%) Epidermoid cysts: 5 (38.47%)	- No recurrence, testicular atrophy or persistent orchialgia.

TSS: testis-sparing surgery; GCT: germ cell tumours; nv: not valuable; US: ultrasound.

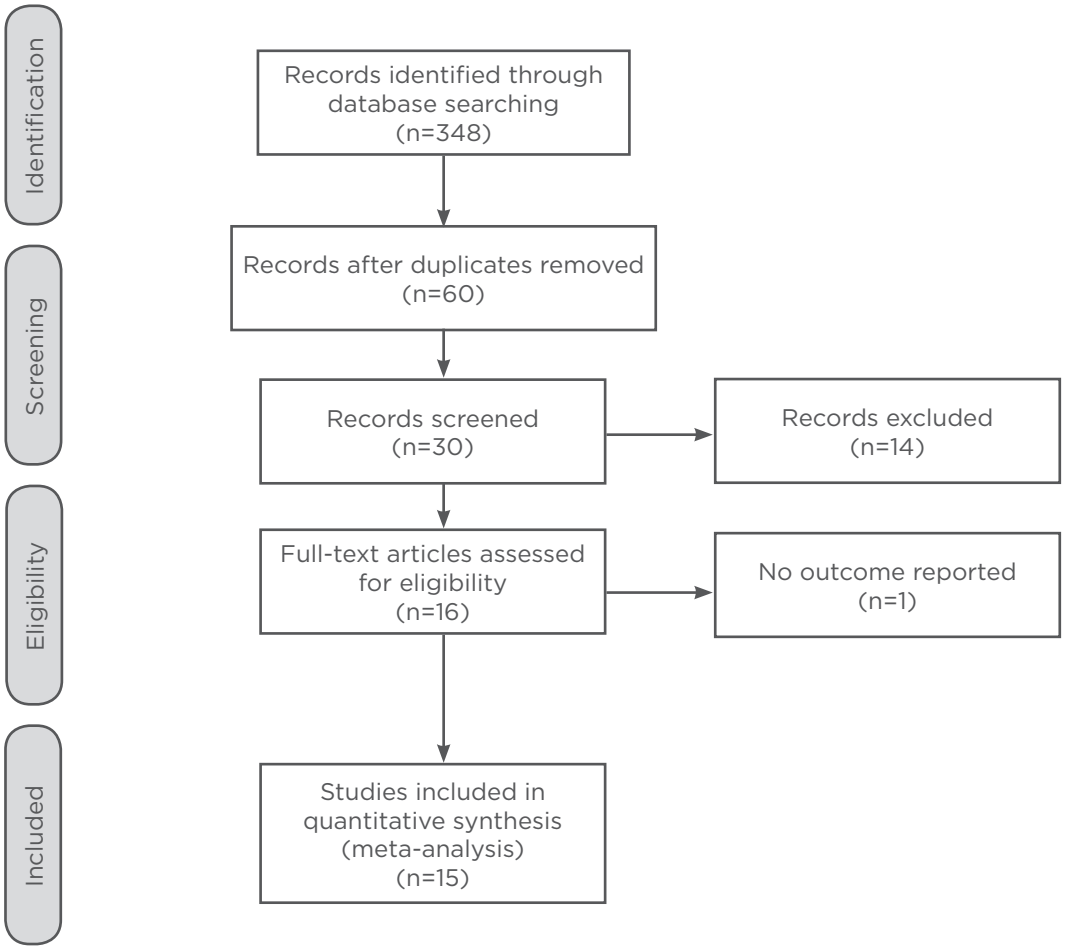

Figure 1: Flow diagram of included studies.

In a single-centre case series TSS was performed in 29 patients with Leydig cell tumour and after 4.6 years of follow-up, no patients had disease relapse.[24] Similarly, a multicentre retrospective clinical study of Bozzini et al.[25] evaluated 22 patients with Leydig cell tumour treated with a conservative technique. The author examined the results after a mean follow-up of 180 months and emphasises the importance of an 'early diagnosis' of leydigomas, suggesting, in these situations, 'a minimally invasive approach' as the 'gold-standard treatment'.

Sertoli cell tumours may be also treated with TSS. However, limited evidence is available for a conservative surgical approach. In most cases, this evidence is based on case reports.[26,27] To the best of our knowledge, literature data such as systematic reviews or meta-analyses are lacking, probably due the rarity of their presentation. Another rare type of tumour stromal cells that can be applied in this technique are tumours of the granulosa: for this extremely rare histotype, there is a case report of a 6-month-old baby affected by bilateral juvenile granulosa cell tumour, treated with conservative surgery.[28] Based on these considerations, histological characteristics should not be taken into account when performing a TSS. However, further studies are warranted in order to better investigate these results.

Oncological Outcomes After TSS

TSS has now been practiced for more than three decades and data on oncological outcomes are recently emerging.[29] Some parameters related to the TSS, such as MIS, the ability to preserve fertility, and the psychological aspect of the patient are factors of great significance for the urologist. On the other hand, it is clear that several doubts still persist about oncological outcomes following the procedure. Uncertainty about the surgical radicality is also highlighted by the EAU guidelines, which have highlighted the possibility of a neoadjuvantradiotherapy.[12] Due to the rarity of some histological types of testis cancer and (therefore) due to the reduced amount of data available, we will examine the oncological outcome of the two most common types: seminomas and non-seminoma.

Since 1984, a number of studies have been reported in the literature related to TSS; Giannarini et al.[29] have recently reviewed a number of case reports. Heidenreich et al.[30] reported a series of 73 patients treated with TSS and the long-term results, with 98% showing no evidence of disease, normal testosterone values, and 5 spontaneous pregnancies.

Leonhartsberger et al.,[31] from January 2003-October 2010, evaluated the oncological outcomes of 33 patients treated with TSS and followed up for a mean period of 50 months. Of these, 19 presented stromal cells, 6 benign lesions, 6 metachronous bilateral GCT, and 1 synchronous bilateral seminoma. After 50 months of follow-up, no evidence of local or systemic relapse was reported. Similar results were obtained in a retrospective review where 27 patients undergoing OSS were oncologically evaluated: 17 of those patients (63%) had malignant lesions (9 seminoma, 3 teratoma, 1 embryonal, 3 Leydig cell, and 1 CIS) and 10 (37%) had benign lesions. CIS was founded in 53% of patients, including seven with seminoma.[19] Two patients finally underwent radical orchiectomy for local recurrence of CIS; one needed an additional treatment with bleomycin, etoposide, and cisplatin, one case of seminoma was treated with radiotherapy, and only in a patient with an histological finding of teratoma was a retroperitoneal lymph node dissection necessary. The remaining five patients with CIS underwent surveillance. The overall disease free survival was 5.7 years.

In a more recent report, TSS was performed in 24 patients (median follow-up of 51.0 months). Seven patients developed local recurrence, of which five had TIN and were subjected to radical orchiectomy, whereas re-do TSS was done in the remaining two patients. The overall survival of the study group was 100%, and the presence of TIN was associated with worse recurrence-free survival (p=0.031).[32] Fortunately more data on TSS are emerging and confirming that this minimally invasive surgical approach is acceptable both from an oncological point of view, in patients with bilateral testicular GCTs and solitary testicle tumours, and for TP functional preservation.

CONCLUSION

In the last two decades, TSS are improving and many more studies have been published on this topic. Some doubts on TSS could concern indications and long-term oncological outcomes, and their relationship with tumour histology. These limits may be exceeded, but there is a clear need for randomised clinical trials and meta-analysis studies. Despite the current evidences and literature data on this topic, several issues need to be addressed. Firstly, information given by the last EAU Guidelines, should be enriched by a clear cut-off regarding the tumour size (as ultrasonography diameter maximum value). For what concerns the histological subtypes, information, for stromal tumours cells especially, is still lacking. In our opinion, new challenges about diagnostic techniques may offer some contributions in predicting the histological features of small testicular masses, mainly in those with negative alterations of neoplastic markers. Finally, fertility is certainly a main concern of survivors after treatment. In this context a lower level of awareness by the medical team or the patient, with regards to the need to bank sperm or a general knowledge of assisted reproductive techniques, may be present. Furthermore, the occurrence of limited time between diagnosis and treatment, as treatment is usually initiated as soon as possible and poor semen quality leads to immotile sperm after cryopreservation, or failure of ejaculation due to high levels of anxiety or weakness, are the next challenges to overcome.[33] In conclusion, TSS outcomes for GCTs are encouraging and we have reported high rates of disease-free survival and a few cases of patients receiving neoadjuvant chemotherapy or radiotherapy. In light of the all examined, TSS could be considered as a viable alternative to radical surgery of the testis, however, it should be performed in specialised centres with competence.

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INCIDENTALLY DETECTED PRIMARY GIANT RENAL CYSTIC ECHINOCOCCOSIS IN A YOUNG PATIENT: AN UNDERESTIMATED ENTITY?

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Disclosure: No potential conflict of interest.
Received: 13.10.14 **Accepted:** 24.11.14
Citation: EMJ Urol. 2015;3[1]:42-45.

ABSTRACT

Echinococcosis is a parasitic infestation caused by *Echinococcus granulosus* and is an endemic disease in many parts of world. The symptoms and signs depend on the location and size of the cyst. Renal cystic echinococcosis or hydatid cyst (HC) disease of the kidney is extremely rare and constitutes only 2-4% of all cases of hydatid disease (HD). We present a 39-year-old male patient who was referred to our outpatient clinic with cystic right kidney mass that was incidentally diagnosed during hepatobiliary ultrasound for chronic hepatitis B evaluation. Routine blood tests were normal without eosinophilia. Indirect haemagglutination test was negative. Abdominal kidneys, ureters, and bladder X-ray showed an 83x95 mm sized curvilinear calcification in the right upper abdominal quadrant. Abdominal computed tomography scan and magnetic resonance imaging demonstrated a 10x9x10 cm sized cystic mass arising from the middle pole of the right kidney, destructing the whole upper pole and extending into the liver. Daughter vesicles were present in the cystic lesion suggesting renal HD. Right retroperitoneal exploration with flank approach and right radical nephrectomy was performed without any complications. Pathology confirmed HC lesion. Following surgery, albendazole 400 mg per os twice daily for 4 weeks was suggested.

Keywords: Renal cystic echinococcosis, renal hydatid cyst, kidney, diagnosis, management.

INTRODUCTION

Echinococcosis is a parasitic infestation caused by *Echinococcus granulosus*. Infestation occurs as a result of ingestion of the larval form of a cestode and humans are intermediate hosts. Cestode larvae reach the liver with portal system, while infection of the kidneys occurs with systemic circulation. Echinococcosis is an endemic disease in many parts of world such as South America, Mediterranean countries, New Zealand, Australia, and South Africa.[1] Keeping in mind that dogs are main hosts and sheep are intermediate hosts; a high index of suspicion for echinococcosis for patients coming from rural areas is mandatory. Laboratory workers who are handling hydatid disease (HD) specimens are also in need of following biosafety level 2 practices for preventing accidental contacts.[2]

Renal cystic echinococcosis (RCE) or hydatid cyst (HC) disease of the kidney is extremely rare and constitutes only 2-4% of all cases of HD.[3] There are no specific clinical symptoms or signs but hydatiduria as a pathognomonic symptom was reported in literature.[4] Routine blood tests are generally within normal limits except for eosinophilia which is observed in 20% of patients.[5] Diagnosis is usually incidental or the consequence of high suspicion index. Radiologic evaluation is the mainstay of diagnostic modalities for HD. In endemic countries, echinococcosis should be included in

the differential diagnosis of lesions in solid organs, especially for liver and kidneys. Herein, we present a young male patient with isolated giant right renal HC disease that was diagnosed incidentally, and discuss its management.

CASE REPORT

A 39-year old male patient was referred to our outpatient clinic with cystic right kidney mass that was incidentally diagnosed during hepatobiliary ultrasound (US) examination for chronic hepatitis B (CHB) evaluation. He had renal cyst history 20 years ago, of which we had no exact radiological report, but verbal history from the patient suggest a small benign cyst. The patient had CHB infection since his childhood but he was excluded from medical follow-up due to his poor compliance. He is a temporary employee in the construction industry. He had no known history of contact with dogs or sheep and has been living in central Turkey.

An abdominal kidneys-ureters-bladder X-ray showed an 83x95 mm sized curvilinear calcification observed in the right upper abdominal quadrant (Figure 1). Abdominal computerised tomography (CT) scan and magnetic resonance imaging (MRI) demonstrated a 10x9x10 cm sized cystic mass arising from the middle pole of the right kidney, destructing the whole upper pole and extending into the liver (Figures 2a and 2b). Daughter vesicles were present in the cyst mass lesion, suggesting renal HD. Chest X-ray and blood tests including complete blood count, blood biochemistry, urine culture, and microscopy were within normal limits. Blood tests for echinococcosis including indirect haemagglutination were negative. Physical examination revealed no additional abnormal findings but a palpable right renal mass.

Right retroperitoneal exploration with flank approach and right radical nephrectomy was performed. Estimated blood loss was 80 cc. Histopathology confirmed hydatid cyst of the right kidney (Figures 3a and 3b). A mass in kidney with 10 cm in diameter, surrounded by vicious capsule that included cystic lesion was reported that involved the superior and middle parts of the kidney. The inferior pole of kidney was normal. Postoperative follow-up was uneventful and the patient was discharged on postoperative Day-3. Albendazole 400 mg per os twice daily for 4 weeks was prescribed. No perioperative (0-30 days) complication was detected.

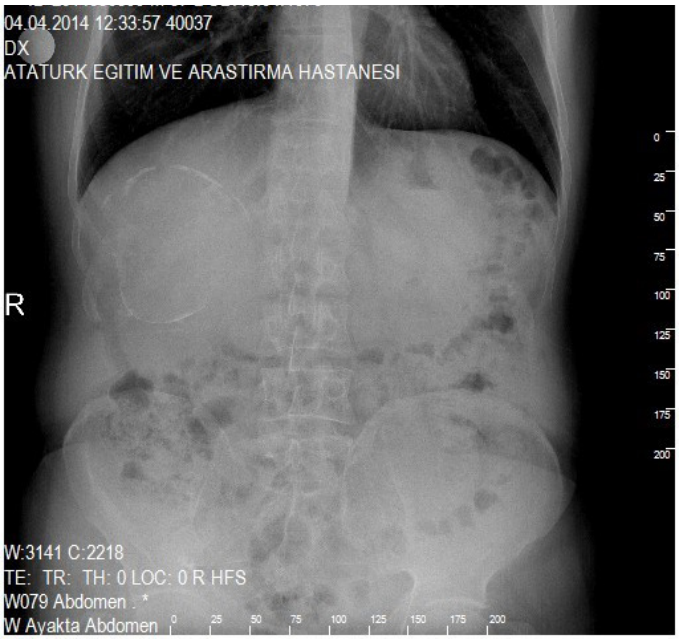


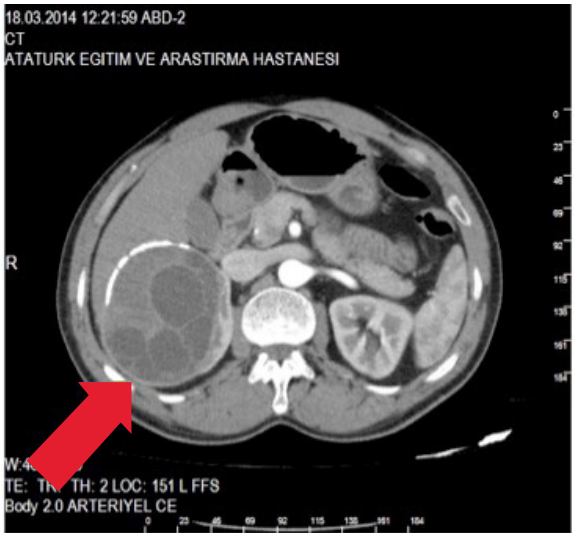
Figure 1: Abdominal X-ray imaging showing a curvilinear calcification on the right upper abdominal quadrant.

