Hurdles in managing renal cancer

‘Sleepless Nights’ session offers insights on legal pitfalls

By Joel Vega

Insights into the legal pitfalls and challenges of offering balanced and optimal treatments to kidney cancer patients were explored and debated in Plenary Session 1, a newly introduced format where a legal veteran subjected three urologists to intense cross-examination regarding their surgical strategies.

In a well-attended and applaudsed session, expert medical litigation lawyer Bertie Leigh (GB) put Professors Alex Bex (NL), Karim Benzalha (FR) and Veselvod Matveev (RO) under intense questioning to elicit insights into the crucial decisions they made for kidney cancer patients.

“Each of these cases, in different ways, raises questions about the conventional ways of treating patients. As a lawyer I am particularly concerned about consent counseling and how patients are handled because these are very difficult positions for urologists to take,” said Leigh, as he stressed that doctors should be “recording their uncertainties in the way in which they communicate with patients.”

Mr. Tim O’Brien, as moderator, presented three cases with the first case involving a small renal mass (less than 3cm) in an elderly patient. Bex was first ‘in the dock’ as he presented his arguments for performing a renal tumour biopsy (RTB). Leigh, who specializes in medical negligence, pressed Bex on his rationale for RTB, to which Bex conceded that there are no reliable approaches for diagnosing an oncloscopy before surgery.

Leigh emphasized that despite the low statistics on risks and complications, patients view the matter in an altogether different way. The loss of a kidney or suffering the consequences of complications is traumatic for patients.

“Doctors should offer patients alternatives which are realistic to them, all of the options available to them, and must relay the information in a form that patients can understand,” added Leigh. “You must make records of the advice you give them. Doctors are diligent in recording the results of their investigations, but when it comes to recording their advice, they write nothing. If it’s not written down, it won’t stand up in court,” said Leigh.

Cutting-edge techniques at Live Surgery

ESUT, ERUS, EULIS pull out all the stops in Live Surgery session

By Joel Vega

Maintaining the EAU’s tradition of presenting Live Surgery sessions, yesterday’s Section offices presented the newest techniques in robotic and minimally invasive surgeries used in aggressive prostate, bladder and kidney diseases as well as stone treatment.

The EAU Section of Uro-Technology (ESUT) collaborated with the EAU Robotic Urology Section (ERUS) and the EAU Section of Uro-Technology (ESUT) to present the newest techniques in robotic and minimally invasive surgeries used in aggressive prostate, bladder and kidney diseases as well as stone treatment.

The ESUT session involved three surgeries broadcasted from Guy’s Hospital with Professors Alexander Haese (DE), Jens-Uwe Stolzenburg (DE) and Peter Wiklund (SE) as the first three surgeons. A five-member panel composed of Mr. Chris Anderson (GB), Dr. Alberto Breda (ES), Dr. Rafael Sanchez-Salas (FR), Prof. Peter Tenke (HL) and Dr. Patricia Zondervain (NL) gave additional commentary and asked the surgeons to explain the preparations and steps they took for the crucial surgical maneuvers.

Professors Alexander Haese (DE), Jens-Uwe Stolzenburg (DE) and Peter Wiklund (SE) were the first three surgeons broadcasted from Guy’s Hospital with Haese demonstrating his technique in robotic nerve sparing RP.

Stolzenburg took the audience through the crucial steps in performing a nerve-sparing approach that involved meticulous dissection.

Despite intermittent disruptions in satellite connections the panel provided insightful commentary and audience questions were also directed to the surgeons.

EAU-RF thanks Mulders

By Look Keizer

Saturday afternoon saw the EAU Research Foundation hold its Special Session, giving delegates an update on currently-running research projects, trials and registries. The session also featured a presentation by Dr. Alvaro Ayala (ES), the EAU’s newest career track fellow. Prof. Peter Mulders (NL) chaired the session, having been succeeded as chairman of the EAU-RF by Prof. Anders Bjartell (SE) at the General Assembly earlier that morning.

Looking back at his eight years as Chairman of the EAU-RF, Mulders reflected on the uniqueness of the Foundation. “The EAU is the only professional association with its own clinical trial office. In that respect, we’ve had a lot of opportunities for conducting trials in prostate, bladder and kidney cancer.” All ongoing EAU-RF projects were presented at the session. Mulders pointed to NIMBUS as one of the studies that generated a huge international database, which will allow the foundation to present data for many years to come.

“A real achievement of the Foundation is the establishment of the career track fellowship for non-urological researchers. This helps us attract such researchers to the EAU to work on urological projects.”

“I’ve always said that the Research Foundation depends on its activities. I will continue to advise the EAU-RF and should I initiate any new projects in the future that could be facilitated by the EAU-RF, that would of course be my first choice.”

For further coverage of projects of the EAU-RF, see pages 20 and 29.

EAU strengthens ties across borders

By Erika de Groot

The EAU’s engagement with the European Union (EU), the different EAU Offices’ new projects, and the announcement of newly elected officers topped the agenda yesterday at the annual General Assembly.

EAU Members

As of March 2017, there are a total of 15,409 EAU members, the majority of whom are active members (13,995), alongside 3,608 junior members, 2,444 active international members, and 351 junior international members.