DISCUSSION

Renal echinococcosis accounts for approximately 3% of all HDs and is the third most common localisation of HD.[1,6] The liver and lungs have been reported to be most frequently affected by HD.[1] Renal echinococcosis may remain asymptomatic for a long period of time.[7] Abdominal pain and hydaturia, which occurs due to a ruptured cyst in the collecting system and leads to passing collapsed daughter cyst-like material in the urine, have been reported as the most frequently reported clinical findings.[8] Fever, lumbar mass, and haematuria might also be present.[8] Renal failure and ureteropelvic junction obstruction due to renal HD were also reported in the literature.[9]

The pathognomonic sign, consisting of hydaturia, should indicate the rupture of cyst and the diffusion of the content in the excretory tracts. While microscopic hydaturia could be seen in 10-20% of patients, macroscopic hydaturia is a rare symptom.[7] Radiological investigations allow clarification of the diagnosis and provide the most interesting evidences for hydatidosis diagnosis. The X-ray allows the display of a thin arc-shaped calcification that is characteristic of HC compared to heterogeneous and more or less diffused calcifications.[10] However, the plain abdominal X-ray could also be normal.[4]

2a



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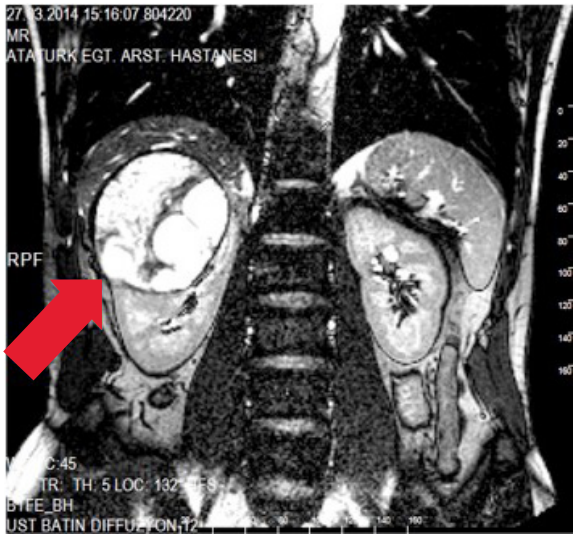
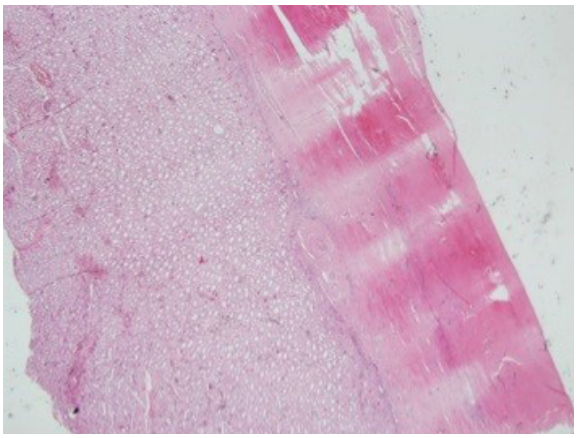


Figure 2: Abdominal computed tomography scan (2a) and magnetic resonance imaging scan (2b) showing a 10x9x10 cm sized cystic mass arising from the middle pole of the right kidney, destructing the whole upper pole and extending into the liver (arrows).

3a



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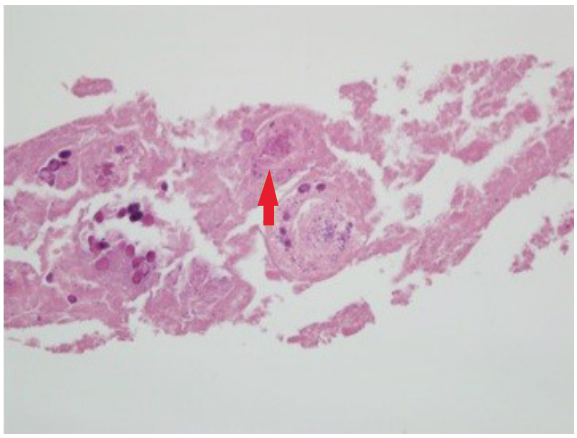

Figure 3: a) Hydatid cyst (HC) involving kidney tubules with cyst wall (haematoxylin and eosin x20); b) HC of the kidney - appearance of the hooklet forms, in the form of birefringent (arrow) (haematoxylin and eosin x200).

In our patient, curvilinear calcification was present in the right upper abdominal quadrant of the X-ray that suggested renal cyst HD.

The diagnosis of HC using US is reliable and it has been reported to be specific in up to 80%[6] of cases, and sensitivity is reported in up to 95%.[11] This technique provides an accurate size of the cyst, its topography, structure, and diagnoses any associated abdominal lesions. Advanced radiologic techniques, such as CT, play an important role in the diagnosis. CT scan shows a spectrum of findings from unilocular cysts, which may have thick calcified walls, to a multiloculated cystic mass with heterogeneous density, and daughter cysts.[4] In our patient, abdominal CT scan and MRI demonstrated a 10x9x10 cm sized cystic mass arising from the middle pole of the right kidney, destructing the whole upper pole and extending into the liver.

There is no specific laboratory finding for RCE. Eosinophilia may be present.[10] Casoni and Weinberg tests have 'historical' importance in cyst hydatid.[1] Counter immunoelectrophoresis against arch-5 antigen test was suggested as highly specific for HD.[7] However, in our patient the serological results

were all negative. In the epidemiological context, the radiological and biological data allow the final diagnosis. Huang and Zheng[11] have reported a retrospective analysis of 19 renal HD patients and the preoperative diagnostic accuracy for US, CT, and serology were 66.7%, 88.2%, and 92.3%, respectively.[11] Other cystic masses of the kidney, such as cystic renal cell carcinoma, nephroblastoma, and abscess should also be considered in the differential diagnosis. Particularly history of the patient and the area of his/her living should alert the clinician about the possibility of the presence of renal HD.

Surgery is the main treatment for the RCE. Medical management with albendezole shows limited effect with potential side-effects.[1] We administered albendezole, which was suggested following a consultation with the Infectious Diseases Department due to the very large size of the cystic renal lesion. Nephron sparing surgery (NSS) or partial nephrectomy should be applied whenever possible and has been reported to be possible in 75% of cases.[12] Laparoscopic cyst excision with irrigation-aspiration was also reported.[13,14] In our case, we performed open retroperitoneal approach due to the large size of the renal cyst that involved most of the kidney. We did not consider transperitoneal laparoscopic approach in order to avoid possible cyst rupture; due to its large size it may have led to intra-abdominal dissemination that could lead to serious complications. However, minimal invasive NSS was also reported that depended on the size and location of the renal hydatid mass lesion.[15] Following surgical resection, excellent outcomes have been reported with complete or partial surgical resection, with most patients having no recurrences.[6,10]

CONCLUSION

In conclusion, renal HD is a rare but significant aetiology of renal cystic lesions and it can mimic renal masses. Disease course is usually silent, common presentation is asymptomatic and a high suspicion index is mandatory for clinical diagnoses. The definitive diagnosis is only possible after histopathological examination. Surgery is the mainstay of treatment in contemporary practice and NSS is feasible in the majority of the cases.

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AN OVERVIEW OF PERCUTANEOUS NEPHROLITHOTOMY

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Disclosure: No potential conflict of interest.
Received: 23.10.14 **Accepted:** 13.11.14
Citation: EMJ Urol. 2015;3[1]:46-52.

ABSTRACT

Urolithiasis is a worldwide problem in the general population, due to its high prevalence and frequency of recurrence. Since the first successful stone extraction through a nephrostomy in 1976, percutaneous nephrolithotomy (PCNL) has become the preferred procedure especially for treatment of large, complex staghorn calculi. Of the minimally invasive treatment strategies, the PCNL procedure is simply based on the creation of a proper percutaneous renal access, through the most appropriate part of the kidney, dilation of this tract, and fragmentation. Most of these complications are related to tract formation and size. During the development of the PCNL technique, the different terminology emerged, mainly according to the tract size such as standard, micro-PCNL, mini-PCNL, and ultra-mini-PCNL. The aim of this study is an overview of the PCNL, including the history, training, procedure and type of PCNL, and possible complications.

Keywords: Urolithiasis, percutaneous nephrolithtomy (PCNL), mini-PCNL, micro-PCNL.

INTRODUCTION

Minimally invasive treatments, such as percutaneous nephrolithotomy (PCNL), retrograde intrarenal surgery (RIRS), non-invasive extracorporeal shock wave lithotripsy (ESWL), and laparoscopy procedures have almost completely replaced open surgery in the management of the urinary stone disease. PCNL which is based on the creation of a suitable percutaneous renal access, dilation of this tract, and fragmentation and elimination of the stone fragments using the nephroscope through an access sheath, is a well-established technique for the treatment of urinary stone in all age groups. Firstly, Goodwin et al.[1] described the use of a needle to decompress a hydronephrotic kidney. PCNL has become the preferred treatment, especially in cases of large, complex, staghorn calculi, since the first successful stone extraction was performed by a nephrostomy in 1976.[2]

Nowadays, except for the situations including contraindications for general anesthesia, anticoagulant therapy, untreated urinary tract infection, atypical bowel interposition, potential malignant kidney tumour, and pregnancy, PCNL has become a standard modality in the treatment of kidney stones that are larger than 2 cm in diameter and that do not respond to ESWL.[3] An abdominopelvic ultrasound (USG), plain abdominal films, and intravenous urography are the diagnostic imaging tools to determine stone size, location, and anatomical clues, as well as for planning treatment. Moreover, computerised tomography (CT) can be used when there is suspicion of hepatomegaly, splenomegaly, aortic aneurysm and retrorenal colon, allergies of the contrast medium, and in patients with non-opaque stone.[4]

Training

PCNL operation requires a certain skill level. There is a steep learning curve for surgeons to gain percutaneous renal access and thereby sufficient training is necessary. A resident has to perform approximately 24 PCNL procedures to provide proficiency during the residence period.[5] When surgical experience increases, the duration of operation and fluoroscopy usage gets shorter and the stone-free rate gets higher. Most complications are seen in the first 20 cases; however, the

complication rate significantly decreases after 45 cases.[6] Due to the high risk of complications seen during the operation, at the learning stage, simulation operations can be done prior to contact with the chosen patients who have a suitable and non-risky kidney anatomy and body posture in the initial steps for refining the techniques and the tactics.[6]

Positioning

Fernstom and Johansson[2] have performed the PCNL in the prone position (Figure 1A). Anesthetic problems, especially in the patients with compromised cardiopulmonary status, high-risk conditions such as morbid obesity or other, have induced to explore alternative positioning. Firstly, Valdivia Uría et al.[7,8] have described supine PCNL performed without needing to turn the patient into prone position in 1987, and they reported the first clinical experience in supine position in 1998 (Figure 1B). According to their experience the advantages seen in the patient's comfort and the feasibility of the technic for the surgeon justify its use. In the subsequent time, the variations in the procedure, such as Galdakao modification of Valdivia positioning, which is more challenging but has much lower risk of the anesthesia, is allowed simultaneous anterograde and retrograde access to the whole urinary tract.[9]

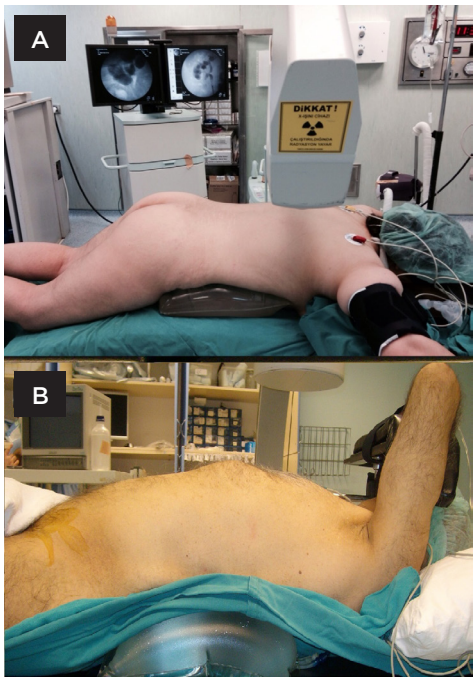

Figure 1: The position in prone (A) and supine (B) percutaneous nephrolithotomy.

De Sio et al.[10] compared prone technique done in 39 patients with supine technique done in 36 patients via forming the homogeneous groups in which the upper calyx puncture and the complete staghorn calculi were excluded. There were no significant differences in colonic injury or other complications between the two groups; however operation time was significantly lower in the supine group. Another randomised study reported by Falahatkar et al.[11] compared supine with prone PCNL. In this study, the stone-free rates were similar in both groups. Although the operation duration was lower but transfusion rate was higher in the supine group.

In a prospective study, the Clinical Research Office of the Endourological Society (CROES)[12] has evaluated the patients treated with PCNL in 96 centres between 2007 and 2009. The results of this study suggested that prone position was still the most popular (80.3%) approach for PCNL; however, there were differences between the centres: for example, although PCNL was done in prone position in 98.5% of the patients in North America, this rate was 76.5% in Europe. While the mean operation duration was lower in the prone group, the rate of blood transfusion and stone-free was higher.

PCNL PROCEDURE

Percutaneous renal access can be considered the most important point in PCNL, and directly affects the success and the complication rates of this surgery. Also ensuring the correct depth of initial percutaneous needle insertion is considered one of the major impediments. It is crucial to puncture through the centre of the calyceal papilla to avoid damage to interlobar and arcuate branches of the renal artery that may occur with puncture directly into the infundibulum or renal pelvis. However, İt is reported that injury to an interlobar vessel was seen in 67% and 13% during the upper-pole infundibulum and lower-pole infundibulum punctures, respectively.[13] There are many imaging techniques, including fluoroscopy, USG, and CT, to assess the intrarenal collecting system. C-arm fluoroscopy is the most commonly used method.[14,15] Biplanar fluoroscopy provides the optimal calyceal access via determining depth of the targeted calyx.[16] On the other hand, multiple calyceal structures can be seen as a single unit due to overlap on vertical plane and the actual depth of appropriate calyx for entry cannot be well evaluated as an inmonoplanar access technique.[14] Two primary

methods under biplanar fluoroscopic guidance have been described: 'triangulation' and the 'eye of the needle' (or bull's eye) techniques.[16,17] Also, various alternative access techniques, including the all-seeing needle method by Bader et al.[18] or blind puncture technique by Basiri et al.,[19] have been described in the literature over time. All of these methods have been used safely and efficiently in urologic practice.

Radiation exposure is an important point if the calyceal access is performed under fluoroscopic guidance. Renal puncture under fluoroscopy carries a radiation exposure risk for the surgical team and the patient. Total radiation dose of 50 mSv is the proposed annual dose limit for occupational exposure by The International Commission on Radiological Protection.[20] Bush et al.[21] showed that the skin on the flank area, the testes, and the ovaries received 0.25 mSv, 1.6 mSv, and 5.8 mSv of radiation, respectively, during the operation. Kumari et al.[22] reported that the mean radiation exposure dose to the urologist was 0.28 mSv, while the mean radiation exposure to the finger of the patient was 0.56 mSv. The biological effects of radiation include infertility, cataract, skin damage, and haematopoietic, gastrointestinal tract, and genetic changes, such as cancer.[23]

In recent studies, the success of USG-guided PCNL has been reported more frequently.[24-26] Gamal et al.[24] reported a PCNL series in which only USG, instead of fluoroscopy, was used during the whole procedure. It was applied to 34 patients and 94% of these patients were stone free. The advantages of USG guidance included the absence of radiation exposure, the ability to evaluate the residual non-opaque and semi-opaque stones that could not be visualised by fluoroscopy, imaging of the intervening structures between the skin and kidney (retrorenal colon), the ability to distinguish between anterior and posterior calyces.[25,26] In another study, Osman et al.[27] reported that puncture under USG guidance and dilatation under X-ray lowered the blood loss or major complications.

The dilation of renal tract is one of the major cost facts and steps in PCNL. This process can be performed with three different basic techniques, including Amplatz dilation (AD), metal telescopic dilation (MTD), and balloon dilation (BD) methods, which can add different operation costs.[28] BD has been generally regarded as the most modern and safe technique. Handa et al.[29] showed the superiority of a BD over AD via reducing the incidence of haemorrhage, blood transfusion, and morbidity, as well as providing a shorter surgery time and recovery period. AD still remains as the best and first method by many urologists for tract dilatation. In a study, Gönen et al.[30] compared BD with AD and reported that there were no significant differences in the operation time or blood transfusion rate between both groups. Metal telescopic dilation is usually selected for usage when the other methods of dilation have been failed or in the patients with severe perinephric scar tissue detected during diagnostic evaluation.[31] In previous years some innovative dilation techniques, such as one-shot dilatation that was firstly introduced be Frattini et al.,[32] have been developed.

In comparing these methods, BD is found to decrease the tract dilatation fluoroscopy time for both patient and urologist, so it has been regarded as the most safe and effective method for renal tract dilation.[33] Unsal et al.[31] evaluated the impact of tract dilatation methods on global and regional renal function using quantitative single-photon emission computed tomography of technetium-99m–dimercaptosuccinic acid (QSPECT of ^{99m}Tc-DMSA). They found that there were no significant differences for total uptake and area of the treated kidneys, serum creatinine, and blood pressure before and after PCNL. There are some instruments used during intracorporeal lithotripsy (ICL). Ultrasonic and pneumatic lithotripsy are usually used with rigid nephroscope; however, holmium YAG (Ho:YAG) laser is more feasible to use with flexible instruments.[3]

The last step before completion of PCNL, placement of a nephrostomy tube is considered as standard procedure. Besides providing haemostasis, nephrostomy tube also prevents urinary extravasation and maintains adequate drainage of the kidney, even if it causes discomfort, pain, and prolonged hospitalisation for the patients. That is why several authors have described new modifications, such as retrograde applied ureteral catheter or double J stent, used to alternatively drain the renal unit, known as tubeless PCNL.[34,35]

Wickham et al.,[36] who firstly described tubeless PCNL in 1984, reported 94% stone free rate, the average hospitalisation of 2.8 days, and 6% transfusion rate. Although Bellman et al.[37] placed a nephrostomy tube in first 50 patints, but they used just double-J (DJ) stent instead of nephrostomy tube in the subsequent patients in their study. The hospitalisation time, analgesia requirements,

time to return to daily activities, and the cost were significantly lower in the DJ stent group. Tubeless PCNL became popular in many centres, after this study. Istanbulluoglu et al.[38] compared tubeless with standard PCNL in 176 patients, the hospitalisation time and the amount of narcotic analgesics required were significantly higher in the standard nephrostomy catheter group. In their series, the majority of patients, who underwent the tubeless procedure, were discharged from the hospital in less than 24 hours. In another study, Kara et al.[39] compared tubeless with standard PCNL in elderly patients (range, 60-77 years of age). The hospitalisation and analgesic requirements were less than the standard PCNL. Some of the patients in the tubeless group may complain of the symptoms such as dysuria and increased urinary frequency. A short-time ureteral catheter can be used instead of a DJ-stent. Al-Ba'adani et al.[40] performed tubeless PCNL leaving only a 6 Fr retrograde ureteral catheter in 121 patients. The ureteral catheter was kept for 7-72 hours. There was low postoperative pain, and little need for postoperative analgesia with this procedure Lojanapiwat et al.[41] used ureteral catheter after PCNL in the selected patients. Their criteria were to be single access site, a non-obstructed renal unit, non-significant perforation of the collecting system, and bleeding. In their study, the mean hospitalisation time was 3.63 days, which was so long when compared with other studies. In a recent prospective randomised study, totally tubeless (no nephrostomy and no DJ stent) PCNL was reported as a safety method by Sabnis et al.[42]

MINIMALLY INVASIVE PCNL

Although different sized nephroscopes have been used according to the tract size, a 26–30 Fr access tract can be big enough for standard PCNL. In parallel with the development of technology, reducing the nephroscope diameter became the main goal of minimising the surgical morbidity of PCNL. Thus, mini-PCNL and micro-PCNL have been developed (Figure 2).[43,44] The percutaneous tract is serially dilated to 16-20 Fr in mini-PCNL. Nowadays, mini-PCNL is generally defined for PCNL procedure performed through the access tract of 18 Fr. Previously, this has been used in paediatric cases, but it has also been shown to be highly efficient and safe in adults. In a study reported by Abdelhafez et al.,[45] 73 patients with 83 renal units were treated for large renal stones (>20 mm in diameter) with mini-PCNL. They assessed the stone-free rate, the complications, the decrease in haemoglobin and creatinine level, and the duration of operation and hospital stay. The only significant difference was the stone-free rate which was 96.9% and 66.7% in simple and complex stones, respectively. Zeng et al.[46] reviewed >10,000 cases involving simple and complex calyceal stoneswere treated with mini-PCNL. A 24-34 Fr nephrostomy tract was used for this procedure. The stone-free rate was 77.6% and 66.4%, respectively.

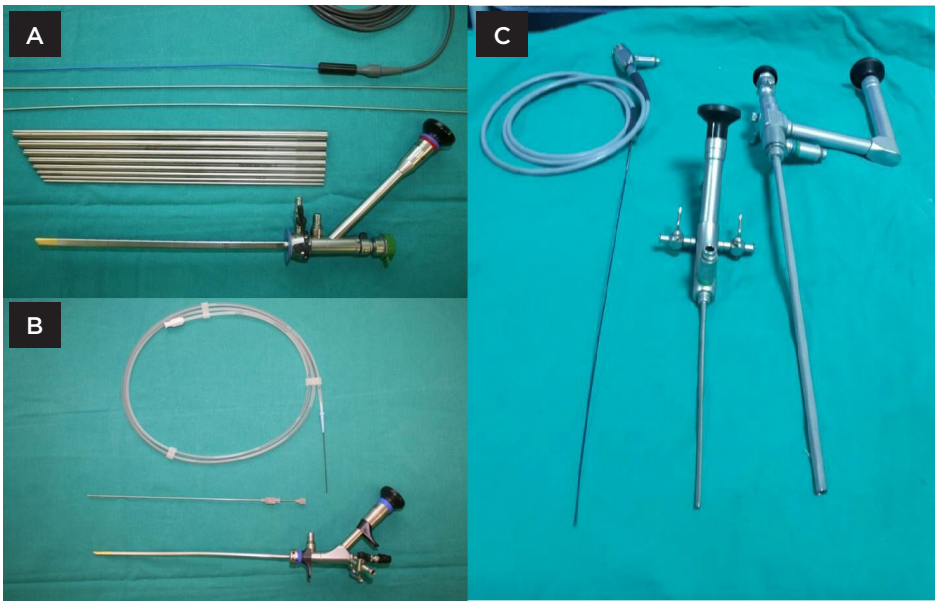

Figure 2: Nephroscopes with different diameters and their equipment. A) 22 Fr nephroscope; B) 16 Fr nephroscope; C) micro-percutaneous nephrolithotomy (PCNL), ultra-mini PCNL, and mini-PCNL nephroscopes.

The blood transfusion rates were 2.2% for simple stones and 3.2% for complicated stones in this study.

The aim of mini-PCNL procedure is to decrease the size of nephrostomy tract. Although there was no significant difference in the loss of functional tissue and postoperative renal scarring between standard PCNL and mini-PCNL.[47] But mini-PCNL is known to be less invasive with a lower transfusion rate. On the other hand, the rate of complex calculi treated in this study was not enough to define a clear conclusion. The absence of large-scale randomised controlled trials limits to demonstrate the superiority of mini-PCNL to standard PCNL.[48]

Desai and Solanki[49] designed a new technique ultra-mini PCNL (UMP) in which the renal tract was dilated to 11-13 Fr and any expensive stone retrieval instruments such as baskets and graspers were not required. UMP had a minimal complication rate, a high rate of stone-free and a very low rate of auxiliary procedures; however, it can be useful for the stones <20 mm in diameter and in lower calyx. On the other hand, when compared with ESWL, it has an advantage only in lower calyx stones with long and narrow calyces and a pointed angle where fragments do not pass easily.

In order to decrease the complications, Desai et al.[44] described the concept of 'All-seeing needle' to provide a one-step PCNL through a 4.85 Fr tract in 2011. This was the first clinical article on the safety and efficacy of microperc in the treatment of renal stones. In this single-step procedure technique, an access tract even smaller than those of mini-PCNL or UMP was used. As in micro-PCNL, the stone fragments were extracted via vacuum cleaner effect without requirement for any extraction instrument; however, Ho:YAG laser was required for ICL in this type of PCNL.

The most important advantage of micro-PCNL is to reduce blood loss. In micro-PCNL, single-step access under direct visualisation helps to prevent complications, such as bleeding, occurring during access, and dilatation of the tract. In the first micro-PCNL study, the mean decrease in haemoglobin level was 1.4 mg/dL. The blood loss requiring transfusion, which was 0.71%, was reported in one of the subsequent studies.[50] In this type of PCNL, drainage of the collecting system was mainly provided through the ureteral catheter inserted preoperatively, and that stone extraction was not required was another difference of micro-PCNL compared with standard PCNL. One of the most important points of micro-PCNL is to localise the stone exactly under direct visualisation, which facilitates complete and definitive fragmentation of the stone using laser lithotripsy. In addition, the urologist who can perform standard PCNL can easily learn micro-PCNL procedure. Hatipoglu et al.[50] evaluated the results of 136 patients treated with micro-PCNL in four referral hospitals. The overall success rate was 82.14% in this study. Moreover, the mean hospital stay was 1.76 (1-4) days, and the mean drop in haemoglobin level was 0.87 (0–4.1) mg/dL. Three patients (2.19%) had abdominal distension due to extravasation of the irrigation fluid. Sabnis et al.[51] compared micro-PCNL and RIRS for the management of renal calculi <1.5 cm. Although DJ stent usage was highly related with RIRS but higher analgesic requirement and haemoglobin reduction were more prominent in micro-PCNL induced patients.

The Complications

Nowadays, the modified Clavien–Dindo classification of surgical complications is the most commonly used assessment method. De la Rosette et al.[52] reported that no complications were seen in 79.5% of cases in an analysis of CROES. On the other hand, low-grade (Grade 1-2), medium-grade (Grade 3a and 3b) and severe (Grade 4-5) complications were seen in 16.4%, 3.6%, and 0.5%, respectively.

The most important complication seen in PCNL surgery is bleeding, which can occur in forms of perioperative, immediate postoperative, and delayed. The rate of blood transfusion is reported between 0-20% in the related studies. The predicting factors for massive blood loss have been reported as body mass index, multiple punctures, dilation with larger dilators, stone size, long operative time, and the degree of preoperative hydronephrosis.[53] The other potential complications are fever and sepsis. Urinary infection seen with PCNL is a frequent problem; however, very few cases progress to septic shock. All patients should undergo urinalysis and culture before PCNL.[3] The incidence of fever following PCNL ranges between 2.8% and 32.1%.[54] Fever can be due to preoperative bacteriuria, neurogenic bladder dysfunction, renal anomalies, high intrarenal pressure during the surgical procedure that can be occurred via high flow of isotonic solutions to get a better view during bleeding, the stone size, the severity of urinary obstruction, and long surgical time.[55] Antibiotic

prophylaxis is acceptable and recommended by many authors to prevent such complications. The accidental puncture of other intra-abdominal or thoracic organs such as bowel, spleen, liver, and pleura is very rare (<0.5%); however, it can cause fatal complications.[54] Pleural complications, which can be mostly seen in intercostal punctures, are uncommon (<2%).[52] On the other hand, colonic perforation is more common in left-sided procedures. The prominent risk factors are old age and the presence of kidney anomalies such as horseshoe kidney.[56] The mortality rate of PCNL has been reported between 0.04-0.8.[57]

CONCLUSION

PCNL has been successfully and safely used to treat patients with renal stones for more than a quarter of a century. Still, the use of PCNL in treating renal stones in different patient groups, such as children, obese patients, patients with renal congenital anomalies, patients who had previous open renal surgery. Various aspects of the procedure such as patient positioning, renal access, the ideal dilating method, the type of nephrostomy tube used, as well as the actual need for drainage, have been debated.

During the development of the PCNL technique, different terminology emerged, mainly according to the tract size such as standard, micro-PCNL, mini-PCNL and UMP. Miniaturisation of instruments in PCNL has spawned an interest in so-called 'microperc' in which the procedure is carried out through a 16-gauge needle. Miniperc has generated a lot of enthusiasm in the last few years. Miniperc utilises tract size of 20 Fr or less, hence the complication rates are much less. Haematocrit drop is significantly reduced and blood transfusion rates have gone down. Reduced pain and hospital stay without affecting success rate is the remarkable achievement of this procedure. Although initially it was supposed to be for small sized stones, many authors have utilised mini-PCNL even for large and complex stones with good clearance rate. The quintessential element of an innovative PCNL, which is termed as UMP is using a novel 6 Fr mini nephroscope through an 11–13 Fr metal sheath to perform Ho:YAG laser lithotripsy. Dilation is achieved in one step with much less fluoroscopy time, and the cross-section of the puncture channel is only approximately 30% of that required with the conventional mini-PCNL. This miniaturisation is the main reason why no blood transfusion and nephrostomy tube are routinely placed in this group of patients.

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EFFICIENCY OF IMAGING METHODS PRIOR TO PERCUTANEOUS NEPHROLITHOTOMY

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Disclosure: No potential conflict of interest.
Received: 09.10.14 **Accepted:** 03.11.14
Citation: EMJ Urol. 2015;3[1]:53-56.

ABSTRACT

The most important step of percutaneous nephrolithotomy (PCNL) is planning the puncture site. A well selected puncture will facilitate nephroscopic navigation and stone clearance. The traditional methods for planning the puncture are intravenous urogram or retrograde pyelogram. Either of these imaging tools is adequate, but new tools such as 3D reconstructed tomography should be more accurate. Many recently developed imaging tools are promising, but no one is still ideal. The imaging techniques that we currently use have specific advantages and disadvantages. The purpose of this review is to summarise different imaging tools and their effectiveness prior to PCNL.

Keywords: Imaging, percutaneous nephrolithotomy, renal stone.

INTRODUCTION

The purpose of the present study is to evaluate the effectiveness of imaging methods prior to percutaneous nephrolithotomy (PCNL). Radiological imaging techniques constitute the most important step in both diagnosis and treatment planning of urinary stone disease. Before interventions, contrast enhanced re-imaging such as intravenous urography or computerised tomography is recommended to evaluate anatomy of the renal collecting system. Despite this recommendation, most urologists do not perform any contrast enhanced imaging before PCNL. The most important reason for this is radiation exposure, and the risk of allergic reactions and contrast nephropathy due to the contrast agents. Our aim is to find the optimal imaging tool prior to PCNL.

PLAIN ABDOMINAL RADIOGRAPHY (KIDNEY, URETER, AND BLADDER [KUB])

Although most of the stones, especially calcium containing stones, are opaque and can be visible on plain abdominal radiography, uric acid, or urate containing stones are not visible. In clinical practice KUB is the most often used radiographic imaging modality for urologists. Its limiting factors are bowels, gas, and non-opaque or poor opaque renal stones, and some other extra-renal calcifications, such as mesenteric calcifications.[1] In studies that compare the computed tomography (CT) and KUB, the KUB has a lower sensitivity in the diagnosis of stones, ranging between 45-56%, and with specificity between 67-69%.[2-6] Yet a combination of KUB and ultrasonography increases its sensitivity.[7] Its main advantages are availability, stone size measurement, and postoperative follow-up for residual stones. The disadvantages are radiation exposure, no information about kidney anatomy and surrounding organs, radiolucent stones, and limitations of the bowel gas.[8]

Intravenous Urography (IVU)

IVU remains the first line radiologic method to diagnose urinary system stones for many urologists. Performing the IVU is relatively safe and easy for many departments.[1] The risk for anaphylactic reactions with low osmolality contrasts is

approximately 9/1,000,000.[9] The site and size of the stones, detailed pelvicalyceal anatomy, renal function, calyceal diverticula, duplex systems, and renal obstruction can be easily defined with IVU.[10,11] It also shows the relationship of the pelvicalyceal structure and the ribs. The risk and planning of supracostal access could be evaluated with the help of IVU. One of the most important steps to locate the posterior calyx with IVU might be difficult. Some authors[12,13] suggest that the posterior calyxes locate medially. Eisner et al.[14] suggests the opposite, that the second lateral to the medial one is the posterior calyx. The main disadvantage of the IVU is 2D imaging modality, non-opaque stones, and no information of the surrounding organs of the kidney. The major advantage is a detailed pelvicalyceal anatomy and an idea of the function of the kidneys.

Ultrasonography (USG)

Ultrasound is one of the easiest and safest diagnostic tools for urolithiasis but it has some limitations. Over 5 mm diameter renal stones can be easily identified with USG but smaller stones have less acoustic shadow, and thus are very difficult to diagnose.[15] The size and site of the stone can be measured by USG but many urologists want to confirm location with IVU prior to USG. The identification of the collecting system, especially non hydronephrotic systems, is difficult for USG. Other diagnostic problems include poor image quality in obese patients and an inability to differentiate nephrolithiasis and nephrocalcinosis. Planning access prior to PCNL grey scale USG is not reliable enough and, compared with CT pelvicalyceal anatomy and surrounding solid organs identification, is still poor. Fowler et al.[16] found that USG could identify 39% of multiple renal stones so this is a great disadvantage for PCNL access planning. Ekici et al.[17] evaluated the accuracy of KUB and USG combination versus non contrast helical computed tomography (NCCT) and found the combination of KUB and USG highly sensitive (97.9%).

USG has been used by many urologists during the puncturing of the collecting system.[18] USG guidance puncture without fluoroscopy has also been reported.[19] This radiation free puncture technique is a good choice for paediatric populations and the intraoperative identification of kidney-related organs may avoid organ injuries. The 4D USG provides real time 3D images which provide a 360° viewing of the area.[20] The accuracy of the 4D USG has been evaluated during renal puncture on experimental studies; it provides good quality punctures, such as 2D USG, but improvements in the technology should be expected.[21-23] The main advantages of USG are that it is portable, radiation free, cheap, and that radiolucent stones are also visible. The disadvantages are that there is a limited accuracy for renal stones and poor anatomic detail. The European Association of Urology (EAU) guideline suggests USG as the first line imaging modality for paediatric patients with urolithiasis.[10]

CT

NCCT is the gold standard imaging tool for identification of urinary system stones because of its high sensitivity and specificity of up to 100% and 97%, respectively.[11] Except for indinavir and matrix stones, over 99% of the stones can be seen on NCCT.[24] NCCT provides information about size, location of the stones, and surrounding organs such as the pleura, colon, and liver.[25,26] The incidence of retrorenal colon was reported at 1.7% and many studies have reported colon perforation during PCNL.[27,28] Planning a safe puncture, especially for multicalyceal stones and renal anomaly, is possible with NCCT.[29] However, despite its advantages, the NCCT does not give enough information like that concerning the draining of infundibulum and the function of the kidneys. Similarly, planning the route for the puncture is not as easy as with IVU. Multiplanar reconstructions using 3D volume rendering may overcome these limitations and decrease the need for IVU for planning punctures.[30,31]

The new generation Dual Energy CT (DECT) devices improve imaging of urinary calculi with half dose radiation. DECT provides the same anatomical information and gives far more detail about stone information without extracting the stone.[32] DECT reports the stone information as uric acid or non-uric acid with 100% sensitivity and specifity.[33,34] Jepperson et al.[32] showed the ability of DECT to differentiate between small fragments adjacent to ureteral stents or nephrostomy tubes. Toebker et al.[35] evaluated the split bolus CT protocol. They injected Iomeron® at 15 ml 10 minutes before, and 80 ml 65 seconds before the scan. The protocol allows the combining of three phases (true and virtual non-contrast phases, and a contrast enhanced phase) and reconstructs transverse and coronal images. This technique provides the determination of stones 5 mm or larger with CT urogram images.

Patel U et al.[36] recorded the CT pyelographic movie and watched it in the operating room to plan the renal access and endourologic navigation before the PCNL procedure. There is an instrument that combines flat-panel fluoroscopy with CT capability and makes 3D reconstructions called DynaCT (Siemens, Germany). DynaCT provides real-time intraoperative and postoperative data, enabling preoperative planning and results with high accuracy imaging.[37] CT is recommended prior to PCNL in patients with anatomical or renal anomalies, radiolucent stones, renal insufficiency, and contrast allergy.[38] In addition, stone density can be calculated and the composition of stones can be obtained.

The major problem with repeated NCCT is high cumulative radiation exposure. The international Commission on Radiation Protocol recommends not exceeding 20 mSv per year during a 5-year period, or 50 mSv in only 1 year.[7] Using risk models, it has been estimated that 1/1,400 patients at 60 years old and 1/1,000 patients at 40 years old, undergoing NCCT, would develop solid organ cancer and leukaemia due to radiation.[39] Paediatric patients are more sensitive to radiation because of actively dividing cells. Tepeler et al.[38] evaluated the CT examination and IVU prior to PCNL in paediatric patients and found no difference in successes and complications between the two modalities.

The mean radiation dose of the abdomen CT, enhanced CT, and IVU are about 5 mSv, 25-35 mSv, and 1.3-3.5 mSv, respectively.[40] Low dose CT has decreased the radiation dose to 0.5-3.5 mSv. EAU guidelines recommend low dose NCCT to patients with body mass index <30 if CT is indicated.[10] The major advantages of the CT are high diagnostic accuracy, where almost all stones are visible, and that information of the kidney-related organs and calyceal anatomy may be reconstructed. The disadvantages are radiation exposure, limited availability, and no information about kidney function with NCCT.

Magnetic Resonance Imaging (MRI)

MRI provides better imaging of the soft tissue in comparison with CT but it is not reliable for urinary system stones.[11] MRI is a radiation free technique and may be considered as an alternative to USG for pregnant and paediatric patients. Magnetic resonance Urography (MRU) may be an alternative to IVU. The site of the obstruction may be seen clearly but the identification of the stone by signal void may be difficult.[41] The accuracy of MRU in urinary stones when combined with tesla 2-weighted 3D series is 92.8% with sensitivity between 96.2-100% and specificity of 100%.[42] 3D MRI and 3D CT images with volume and surface rendering software provide an endoscopic view of the organs; the technique is known as virtual endoscopy. Virtual cycstoscopy and ureteroscopy have been performed with high sensitivity.[43] The main advantage of MRI is that there is no ionising radiation. The disadvantages are limited availability and limited experience.

CONCLUSION

EAU guidelines recommend a contrast study (enhanced CT or IVU) if stone removal is planned, because the anatomy of the renal collecting system needs to be assessed prior to stone surgery or shock wave lithotripsy. But use of repeated CT or IVU would increase the risk of cancer development. We hope that advances in technology will provide us with radiation-free or low-dose radiation imaging with detailed functional urological anatomy.

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COMPLICATED URINARY TRACT INFECTIONS: HIGHLIGHTS ON DIAGNOSIS AND MINIMALLY INVASIVE TREATMENT

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Disclosure: No potential conflict of interest.
Received: 27.10.14 **Accepted:** 24.11.14
Citation: EMJ Urol. 2015;3[1]:57-61.

ABSTRACT

Complicated urinary tract infection (UTI) has always been a challenging subject to diagnose and treat. New, less invasive, techniques have been introduced in the last decade with the development of the new generations of high definition endoscopes and the robotic platforms to treat the surgically correctable pathologies underlying UTIs. This review will discuss the different underlying pathological conditions for complicated UTI and their management.

Keywords: Urinary tract infection (UTI), minimally invasive, complicated, complex.

PATHOPHYSIOLOGY

Background

Complicated urinary tract infections (UTIs) are urinary infections secondary to functional or structural abnormalities of the urinary tract.[1] A UTI is the inflammatory response of the urothelium to invasion by microorganisms, commonly associated with bacteriuria and pyuria. Certain other patient factors, including an immune-compromised host or genitourinary tract manipulation, can also lead to inclusion in the term 'complicated'. Various thresholds are used to define the amount of colony forming units (CFU) required to diagnose an infection. By definition all UTIs in men are complicated and the latest EAU guidelines use a threshold of $>10^4$ and $>10^5$ cfu/ml for complicated UTI in men and women, respectively. This is higher than the value of 10^3 cfu/ml for acute uncomplicated cystitis in women.[2] The most common pathogens include *Escherichia coli*, *Enterococci*, *Pseudomonas aeruginosa*, *Candida* species, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, and *Klebsiella pneumoniae*.[3] As uncomplicated urinary infection is rare in men, any male urinary infection is usually considered complicated.[4]

The main significance of complicated UTIs is their challenging ability to resist normal treatment protocols. The pathogenesis of complicated UTI is multifactorial; they are generally caused by urine stasis, either due to obstruction (structural) or failure of emptying (functional), leading to by passing the normal host defence mechanisms with formation of nidus for infection that can be resistant to usual antimicrobial agents.[5]

Structural Abnormalities

Ureteric or urethral strictures, tumours of the urinary tract, urolithiasis, prostatic hypertrophy, diverticulae, pelviureteric junction obstruction (PUJO), renal cysts, and congenital abnormalities are all causes for urinary tract obstruction (UTO) which is the most important factor leading to complicated UTI. Overdistension will result in a residual urine pool providing a continuous medium for bacterial growth and interfering with the local mucosal defence mechanism.[1,6] Vesicovaginal fistula (VVF) and colovaginal fistula (CVF) are also a known cause of the development of recurrent UTIs.

Instrumentation

Indwelling urethral catheter, intermittent catheterisation, ureteric stent, nephrostomy tube,

and urological procedures can all allow easy access of pathogens into the urinary tract, which can lead to formation of biofilms and subsequently provide a nidus, making it difficult to eradicate infections with antimicrobial agents.[1,5]

Impaired Voiding

Neurogenic bladder, spinal cord injuries, cystocoeles, vesicoureteral reflux, and ileal conduit are all factors that can lead to incomplete drainage of urine and therefore impair normal flushing of bacteria from the urinary tract, with imbalance in one of the major host defence mechanisms contributing to complicated UTI.[7]

Metabolic Abnormalities

Nephrocalcinosis, medullary sponge kidney, renal failure, and diabetes mellitus can mainly affect the host mechanisms leading to severe forms of complicated UTIs including intrarenal and perirenal abscess, emphysematous pyelonephritis (EPN) and papillary necrosis, and xanthogranulomatous pyelonephritis.[8]

Immunocompromised

Those who have had a renal transplant and patients with acquired immune deficiency syndrome have significantly impaired host defence mechanisms making it difficult and sometimes impossible to achieve an effective response to the antimicrobial agents. In complicated UTIs, less virulent uropathogens, that rarely cause disease in a normal urinary tract, can cause significant damage to the urinary tract; associations between Group B streptococcal bacteraemia, *Candida*, and *Enterococci* were identified in some studies with complicated UTIs in vulnerable patients.[9,10]

DIAGNOSIS

This diagnosis of a complex UTI is based on three main features: the clinical picture, microbiological tests, and radiological investigations. Physicians should always consider atypical microbiology and the potential for UTO, which may require prompt drainage in this patient group.

Clinical Picture

The most common clinical presentations of UTI include acute cystitis, pyelonephritis, and less commonly acute prostatitis, but patients with abnormal urinary tracts can present more atypically. A carefully taken history is an essential diagnostic tool, with particular attention to the symptoms of frequency, dysuria, haematuria, suprapubic, and/or loin pain. Focussed questioning on preceding urological complaints/surgery, any indwelling catheters/stents, history of neurological disease, and diabetes/immunosuppression are vital. It has been suggested that the acute onset of dysuria and frequency without any vaginal symptoms can have a positive predictive value as high as 90%.[11] Clinical examination is crucial to reveal features which can alert the physician to underlying urological disease, but also to enable the recognition of the acutely unwell patient who may be suffering from urosepsis, which can be clinically evident as severe infection of the urinary tract and/or the male genital tract (e.g. prostate); features consistent with systemic inflammatory response syndrome, such as fever, tachycardia, tachypnoea, and respiratory alkalosis, which were earlier considered mandatory for the diagnosis of sepsis, are now considered to be the alerting symptoms. It may be associated with multiple organ dysfunction, hypoperfusion, or hypotension.[12] If this diagnosis is made, prompt resuscitation and treatment is mandatory.

Laboratory Tests

Basic laboratory tests may reveal elevated inflammatory markers and renal function should be recorded. The urine dipstick is a simple and cheap bedside test and is very useful in confirming a diagnosis of UTI. The sample should be collected as a 'clean-catch' midstream specimen with appropriate cleaning of the glans in men, although recent reports have suggested no difference in rates of contamination between cleaned and uncleaned groups.[13] The presence of nitrates and leukocytes in the urine are strongly suggestive of infection. Most Gram-negative bacteria (the most common infective agent) convert nitrates to nitrite and this forms a pink colour in azo-dye when it comes into contact with the aromatic amine reagent of the dipstick. The specificity of this test has been reported to be as high as 100% although the sensitivity is less.[14] Leukocyte esterase is produced from neutrophils within infected urine and this also results in a colour change on the dipstick. Combining both increases the specificity but may reduce the sensitivity.

Urine should be sent for Gram stain, culture, and sensitivity. Microbiology can help provide crucial information including the identity of the infective organism and providing antibiotic sensitivities. If clinical evidence of sepsis is identified, blood culture

and inflammatory markers including C-reactive protein and leukocyte count should be included in the initial investigations.[12]

Radiological Tests

In the context of a complicated UTI, imaging is used to alert the urologist to a structural problem which requires intervention. This can include serious conditions such as an infected and obstructed system, renal/perirenal abscess, EPN, and also prostatic abscess formation. Patients who show prompt clinical improvement with antibiotic treatment may not require acute imaging. However, in patients who do not improve, or if there is diagnostic uncertainty, then urgent imaging is indicated. A plain radiograph may enable visualisation of a renal/ureteric stone or intrarenal gas. Ultrasound provides a good assessment of the renal parenchyma with identification of hydronephrosis, perinephric collections, and renal abscess.[15] Computerised tomography (CT) scanning can be performed either with or without intravenous contrast. If there is a diagnostic concern, a non-contrast CT of the kidneys, ureters, and bladder is a highly effective technique to confirm/rule out ureteric colic with low dose techniques reducing the radiation exposure.[16] Contrast CT enables accurate identification of acute pyelonephritis, renal abscess, infected renal cysts, and EPN.[17] In the acute setting magnetic resonance imaging can be utilised in the presence of an allergy to iodinated contrast media used in CT and in pregnancy (after the first trimester) or if prostatic abscess is clinically suspected.[17] In the paediatric population, voiding cystourethrography can be helpful in demonstrating ureteric reflux. However it is an invasive test with significant radiation exposure and it is debate as to the predictive value of reflux in causing renal scarring.[18]

MANAGEMENT

After the initial diagnosis and antimicrobial or conservative treatment of the underlying cause of the complicated UTI, historically the next step has been an open procedure in many cases. With the introduction of new endourological techniques in the last 50 years, and the more recent introduction of laparoscopy and subsequently the robot, patient outcomes have greatly improved. It is important to remember that there are many functional causes of complicated UTIs, which is where the multidisciplinary team approach can be very useful. With the expertise of the specialist nurses, neurologists, and endocrinologists, and the development of novel clean intermittent self-catheterisation catheters, to reduce rates of bacterial colonisation, many patients can now be managed in the long term with minimal significant problems.

The introduction of flexible ureteroscopy in the 1960s fundamentally changed the way in which urologists managed upper tract calculi. Rigid and flexible ureterorenoscopy can both increase intra renal pelvic pressure and subsequent backflow, both intrarenal and pyelolymphatic. Together with potential extravasation, this can result in post-operative sepsis. A porcine model has also shown irreversible damage to the renal parenchyma due to these raised pressures.[19] There are different methods of breaking up ureteric and renal calculi with a laser fibre. For softer calculi, and to prevent the formation of multiple small fragments, the technique of dusting/painting may be used. In these cases the laser fibre is used to reduce the bulk of the stone in fine layers producing only 'dust'. A quicker method is to drill down into the calculi at multiple points thus shattering it into smaller fragments which can be removed with a basket. Finally, the term 'popcorning' refers to moving a calculi or fragment into a calyx and holding the fibre in the middle of the calyx. This technique agitates the contents of the calyx and they bounce between the fibre tip and the wall. This results in fragmentation which may obviate the need to use a basket. As technology has advanced, allowing smaller scopes and better vision, new robotic devices are currently being trialled. A preliminary study has shown that the Roboflex Avicenna significantly improves ergonomics with the next step looking at clinical outcomes.[20]

The current standard of care in cases of significant nephrolithiasis is percutaneous nephrolithotomy (PCNL) due to the relatively large calibre access sheath and higher stone-free rates than completely endoscopic techniques. In a large group, patients with urinary tract abnormalities were found to be more at risk of UTIs. These patients underwent PCNL for their stone burden and had lower stone-free rates than the normal population.[21] The trend, however, is a decrease in the size of the PCNL tract due to advances in lenses and other associated equipment. There are multiple benefits, including better preservation of renal function and reduced morbidity with similar rates of stone clearance in a selected group as standard PCNL. The recent description of ultraminiperc in literature using

a 6 Fr scope through an 11 Fr to a 13 Fr access sheath, has shown 1 month stone-free rates of 97.2% when treating a group with a mean stone size of 14.9 mm.[22]

Despite the limited use of broad spectrum antibiotics impregnated stents, still some studies have proven a marked impact on biofilm formation, encrustation, or infection development. The triclosan eluting stent is an example of those that have led to significant reductions in several common ureteral-stent-related symptoms and UTI incidence.[23,24]

A VVF can be an unusual cause for recurrent UTIs especially after pelvic surgery and the administration of pelvic radiotherapy. In the first instance conservative management can be undertaken, with the insertion of a urethral catheter and the administration of antibiotics in small VVFs, allowing the fistulous tract to close by its own volition. However, many cases do proceed to surgery and traditionally have been performed as open procedures using an omental flap to prevent the fistula from recurring. With the advent of robotic surgery and its increasing use in the urology and gynaecology arenas, more complex operations are able to be carried out minimally invasively. There is published evidence of repairing high VVFs with a peritoneal flap inlay.[25] Certainly in comparing minimally invasive and open surgery in patients with recurrent VVFs, there is no difference in success rates but there is a reduced morbidity and decreased hospital stay in the robotic-assisted laparoscopic group.[26] The next evolution has been the trial of laparoendoscopic single-site surgery in this group with decent early results.[27] It follows that robotic surgery has also been shown to be feasible in the treatment of CVFs after prostatectomy.[28]

Ureteric reimplantation for vesicoureteric reflux in children has historically been performed via an open procedure due to the lack of intra-abdominal space, meaning laparoscopy alone has not been a viable option. With the instrument articulation allowed by the robot, the role for minimally invasive surgery has come to the fore. In a small group, robotic assisted ureteric reimplantation has been shown to be a feasible procedure with satisfactory outcomes.[29]

There are a number of options in the definitive management of PUJO. Endoscopically, retrograde laser (Holmium-YAG) endopyelotomy has respectable success rates documented at 77% in cases of primary PUJO.[30] Currently, the gold standard is robot-assisted laparoscopic pyeloplasty (RLP) for both primary and secondary PUJO. A large, multicentre study has shown the benefits of RLP over the conventional laparoscopic approach. Success has been shown in 96% at nearly 4 years with overall low complication rates (6.6%) and short hospital stay.[31]

The daVinci robotic system (Intuitive Surgical Inc., Sunnyvale, CA, USA) and newer endoscopic robots such as the Roboflex Avicenna have, and will, play an integral part in the future of urological practice. The daVinci robot has been shown to reduce hospital stay and allows greater dexterity when compared to laparoscopy in certain cases. One must, however, bear in mind the associated costs, particularly with newer robotic technologies, and weigh this up with any decision making. With the advent of robotic technology, telementoring and remote operating have developed greatly in recent times and have been used to help clinicians attenuate their learning curve when picking up this new skill. Telementoring has also been shown to be of great benefit in the training of urology trainees.[32]

CONCLUSION

Minimally invasive techniques have long played an integral role in the diagnosis and treatment of many urological conditions. With developments in technology, robots are more accessible and subsequently being employed for a wider variety of procedures. Recent reports have described that the administration of antibiotics in primary care and hospitals are on the rise, leading to increased levels of antibiotic resistance. Therefore, addressing the cause of complicated UTIs is of paramount importance and if they can be managed via a minimally invasive approach, the patient will benefit from lower morbidity and potentially better outcomes.

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URINARY TRACT INFECTION: HOW IT HAPPENS?

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Disclosure: No potential conflict of interest.
Received: 13.10.14 **Accepted:** 12.12.14
Citation: EMJ Urol. 2015;3[1]:62-67.

ABSTRACT

Urinary tract infections (UTIs), including cystitis and pyelonephritis, affect a large proportion of the world population and account for substantial morbidity and medical costs. Classification of the UTIs is based on the anatomical level of infection, the grade of severity of infection, the underlying risk factors, and the microbiological findings. Uropathogenic *Escherichia coli* is the causative agent in 70-95% of community-acquired uroinfections and about 50% of all cases of nosocomial uroinfections. Virulence factors associated with uropathogenic strains of *E. coli* contain toxins such as haemolysin and cytotoxic necrotising factor, capsules, lipopolysaccharide, the siderophore aerobactin, and adhesive organelles. The ability to attach to urothelial cells is the most important determinant of pathogenicity. An adherence is followed by inflammation involving the urothelial cells' cytokine response. Whereas interleukin (IL)-6 can cause the fever and systemic response of the UTIs, IL-8 can function as a neutrophil chemoattractant. Cytokines released by T cells and monocytes modify initiative urothelial cells' cytokine response to bacteria. Nevertheless, antibiotic treatments can effectively sterilise the urine, but bacteria can survive and persist in the bladder tissue, serving as a reservoir for the recurrent UTIs. The severity of UTI reflects the quality and magnitude of the host response. While strong local and systemic innate immune activation occurs in patients with acute pyelonephritis, the response to asymptomatic bacteriuria is low. It should be reasonable to 'individualise' diagnosis and therapy by interconnecting information on uropathogenic bacterial virulence and the host response.

Keywords: Urinary tract infection, *Escherichia coli*, virulence, interleukin.

INTRODUCTION

Urinary tract infections (UTIs) are assumed to be the most common bacterial infections accounted in the United States for approximately 7 million office visits, 1 million emergency department visits, and >100,000 hospital admissions annually, most often for acute pyelonephritis. A diagnosis depends on both the presence of symptoms and a positive urine culture, although in most outpatient settings a diagnosis is based on dysuria, frequency, urgency, and suprapubic pain. These lower urinary tract symptoms are classically present in cystitis, whereas pyelonephritis is associated with fever, chills, and flank pain. Women are more likely to experience UTI than men. Almost half of all women will experience one UTI episode during their lifetime. Specific subpopulations at increased risk of UTI include pregnant women, infants, the elderly, and patients who have diabetes, underlying urological abnormality, urinary catheter, spinal cord injury, multiple sclerosis, and immunodeficiency syndrome. Catheter-associated UTI is the most common nosocomial infection, accounting for >1 million patients in hospitals and nursing homes. The risk of UTI increases with duration of catheterisation. In nonobstructed and non-pregnant women, acute uncomplicated UTI seems to be a benign disease with no long-term sequelae. Nevertheless, UTI increases the risk of premature delivery and foetal mortality among pregnant women as well as pyelonephritis, impaired renal function, and end-stage renal disease among paediatric patients. The estimated annual cost of community-acquired UTI is significant, costing approximately $1.6 billion in the United States.[1]

ASCENDING ROUTE OF INFECTION

UTIs represent the inflammatory response of the urothelial cells to bacteria mostly entering from the bowel reservoir via an ascending route through the urethra into the bladder. This route is further enhanced by significant soilage of the perineum with faeces, utilisation of catheters, or spermicidal agents.[2,3] Indwelling catheters with open-drainage systems result in bacteriuria in almost 100% of cases within 3-4 days. The more compromised natural defence mechanisms with, for example, urinary obstruction or catheterisation, the fewer the virulence requirements of any bacterial strain to induce UTI. Although cystitis is restricted to the bladder, approximately 50% of UTIs can extend into the upper urinary tract. The most episodes of pyelonephritis are caused by retrograde ascent of bacteria from the bladder through the ureter to the renal pelvis and parenchyma. Although reflux of urine is probably not required for ascending infections, oedema associated with cystitis may cause sufficient changes in the ureterovesical junction to permit reflux. Once introduced into the ureter the bacteria may ascend to the kidney, and this ascension would be considerably facilitated by any process that interferes with the regular ureteral peristaltic functioning. Gram-negative bacteria and their endotoxins, as well as pregnancy and ureteral obstruction, have a significant antiperistaltic effect. Bacteria that reach the renal pelvis can enter the renal parenchyma by means of the collecting ducts at the papillary tips and then ascend upward within the collecting tubules. This process is accelerated by elevated intrapelvic pressure from ureteral obstruction or vesicoureteral reflux as well as in the presence of intrarenal reflux.

The vast majority of UTIs are caused by bacteria usually originating from the bowel flora. *Escherichia coli* is the most common uropathogen, responsible for over 80% of community-acquired and approximately 50% of hospital-acquired UTIs. Other Gram-negative Enterobacteriaceae such as *Klebsiella* and *Proteus* as well as Gram-positive *Enterococcus faecalis* and *Staphylococcus saprophyticus* are responsible for some of the other community-acquired UTIs. Nosocomial infections are caused by *E. coli*, *Klebsiella*, *Citrobacter*, *Enterobacter*, *Serratia*, *Pseudomonas aeruginosa*, *E. faecalis*, and *Staphylococcus epidermidis*. Uropathogens such as *S. epidermidis* and *Candida albicans* originate from the flora of the vagina or perineal skin.[4,5]

Bacterial Adherence

Uropathogenic E. coli (UPEC) can infect the urinary tract not by chance but rather by the expression of virulence factors that enable them to adhere to and colonise the perineum and urethra and migrate to the urinary tract, where they establish an inflammatory response in the urothelial cells (Table 1).[6] Genomic analysis of a UPEC strain revealed the presence of genes for putative chaperone/usher systems such as autotransporter proteins that may function as motility mediators, adhesins, invasins, proteases, and serum resistance factors.[7] Autotransporter serine protease Sat may cause cytoplasmic vacuolation and severe histologic damage.[8] Alpha-haemolysin forms pores in the urothelial cell membranes.[9] UPEC produces several iron acquisition systems and iron system. Most UPEC strains generate an acid polysaccharide capsule that protects the bacteria from phagocytosis by human polymorphonuclear leukocytes and inhibits activation of complement.[10] UPEC expresses a number of adhesins that allow attachment to the urothelial cells.[11] Bacteria assemble adhesins on their surface as monomers, oligomers, or supramolecular fibres called fimbriae or pili. The adhesive organelles that are associated with UPEC strains include S pili, Dr family adhesins, P pili, and Type 1 pili.[12] S pili recognise sialyloligosaccharide residues on urethelial cells and can help colonisation of the upper urinary tract. Dr family adhesins bind the Dr^a blood group antigen present on decay accelerating factor. P pili bind the α-D-glucopyranosyl-(1-4)-β-D-galactopyranoside moiety present in the globoseries of glycolipids that are expressed by erythrocytes and kidney endothelial cells. Therefore, P pili act as a major virulence factor of pyelonephritis. Type 1 pili are the most widely distributed among UPEC strains.[13] Type 1 pili consist of a 7 nm thick helical rod made up of repeating FimA subunits connected to a 3 nm wide distal tip fibrillar structure containing two adapter proteins FimF and FimG joined to the adhesin FimH.[14] FimH binds mannose containing glycoprotein receptors and may mediate UPEC attachment.[15] The FimH adhesin constitute a COOH terminal pili domain involved in the incorporation of FimH into Type 1 pili and an NH_3 terminal adhesin domain consisting carbohydrate binding pocket capable of receiving a D-mannose.[16] Interaction of the FimH with glycoprotein receptor on the bladder uroepithelial cell is a crucial step of the UPEC colonisation and the onset of the cystitis.[13,16,17]

Table 1: *Escherichia coli* virulence factors.

Fimbriae/adhesins
- Type 1, Type 3, P-fimbriae, S-adhesin family, Afa/Dr adhesin family, Curli
Toxins
- α-haemolysin, cytotoxic necrotising factor 1
Autotransporter adhesins
- Antigen 43, UpaG
Autotransporter serine proteases
- Sat, Vat
Iron acquisition systems
- Enterobactin, Aerobactin, Yersiniabactin, Salmochelin, Iha, Haem receptors Hma, ChuA
Extracellular polysaccharides
- cellulose, poly-β-1,6-N-acetyl-D-glucosamine
Flagella
Capsule
O antigen

The luminal surface of the inner bladder wall is covered by 3-4 layers of a stratified urothelium. A thin basement membrane and lamina propria divide the urothelium from the smooth muscular and serous layers of the outer bladder wall. The urothelium contains small-size undifferentiated basal and intermediate epithelial cells underlying a single layer of large-size highly differentiated multinucleate luminal facet cells known as umbrella cells. These umbrella cells deposit on their luminal surfaces uroplakins as a quasi-crystalline array of hexagonal complexes holding four integral membrane proteins.[18] Uroplakins UPIa, UPIb, UPII, and UPIII cover almost entirely the luminal surface of a bladder. An asymmetric unit membrane (AUM) as thick luminal uroplakin-embedded membrane is a permeable barrier that strengthens and stabilises facet cells, preventing a bladder wall from rupturing after accumulating a considerable volume of the urine. Type 1 pili of the UPEC can specifically bind to uroplakins UPIa and UPIb as a first step of bacterial invasion.[19] This binding can be inhibited by enzymatic deglycosylation of UPIa nad UPIb or by D-mannose as the soluble FimH receptor analogue.[20,21] Therefore, the FimH-containing tips of Type 1 pili mediate bacterial attachment to the uroplakin-embedded AUM of the facet cells lining the bladder lumen. Bacteria attach to the grooves and niches formed by the AUM of facet cells singly and in large biofilm-like colonies.[15]

Bacterial Invasion

The facet cells lining the luminal surface of the bladder internalise bacteria that are observed free within the cytoplasm and within membrane-bound vacuoles.[22] The AUM of the luminal facet cells may zipper around and envelop adhered bacteria via interactions with Type 1 pili.[15] FimH can function as an invasin and internalin A in such a manner that FimH mediated bacterial invasion of bladder urothelial cells requires the activation of signal transduction cascades including protein tyrosine kinases, phosphoinositide-3 kinase, and actin cytoskeletal rearrangements.[23] Moreover, FimH mediated invasion correlates with the formation of complexes between adhesin kinase and phosphoinositide-3 kinase and between the cytoskeletal components α-actinin and vinculin. These occurrences contribute to the modulation and stabilisation of actin cytoskeletal alterations that can lead to envelopment and internalisation of UPEC subsequent to FimH mediated bacterial adherence.

A micturition can work to wash out nonattached or weakly attached bacteria from the bladder urothelium.[12] The low pH and osmolarity of the urine can be inhibitory factors to bacterial growth. The salts, organic acids, and urea from the urine can reduce bacterial survival in the bladder. A lactoferrin present in urine can scavenge essential iron away from incoming bacteria. Additionally, Tamm-Horsfall protein, secretory immunoglobulin A, uromucoid, and low molecular weight sugars can act as anti-attachment factors competitively inhibiting bacterial adherence to the bladder urothelium. A continued presence of bacteria within the bladder can trigger the activation of additional local defence mechanisms.

Neutrophil Recruitment and Cytokines

Exfoliated bladder cells associated with bacteria are often found in the urine of patients having UTIs.[22] Such clearance of infected and damaged bladder cells can function as a defence mechanism. The FimH mediated bacterial adhesion and afterwards invasion is crucial in the induction of bladder urothelial exfoliation during an UTI. Bladder cell exfoliation as a response to UTI with Type 1-piliated *E. coli* occurs via an apoptosis-like mechanism including DNA fragmentation and an activation of proteolytic enzymes known as caspases.[15] These cysteine proteases are critical components in the initiation and execution of apoptotic pathways.[24] Rather than directly triggering the exfoliative process, FimH mediated bacterial adhesion and invasion can serve to deliver other bacterial virulence factors such as lipopolysaccharide (LPS). Within 6 hours of Type 1-piliated UPEC attachment and invasion with obvious bladder cell exfoliation, neutrophils may be seen entering the bladder urothelium and lumen. Neutrophils and macrophages provide the first line of defence of the innate immune system by phagocytosing, killing, and digesting bacteria. Killing is accomplished by digestive enzymes and by oxygen free radicals and other reactive oxygen species, generated by the NADPH oxidase, and oxidised halides produced by myeloperoxidase. The oxidase pumps electrons into the phagocytic vacuole, which produces conditions conductive to microbial killing and digestion by enzymes released into the vacuole from the cytoplasmic granules. This process is greatly enhanced by the complement proteins that not only are cytotoxic but are also attractants for phagocytic cells and facilitate inflammation and cell adhesion. The combination of innate and adaptive immunity is required for complete eradication of the offending organisms.

Neutrophils or polymorphonucleocytes (PMNs) are phagocytic inflammatory cells that may mediate bacterial killing through the creation of reactive oxygen intermediates and release of preformed antibacterial peptides. Neutrophil recruitment is critical for bacterial clearance from the urinary tract, therefore the pyuria (presence of neutrophils in the urine) is a hallmark of UTI.[25] Interactions between the neutrophil receptor CD11b/CD18 (Mac-1) and the adhesion molecule intercellular adhesion molecule-1 (ICAM-1) on the bladder urothelium have been shown to be crucial for neutrophil influx into the urothelium. Thus, a bacterial infection induces the expression of ICAM-1 by the bladder urothelium.[26] Elucidation of the molecular mechanisms included in neutrophil recruitment into the urinary tract has highlighted the importance of cytokines and chemokines. These soluble molecules are produced in response to a variety of different agents (such as LPS) and may regulate the inflammatory process. In patients with UTIs the cytokine interleukin (IL)-6 and chemokine IL-8 are present in the urine, thereby suggesting that urothelial cells seem to be a major source of IL-6 and IL-8 following UPEC infection.[27,28] IL-6 is a pleiotropic cytokine with different immunoregulatory functions such as amplification of signals included in a neutrophil recruitment.[29,30] Urine IL-6 values from patients having UTIs correlate with disease severity.[31] IL-8 is a member of the CXC chemokine family and a potent neutrophil chemotactic molecule, therefore the induction of IL-8 following UPEC infection correlates with the presence of neutrophils in the urine.[32] Type 1 and P-piliated UPEC strains induce considerably more cytokines than their nonpiliated isogenic counterparts.[33] P pili may activate urothelial cytokine production via a ceramide and serine/threonine kinase-dependent signalling pathway.[34] Type 1 pili indirectly activate urothelial IL-6 production by mediating bacterial internalisation.

BACTERIAL VIRULENCE VERSUS HOST SUSCEPTIBILITY

Bacterial virulence factors influence the site and severity of UTIs. A general background of UTI pathogenesis is based on the mechanisms of UTI susceptibility, with a particular focus on genetic variation affecting innate immunity. The innate immune response (IIR) of the host is critically important in the antibacterial defence mechanisms of the urinary tract and bacterial clearance normally proceeds without sequelae. The symptoms of acute pyelonephritis are caused by the IIR, therefore an inflammation in the urinary tract decreases renal tubular function and may lead to renal scarring, particularly in childhood. On the other hand, in children with asymptomatic bacteriuria (ABU) uropathogenic bacteria persist without causing symptoms or any pathology. ABU strains are phylogenetically related to strains that cause symptomatic UTI. Most ABU strains adhere poorly to epithelial cells, but identified is a subgroup of strongly adherent strains that are unable to stimulate an epithelial cell IL-6 cytokine response.[35] Invading bacteria trigger a response determined by their virulence factors, mediating

adherence to the urothelial cells by means of signalling through Toll-like receptors (TLRs) and activating the defence mechanisms. In ABU strains such virulence factors are in the majority of cases not expressed. Thereby genetic alterations that reduce TLR4 function are associated with ABU, while polymorphisms reducing interferon regulatory factor 3 (IRF3) or CXC chemokine receptor 1 (CXCR1) expression are associated with acute pyelonephritis and consecutive renal scarring. The IRF3-dependent signalling pathway is critical for distinguishing uropathogens from normal flora at the urothelial barrier. TLR4 signalling was initiated after ceramide release from glycosphingolipid receptors through TRAM, CREB, Fos, and Jun phosphorylation and p38 mitogen-activated protein kinase-dependent mechanisms following with nuclear translocation of IRF3 and activation of IRF3/interferon beta-dependent antibacterial effector mechanisms. This TLR4/IRF3 pathway of uropathogen discrimination is activated by ceramide and by P-fimbriated UPEC that use ceramide-anchored glycosphingolipid receptors. The relevance of this pathway was supported by polymorphic IRF3 promoter sequences differing between children with severe acute pyelonephritis and children who are asymptomatic bacterial carriers.[36-38]

RECURRENT UTIs

The UPEC survival in the urinary tract depends on the infected bladder epithelial cells' exfoliation and the neutrophils' influx. The urothelial cells production of antibacterial factors such as nitric oxide and defensins, together with activation of immune cells like mast cells and macrophages, may help to control UTIs. In addition to both innate and adaptive defence mechanisms is the possible dissemination of UPEC within the urinary tract and persistance within bladder urithelial cells for days or even weeks. Antibiotic treatment can effectively reduce an amount of bacteria in the urine, but still UPEC strains can persist within bladder tissue.[39] UPEC is capable of fluxing into and out of the bladder urothelial cells. It means that invading uropathogens may multiply and afterwards escape out of the urothelium before the exfoliation process is completed. UPEC can persist for a long period of time in a quiescent state, serving as a source for recurrent UTIs, and can still be undetectable in the urine.

ANTIBIOTIC RESISTANCE

UTIs are responsible for a considerable portion of antibiotic use, thus representing a significant social and economic burden. Widespread use and extensive misuse of antibiotics directly correlates with the emergence of antibiotic resistance. The World Health Organization has recently issued a factsheet emphasising the worldwide dramatic increase in antibiotic resistance. In light of a very serious public health problem, the World Alliance against Antibiotic Resistance has proposed a 10-point action plan to combat the rapid rise of worldwide antibiotic resistance. UTI may present clinically as benign, uncomplicated cystitis or severe, life-threatening urosepsis as well as urethritis or multidrug-resistant tuberculosis. Due to the heterogeneity of UTIs, the European Association of Urology/European Section of Infections in Urology introduced the ORENUC classification system based upon the clinical presentation, categorisation of risk factors, and the antibiotic susceptibility of the causative uropathogens. In the scenario of urosepsis, early diagnosis and a vigorous therapy are mandatory. Where appropriate, a successful decompression of the obstructed urinary tract is crucial for survival.[40,41]

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KIDNEY STONES AND CEFTRIAXONE

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Disclosure: No potential conflict of interest.
Received: 20.10.14 **Accepted:** 01.12.14
Citation: EMJ Urol. 2015;3[1]:68-74.

ABSTRACT

Metabolic causes such as hypercalciuria, urinary tract infection, and obstruction are the most common aetiologies of urolithiasis, and drugs, although important in this regard, are rarely the cause of urolithiasis. Administration of one of these drugs, ceftriaxone (CTX), has been associated with biliary pseudolithiasis in adult and paediatric patients, and rarely may cause urolithiasis. Several factors, including drug concentration and incubation time, are very important for determining the degree of CTX/calcium (Ca) crystallisation in the urine. According to this data, CTX crystallisation was a dose and time-dependent reaction. It is particularly important to monitor patients on high-dose long-term CTX treatment with the urinary Ca to creatinine ratios, ultrasound sonography, and renal function testing, as these individuals may be at greater risk of large stones and renal damage. This type of screening may help prevent permanent complications in the future. This underlying review will help to educate readers on the pathophysiology and interaction between CTX and urolithiasis.

Keywords: Ceftriaxone, urolithiasis.

INTRODUCTION

The prevalence of urolithiasis requiring medical or surgical treatment is 5-10% and increasing worldwide.[1] Calcium (Ca) oxalate is the most prevalent type of kidney stone disease in the United States and has been shown to occur in 70-80% of the kidney stone population.[2] The prevalence of recurrent Ca oxalate stones has progressively increased in untreated subjects, approaching a 50% recurrence rate over 10 years.[3] The lifetime risk for kidney stone disease currently exceeds 6-12% in the general population.[4] In the final quarter of the twentieth century, the prevalence of kidney stone disease increased in both males and females, and all ethnicities.[4]

Metabolic causes such as hypercalciuria, urinary tract infection (UTI), and obstruction are the most common aetiologies of urolithiasis, and drugs, although important in this regard, are rarely the cause of urolithiasis. Drugs may be responsible for 1–2% of all renal calculi.[5] This drug adverse event most often affects patients who have received high-dose and/or long-term treatment of some drugs with lithogenic potential.[5] According to mechanisms of calculi formation, lithogenic drugs can be classified into two groups.[5] The first group consists of drugs that induce metabolic abnormalities (e.g. hypercalciuria,[6,7] hypocitraturia,[8,9] hyperuricosuria,[10] and alteration of urine acidity[8,9]) which subsequently provoke formation of metabolic calculi; e.g. Ca-containing stones and uric acid (UA) nephrolithiasis.[5] The second group consists of drugs that can be crystallised directly in the urine due to their high excretory levels and poor solubility.[11-14] The most important drugs are silica-containing anti-acids, furosemide, acetazolamide, ciprofloxacin, sulfonamides, aminophylline, corticosteroids, triamterene, phenytoin, probenecid, lithium, indinavir, and ceftriaxone (CTX).[15] Administration of one of these drugs, CTX, has been associated with biliary pseudolithiasis in adult and paediatric patients, and rarely may cause urolithiasis.[16,17] Although only limited information exists in the literature regarding the incidence of urolithiasis following CTX therapy, the present review is aimed to demonstrate interaction between CTX and urolithiasis.

UROLITHIASIS

Up to 75% of stones are Ca oxalate, the others are struvite (magnesium ammonium [NH] phosphate, 10–20%), UA (5%), 5% contain >50% brushite (Ca monohydrogen phosphate) or hydroxyapatite, and <1% are composed of cystine.[18] Although much progress has been made in understanding the pathophysiological mechanisms of stone disease, allowing for more effective diagnosis and treatment, stones still cause substantial morbidity from pain, urinary-tract obstruction, and infection.[19]

A. Ca Stones

Hypercalciuria, the most common metabolic abnormality found in patients with recurrent Ca stones, is most often familial and idiopathic[20] and is strongly influenced by diet. Gut Ca absorption is increased in persons with idiopathic hypercalciuria, but serum Ca values remain unchanged, since absorbed Ca is promptly excreted.[21] On a low-Ca diet, such persons often excrete more Ca than they eat,[22] and urinary Ca excretion also rises markedly after the intake of Ca-free nutrients such as simple oral glucose; in such cases, the only source possible is bone. Although hypercalciuria is sometimes divided into subtypes (absorptive, resorptive, and renal leak), this classification is not helpful in guiding treatment. However, measurement of serum Ca is indicated to identify patients with primary hyperparathyroidism. Primary hyperparathyroidism, which results from an adenoma in 85% of cases, is associated with mild-to-moderate hypercalcaemia. Hypercalciuria is a result of excess parathyroid hormone, which causes overproduction of 1.25-dihydroxyvitamin D in the kidney; both factors promote bone resorption, increasing the filtered load of Ca and hence calciuria. Other disorders that induce hypercalcaemia can also result in hypercalciuria: malignancies, granulomatous diseases, sarcoidosis, thyrotoxicosis, and immobilisation. Idiopathic hypercalciuria is a familial disorder affecting both sexes equally, in which urinary Ca concentration is raised despite normal concentrations of blood Ca.[23,24]

The level of oxalate excretion is modestly higher among patients with recurrent Ca stones than among those without the condition. The human serum oxalate concentration ranges between 1 and 5 mm, however, due to water reabsorption in the kidney, its concentration is 100-times higher in the urine. At a physiologic pH, oxalate will form an insoluble salt with Ca. As the solubility of Ca oxalate in an aqueous solution is limited to approximately 5 mg/l at a pH of 7.0, assuming that normal urine volume ranges between 1 and 2 l/day and normal urinary oxalate excretion is <40 mg/day, normal urine is often supersaturated with Ca oxalate. However, under normal conditions, the blood is undersaturated in respect with Ca oxalate. As seen in patients with primary hyperoxaluria and renal insufficiency, when the serum oxalate concentration increases to above 30 µM, the blood becomes supersaturated with Ca oxalate. In the plasma, oxalate is not significantly bound to protein and is freely filtered by the kidneys. A recent study reported that urinary Ca is as important as urinary oxalate in raising Ca oxalate supersaturation.[24,25] Finally, citrate chelates Ca in the urine, decreasing supersaturation and reducing the growth of crystals; hypocitraturia is a risk factor for stone formation.[26] Hypocitraturia could result from causes of intracellular acidosis such as renal failure, potassium deficiency, distal renal tubular acidosis, chronic diarrhoeal states, and drugs such as acetazolamide. Many patients with stones have unexplained low urinary citrate; dysfunction of the renal sodium-citrate cotransporter has been proposed as a possible mechanism.[27]

B. UA Stones

Three major factors for the development of UA stones are low urine volume, acidic urine pH, and hyperuricosuria. The aetiologic mechanisms for UA stone formation are diverse and include congenital, acquired, and idiopathic causes. The most prevalent cause of UA nephrolithiasis is idiopathic. Diets high in purines, especially those containing organ meats and fish, result in hyperuricosuria, and, in combination with low urine volume and low urinary pH (as a result of impaired renal ammonia production), can exacerbate UA stone formation. Furthermore, hyperuricaemic disorders including gout (about 20% of patients with gout are hyperuricosuric), myeloproliferative disorders, tumour lysis syndrome, and inborn errors of metabolism (such as Lesch-Nyhan syndrome and glucose-6-phosphatase deficiency) result in an increased filtered load of UA and thus, hyperuricosuria.[28]

The metabolic defect suspected for low urinary pH in UA stone formation was described almost four decades ago. Defective ammoniagenesis or excretion was attributed as a possible pathogenetic

mechanism. Initial studies showing abnormalities in glutamine metabolism, which resulted in the impaired conversion of glutamine to α-ketoglutarate and consequently resulted in reduced renal NH excretion, were not supported by further investigation.[29] Mechanistic studies, however, have shown that the two major factors responsible for abnormally low urine pH are a combination of defective NH excretion and increased net acid excretion.

C. Struvite (Magnesium NH Phosphate) Stones

Struvite stones are associated with chronic UTI with Gram-negative rods capable of splitting urea into NH, which combines with phosphate and magnesium. Usual organisms include *Proteus*, *Pseudomonas*, and *Klebsiella* species. *Escherichia coli* is not capable of splitting urea and, therefore, is not associated with struvite stones. Urine pH is typically >7. UTI does not resolve until the stone is removed entirely.[24]

DRUG-INDUCED UROLITHIASIS

Drug-induced renal calculi (kidney stones) represent 1–2% of the total number of renal calculi analysed in specialised laboratories. Historically, sulfonamides were the first drugs implicated in renal calculi formation and acute renal failure (ARF) episodes early after their use in humans. A number of reports were published on sulfonamides and renal disorders.[30-34] Two main mechanisms are involved in the formation of drug-induced renal calculi: (i) the drug and/or its metabolites are total or partial components of the calculi; and (ii) the drug induces the formation of calculi through its metabolic action by interfering with Ca oxalate or purine metabolism.[35-37] In both cases, a lithogenic substance may deposit on renal calculi already present. Therefore, patients with a history or presence of renal calculi seem to be more exposed to the risk of drug-induced renal calculi, and in our previous study we reported that urolithiasis risk is higher in patients who have urolithiasis.[17] Obviously, only a limited proportion of patients treated with widely used drugs such as triamterene or sulfonamides develop crystalluria, renal colic, or ARF due to tubular obstruction by drug crystals. This suggests that the formation of drug-induced calculi involves an interplay of risk factors specific for the implicated drug, some of which depend on the drug itself and others that relate to the patient.[36-38]

The true prevalence of drug-induced renal calculi is likely to be underestimated in most studies. However, in some cases, changes in urine biochemistry induced by the drug may provoke crystallisation of metabolic compounds with an unusual morphology, which may draw attention to the possibility that there are peculiar conditions for the renal calculi formation.[39] The first large-scale epidemiological study of drug-induced nephrolithiasis was presented in 1980 by Ettinger et al.[40] The authors reported that 0.4% of 50,000 renal calculi analysed over a 6-month period in the United States contained triamterene, but they did not provide data as to the possible other types of drug-induced calculi. In 1986, Asper[41] observed an incidence of 0.1% for drug-containing urinary calculi among a series of 14,165 calculi analysed between 1982 and 1985 in Switzerland.

CTX

CTX is a sterile, semisynthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. The chemical formula of CTX sodium is $C_{18}H_{16}N_8Na_2O_7S_3 \cdot 3.5H_2O$. It has a calculated molecular weight of 661.59. CTX is a widely-used, third-generation, semisynthetic cephalosporin commonly administrated for the treatment of different bacterial infections. Due to its broad spectrum against bacteria, long half-life (7-8 hours), and single daily dosing, physicians prefer to use it more frequently.[42] CTX is used to treat a wide variety of serious infections caused by organisms that are resistant to most other antibiotics. It is often used (in combination, but not direct, with macrolide and/or aminoglycoside antibiotics) for the treatment of community-acquired or mild-to-moderate healthcare-associated pneumonia. It is also a choice drug for the treatment of bacterial meningitis caused by pneumococci, meningococci, *Haemophilus influenzae*, and susceptible enteric Gram-negative rods, but not Listeria monocytogenes.[43] Other uses included the treatment of acute bacterial otitis media, skin and skin structure infections, bone and joint infections, gonorrhoea, intra-abdominal and UTIs, pelvic inflammatory disease (PID), and bacterial septicaemia. It is also approved to be used in surgical (perioperative) prophylaxis.

Like other third-generation cephalosporins, CTX is active against citrobacter, *Serratia marcenscens*, and ß-lactamase-producing strains of haemophilus and neisseria. However, unlike ceftazidime and

cefoperazone, CTX does not have useful activity against *Pseudomonas aeruginosa*. It is not generally active against enterobacter species, and its use should be avoided in the treatment of enterobacter infections even if the isolate appears susceptible because of the emergence of resistance. Like all other cephalosporins, it has no activity against enterococci, atypicals (mycoplasma and chlamydia), or Listeria.[44] CTX can be administered intravenously and intramuscularly. It is not available orally. For most infections, CTX can be injected once every 24 hours at a dosage of 15–50 mg/kg/d. A single daily 1 g dose is usually sufficient. A dose of 2 g every 12 hours is recommended for the treatment of meningitis. A single intramuscular dose of 250 mg is recommended for the treatment of gonorrheal urethritis and cervicitis in conjunction with a single 1 g oral dose of azithromycin or doxycycline 100 mg orally twice daily for 7 days to cover chlamydia co-infection.[45] CTX is mostly eliminated through the kidney and the remainder is eliminated via the biliary system. Its concentration in bile is 20-150-times more than in plasma. It binds with Ca ions producing reversible precipitations that form biliary sludge and/or lithiasis, called psudolithiasis both in children and adults.[44,46-51]

CTX Induced Urolithiasis

CTX is filtered by the kidneys unchanged and forms insoluble salts with Ca in a 1:1 molar ratio. Risk factors for urolithiasis are not well-established but certainly poor urine output, high doses of CTX, and hypercalciuria may favour CTX-induced nephrolithiasis. Stojanovic and Djuric Vijatov[52] reported a paediatric patient who developed nephrolithiasis in a kidney with congenital ureteropelvic junction obstruction.

CTX-induced urinary precipitates may be asymptomatic and detected on routine ultrasound (US) scanning but in some patients they may manifest haematuria or renal colic.[47,53-59] Bilateral obstruction with calculi may lead to ARF in the patient as reported by Prince and Senac.[53] Also, Zhao-Lun Li et al.[60] presented the development of bilateral distal ureteral CTX-associated lithiasis in seven adults. The risk of ureterolithiasis impaction should be considered when treating patients with CTX, even in adults. When using high-dose and long-term CTX, avoiding simultaneous administration of Ca-containing liquid, more aggressive hydration and close clinical observation for urine crystalluria were recommended, especially in children and patients under fasting or post-operative conditions. Often there is coexistence with biliary pseudolithiasis, and confusion may arise in a child with pain in the right upper abdominal quadrant during CTX treatment.[54] Thus, besides examination of the gall bladder, careful US scanning of the kidney and urine analysis should be performed.

The true prevalence of CTX-induced nephrolithiasis is not known. The first case of CTX-induced nephrolithiasis was reported by Schaad et al. in 1988.[61] In their series of 37 children treated with CTX, 16 developed biliary pseudolithiasis and 1 child had concurrent biliary and urinary calculi, manifesting renal colic and obstruction of the kidney. In the recent prospective study by Biner et al.[47] 156 children with various infections treated with CTX at the doses of 50 mg/kg, 75 mg/kg, and 100 mg/kg have been followed by US scan. 27 children (17%) developed biliary pseudolithiasis or sludge, while only 1 child (0.6%) had urolithiasis. Mohkam et al.[58] prospectively followed 284 children with pyelonephritis (185 girls and 99 boys). Nephrolithiasis was identified in four children (1.4%). None of the children had a metabolic risk factor.

The results in a present study clearly demonstrated that CTX at therapeutic urinary excretion levels could directly interact with free Ca at physiologic urinary concentration to generate CTX/Ca crystals.[62] Several factors, including drug concentration and incubation time, are very important for determining the degree of CTX/Ca crystallisation. According to these data, CTX crystallisation was a dose and time-dependent reaction. Therefore, high-dose CTX administration (which leads to increasing urinary CTX levels) and urinary stasis by any causes (which leads to retention of CTX crystals in the urinary tract, allowing crystal growth and aggregation) may aggravate CTX calculi formation. In summary, this present study has shown that CTX could be crystallised in the urine under physiologic conditions. The size of CTX crystal aggregates was much larger than the diameter of renal tubular lumens, implicating that tubular occlusion may be the major mechanism for subsequent development of CTX calculi. In addition, crystal adhesion onto the renal tubular cell surface may also play an important role in the initiation of CTX-induced nephrolithiasis. The findings of this study showed that CTX crystals could tightly adhere to the renal tubular cell surface, suggesting the high adhesive force between CTX crystals and renal tubular cell surfaces. Although the mechanism for such crystal–cell adhesion is still

unknown, one possibility is that CTX/Ca crystals may adhere onto the cell surface via ionic interaction and/or hydrogen bond, similar to other Ca-containing crystals (e.g. Ca oxalate, Ca phosphate). Another possibility is that Madin-Darby canine kidney cell surface may present some (unknown) receptors for CTX crystals. These hypotheses should be further elucidated.

By studying the effect of human physiological urinary pH on CTX-induced crystallisation, Cong et al.[63] showed more acidified urine could inhibit more CTX-induced crystallisation when urinary pH is <5.5. This study also suggests that alkaline urine predisposes CTX-induced crystallisation. Among very limited reports of CTX-induced nephrolithiasis with compositional analysis, Gargollo et al.[64] reported that CTX-induced stones were composed of CTX and Ca phosphate. As we know, Ca phosphate stones are usually formed in alkaline urine.[65] In this study, Cong et al.[63] also demonstrated that citrate is a potent inhibitor of CTX-induced crystallisation as well as its role against Ca oxalate and phosphate stones. Therefore, hypocitraturia should predispose CTX-induced nephrolithiasis. It is well known that UTI is often associated with the decreased urinary citrate concentration because a number of bacteria use citrate for their metabolism, resulting in hypocitraturia.[66] Therefore, patients with UTIs treated by CTX probably favour CTX-induced nephrolithiasis.

In our study published recently, we assessed the adult patients and found that after the CTX therapy 24-hour urine Ca excretion was higher than before the therapy.[17] It is possible that the reaction and subsequent precipitation of CTRX with Ca within renal tubules lead to the disturbance of tubular reabsorption of Ca, resulting in excessive urinary excretion. It has been reported that >95% of the Ca filtered from the blood into urine is reabsorbed in the renal tubules under physiological conditions, with approximately 70% of the Ca being absorbed in the proximal tubules, about 20-30% being reabsorbed in the loop of Henle, 5-10% being reabsorbed in the distal tubules, and the remaining (5%) Ca present in the renal collecting duct.[67] In contrast to the distal tubules, where Ca is reabsorbed actively by parathyroid hormone, Ca is passively reabsorbed by way of paracellular diffusion mediated by convection (solvent drag) across the tight junction in the proximal tubules. In conjunction with the findings in our study that there were no significant changes in serum Ca concentration, which mainly regulates parathyroid hormone, it seems reasonable to speculate that CTRX in urine prevents passive paracellular reabsorption of Ca in the proximal tubule, leading to excessive excretion of Ca and resulting in precipitation via the formation of an insoluble salt.

CONCLUSION

CTX can significantly increase the urinary excretion of Ca in adults, especially in those who have urolithiasis. Physicians should be aware of this side-effect and pay attention to the patient's hydration status and encourage mobilisation during cephalosporin treatment. Ampicillin may be preferred for prophylactic use of antibiotics because it does not escalate urinary excretion of Ca in stone patients. It is particularly important to monitor patients on high-dose long-term CTX treatment with the urinary Ca to creatinine ratios, US sonography, and renal function testing, as these individuals may be at greater risk for large stones and renal damage. This type of screening may help prevent permanent complications in the future. CTX urolithiasis was self-limited without long-term complications in all patients, and the use of this effective drug can be safely continued. We recommend close monitoring of CTX-treated patients with regards to possible kidney stone formation.

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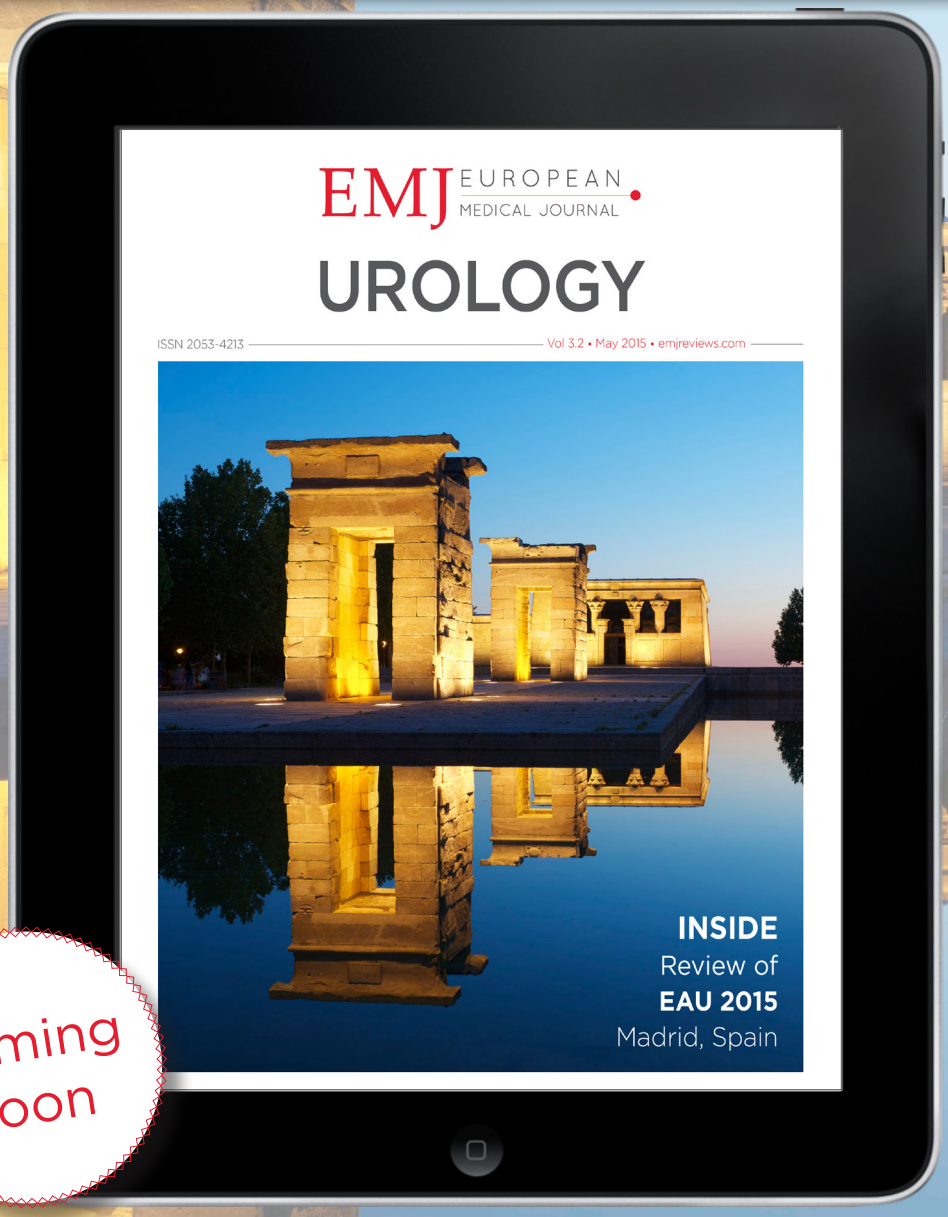

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HOW I TREAT: PROSTATE CANCER WITH MINIMALLY INVASIVE TECHNIQUES

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Currently, 17-35% of newly diagnosed cases of prostate cancer (PrC) are classified as high-risk. This group of patients has the highest rate of metastasis and cancer-related death, making management of high-risk prostate cancer (HRPC) a top priority for improving PrC outcomes. We will then focus this discussion on our management of HRPC.

Following the introduction of prostate-specific antigen screening into clinical practice in 1980, there was a stage-migration of newly-diagnosed PrC cases towards more localised disease. However the Surveillance, Epidemiology, and End Results database shows that the incidence of pT3a disease has remained relatively constant throughout the past 15 years. Between 2000 and 2008, a period when urologists were more prone to operate on low-risk cases, 52% of our laparoscopic radical prostatectomy (LRP) patients were low-risk and only 18% were high-risk. An analysis of our cases from 2013-2014 shows a significantly different profile: 21% low, 50% intermediate, and 29% high-risk patients. We also consider surgery an option for locally advanced PrC patients as part of a multimodality treatment. Furthermore, as shown in the National Prostate Cancer Audit regarding patients from 2006-2008, almost 40% of locally advanced PrC patients in our Cancer Network received local treatment, either in the form of radical prostatectomy (RP) or external beam radiotherapy +/- brachytherapy.

Over the past years, multiparametric magnetic resonance imaging (mMRI) of the prostate has gradually evolved, with special interest on diffusion-weighted imaging (DWI) given that PrC areas seem to have lower apparent diffusion coefficient than benign areas. As recognised in the European Association of Urology (EAU) guidelines, mMRI has shown to have excellent sensitivity for detecting aggressive Gleason >7 cancers and is especially useful in detecting anterior tumours, commonly missed on transrectal ultrasound-guided (TRUS) biopsy. The same guidelines recommend that mMRI be done if it can trigger a (targeted) repeat prostate biopsy. In our Cancer Network, the majority of patients have an mMRI as a pre-biopsy triage, the result of which will determine if a biopsy is indicated. Any areas with prostate imaging-reporting and data system score 4 or 5 trigger a targeted biopsy with a template biopsy of the remaining prostate. This will be done transperineally if there is a need to sample the anterior part of the prostate. Patients with palpable disease may go directly to a TRUS biopsy and have a MRI or computed tomography for staging. All high-risk patients will also have a bone scan.

Traditional staging with digital rectal examination has shown to be inaccurate. While not consensual, it seems that mMRI, and especially tesla 2-weighted imaging, may be useful in staging selected patients with intermediate-to-high-risk PrC. Despite low sensitivity to detect focal (microscopic) extraprostatic extension, and MRI sensitivity, specificity and accuracy for detection of more extensive pT3a disease rises to 62%, 95%, and 88%, respectively, and may be even higher with DWI.[1] EAU recommendation is to use multiparametric MRI only in intermediate or high-risk PrC and if it can change patient management. Most of our patients have mMRI before prostate biopsy, so even low-risk patients have an mMRI at the time of decision on management. This is important, as mMRI with DWI seems to have a role in reducing positive surgical margins (PSM) caused by inadequate nerve-sparing surgery (NSS) by predicting extraprostatic extension. Initially, in our group, neurovascular bundle preservation was being carried out only in potent men with low/intermediate-risk disease and no palpable tumour on the side of the nerve preservation. This has gradually changed to include men with erectile dysfunction with the aim of improving continence, palpable disease (leading to incremental preservation), and high-risk patients if the location of the cancer permits it. Currently our only absolute contraindication for NSS is

suspected T3 disease on the side of the nerve spare. Our LRP series has shown that overall PSM rate correlates with pathological T stage but is not influenced by NSS.

Since starting to perform LRP in 2000, the technique done by this group has evolved in many ways. Nowadays, only low-risk patients have extraperitoneal LRP. D'Amico intermediate and high-risk patients have extended pelvic lymph node dissection (PLND) done transperitoneally to minimise the risk of lymphocele and enable easier access to the common iliac artery bifurcation for higher lymph node (LN) yield. Over the years, other adjustments to the surgical technique were made that reduced complications: nerve-sparing surgery with bipolar diathermy gave place to titanium clips to minimise thermal injury; closure of large port sites with Endo Close™ prevented hernias; and padding of arms prevented ulnar nerve neuropraxia. On the other hand, even without administration of prophylactic low-molecular-weight heparin, only four patients (0.4%) had thromboembolic events, which is in line with most European and American referral centres. This leads us to believe that early mobilisation and use of compressive stockings is sufficient for most patients post-operatively.

Contrasting with the discussion in intermediate-risk PrC, there is a consensus that PLND is indicated in HRPC, as the risk of nodal disease is significantly higher and PLND provides important information for prognosis that cannot be matched by any other staging tool. It is now clear that PLND should be done following an extended template, as 19-35% of positive LNs are exclusively outside the area of standard PLND. Therefore, we perform extended PLND including the common iliac nodes up to the ureteric crossing and the nodes medial and lateral to the internal iliac artery. The next step in the development of our technique will be to include the presacral area for high-risk patients, which should reduce the incomplete clearance of nodes to 3%. In our series, the replacement of standard PLND by extended PLND in 2008 led to a 3-fold increase in LN yield and a 10-fold increase in the rate of detection of LN involvement. The cases done in 2013-2014 had a median LN yield of 17 (range 5-37) and a 27.3% rate of node-positivity, which is a result of the profile of the PrC patients operated at our centre.

It is important to know if there is nodal disease, but it has also been shown that considering the number of positive nodes enhances the predictive accuracy of nodal staging (60.1-65.0%). Briganti et al.[2] reported that patients with up to two positive nodes on extended PLND (ePLND) have significant and better long term cause-specific survival (CSS) than the ones with three or more (84% versus 62% at 15 years; p<0.001).[2] The same type of conclusion came from a study by the University of Bern group, where the progression free survival was significantly higher for patients with only one positive node (38.5%) when compared with the patients with two or more positive nodes (12.2%).[3] The same study found that the number of positive nodes significantly affected the time for biochemical recurrence, symptomatic progression, and cancer-related death. It is our belief that there will soon be enough evidence to change the tumour, LN, and metastases staging classification for prostate cancer in order to divide node-positive patients into N1 and N2 depending on the number of positive nodes, as they carry different prognosis.

Besides its prognostic importance, PLND seems to play a role in improving survival. Level 1-evidence of PLND's therapeutic benefit came from a randomised prospective study of 360 consecutive patients receiving extended versus standard PLND. After a median follow-up above 6 years, they concluded that an extended PLND increased biochemical PFS in intermediate (73.1% versus 85.7%; p=0.042) and high-risk patients (51.1% versus 71.4%; p=0.036).[4] Several studies corroborate that RP with ePLND may be an option for node-positive patients, especially in case of oligometastatic nodal disease. Studer's group published a study on a series of 122 consecutive node positive patients with no neoadjuvant or adjuvant androgen deprivation therapy (ADT). They reported a 10-year CSS of 78.6% for patients with two or fewer positive nodes and 33.4% for three or more nodes (p<0.001). Once again, the number of positive nodes (HR=1.38; p<0.001), ≥3 positive nodes (HR=5.64; p<0.001), high pathologic tumour stage (HR=4.05, p=0.021), and high pathologic Gleason grade (HR=2.42, p=0.02) were significant predictors of negative outcome.[5] Following these data, EAU guidelines consider ADT to be the treatment of choice for patients with more than two positive nodes on ePLND, irrespective of having RP or radiation therapy. They also recommend that ADT monotherapy should only be given to patients who are unfit for any type of local therapy. In accordance to this, we offer LRP with ePLND as an option for patients with limited nodal disease as a part of a multimodality approach.

In conclusion, times are changing for RP. Fewer low-risk patients are being operated on, but RP has been shown to improve outcomes in high-risk localised, locally advanced, and oligometastatic nodal PrC. New clinical trials may even extend these boundaries to oligometastatic bone disease. In any situation, it is important that the patient is aware of the specifics of surgery in HRPC and the possible need for multimodality treatment.

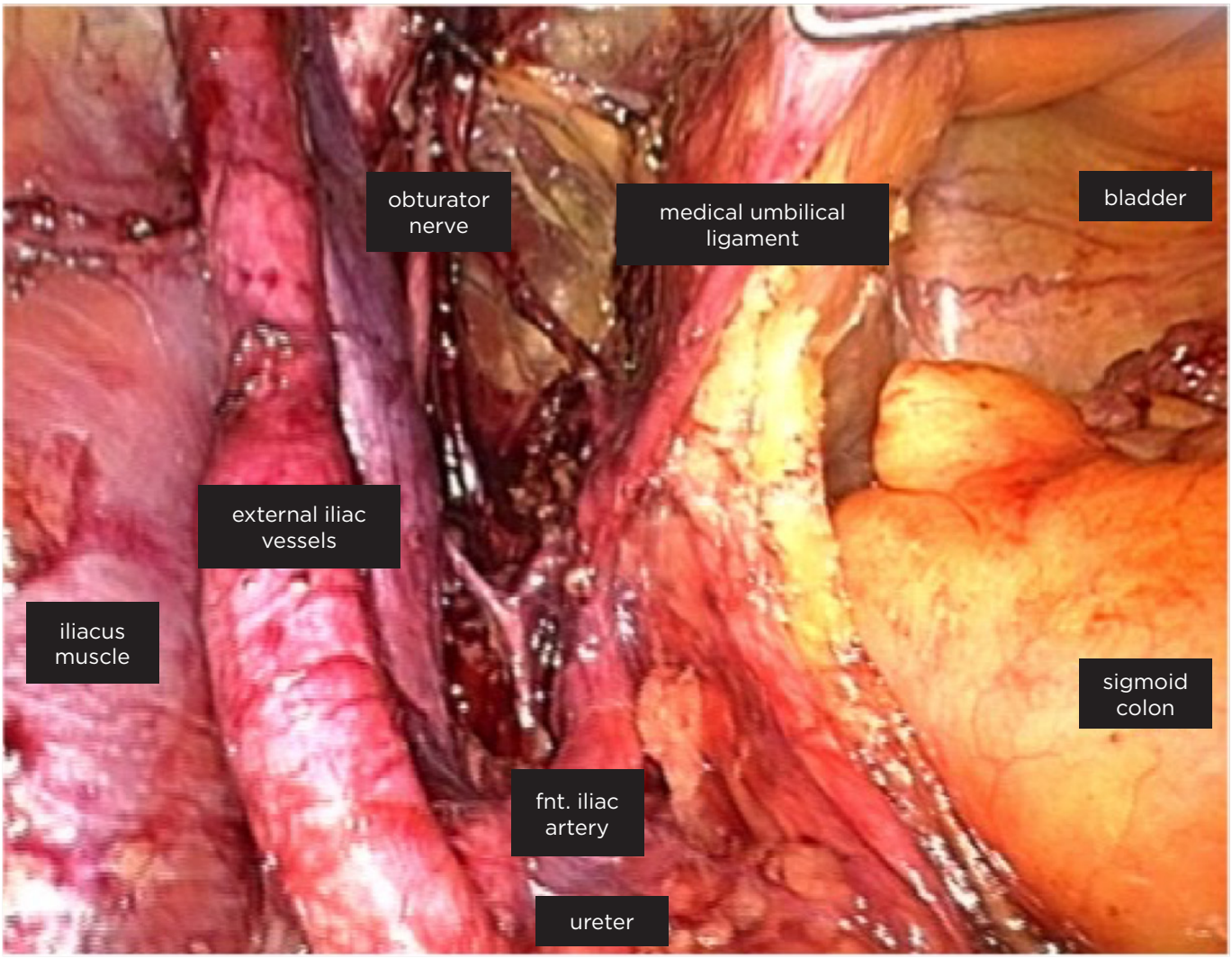

Figure 1: Extended pelvic lymph node dissection template.

Figure 2: Negative surgical margin in pT3a cancer.

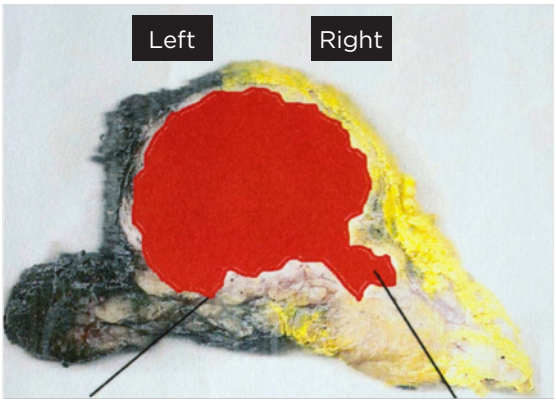

Figure 3: Negative surgical margin in pT3b cancer.

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