New appointments

New roles were announced during the meeting. Prof. Jens Sønksen (DK) was elected as the new EAU Adjunct Secretary General – Clinical Practice with 97% of the vote. He said: “My plans include strengthening urological practice in Europe through expansion of the clinical update meetings; continued work with dissemination and evaluation of the EAU; the clinical guidelines and growth of our online profile; and through the EAU Junior Ambassadors.”

Other appointments included Prof. Anders Bjartell (SE), a member of the Guidelines Office Board who took on the role of EAU Research Foundation Chairman, succeeding Prof. Peter Mulders (NL). Assoc. Prof. Christian Gratetzki (DE), Associate Editor of European Urology and member of the EAU Guidelines panel on BPH/male LUTS, is the new Editor-in-Chief of European Urology Focus. Prof. Alberto Briganti (IT), member of the Scientific Congress Office and the EAU Guidelines Office Board, is the Editor-in-Chief of the new publication European Urology Oncology.

EU engagement

The EAU cited stronger links with Members of the European Parliament (MEPs) and other EU partners as the advisory tasks it has fulfilled. EAU Secretary General Prof. Chris Chapple (GB) said the EAU raises not only its own profile but also that of urology, as well as building relationships, by providing scientific advice to MEPs and the European Commission through initiatives such as the EAU white paper on prostate cancer and the strategic relationships with the EU Joint Action on Cancer Control (CANCON) and MEPs Against Cancer (MAC).
A new study, coming from the Dutch part of the European Randomised Study for the Screening of Prostate Cancer (ERSPC) has found that MRI-based screening can reduce overdiagnosis by 50% and reduce unnecessary biopsies by 70%, potentially changing the equation for prostate cancer (PCa) screening.

This work, the first to confirm that the use of MRI in a population-based screening setting may be viable, was presented at this congress. Dutch researchers have compared the outcomes from the TRUS-biopsy approach with an MRI-based screening approach in a group of newly pre-screened men. They took 6- to 8-TRUS-biopsy samples from 277 men, and 12- to 12-core-TRUS-biopsy samples from 158 men: the 158 men who received a 12-core TRUS-biopsy had first been given an MRI scan. If the MRI showed a suspicious area, then further MRI-targeted biopsy samples were taken.

“This could change the balance of the equation” said lead author Dr. Arno Alberts (Erasmus Medical Centre, Rotterdam). “It means that population-based prostate cancer screening with MRI instead of TRUS-biopsy has a significantly better risk/benefit ratio and could offer real benefits to men at risk of prostate cancer. Now we have shown that MRI screening has potential, we need confirmatory studies in a true screening setting to ask us to get a better handle on the statistics and costs.”

The researchers found that the 6-core TRUS-biopsy, 12-core TRUS biopsy and MRI-targeted biopsy method all had a similar detection rate for more dangerous (high-risk) cancers; however using the MRI-targeted biopsy method the majority of men (76%) did not need a biopsy at all as the MRI scan had shown no suspicious areas. In addition to potentially eliminating 70% of biopsies, the MRI-targeted biopsy only approach meant that the number of men who were overdiagnosed with non-aggressive cancer was reduced by half.

Alberts said MRI screening for prostate cancer will be more expensive than the currently used approach, but introducing mammography screening in a generation ago was also expensive. “We have to decide if it’s worthwhile. In this study we achieved a 70% reduction in biopsies and a 50% reduction in overdiagnosis of insignificant prostate cancer. If larger studies can reproduce these results it will mean a considerable saving further down the line,” explained Alberts.

MRI: A game changer in PCa screening?
Imaging and prostate cancer
Imaging technologies have still some way to go

By Tom Parkhill

At the 2015 conference we asked, “Is the train of prostate imaging gathering speed?” Well now we can say it is not only gathering speed, it is roaring ahead.”

With these words, Prof. Jochen Walz introduced the session addressing the hottest topics in urological imaging “How to get the most out of prostate cancer imaging” organized by the EAU Section of Urological Imaging (ESUI) and the European Society of Nuclear Medicine (ESNM).

But despite this progress, the session concluded with considerable caution about the distance yet to be travelled before imaging becomes routine.

The meeting heard that the growth in the field has been impressive, with 1400 published papers in the last year. Walz also introduced the new chair of the ESUI, Prof Georg Salmon (DE), who will take the group forward to the winter meeting in Barcelona.

Prof. Nicolas Mottet (FR), Chairman of the EAU Prostate Cancer Guidelines Panel confirmed the evidence base. “Can we use an MRI to rule out biopsy, the answer is probably ‘no’, certainly not yet”. He stated that imaging is only useful if it can change the outcome, but noted that we don’t yet have clear data to justify routine MRI use; and it still needs to be used in conjunction with other diagnostic techniques – it can add information, rather than replace other techniques.

Mottet noted that just about all the published reports come from expert centres, with high levels of expertise and strong teams, so it is not yet a routine technique.

Prof. Alberto Briganti (IT) confirmed the cautious approach “Imaging is here to stay, and we are looking forward to the next developments, but we still need to study the ability of images to rule out significant diseases”.

Walz summed up the session: “We learned that we probably get less benefit than we should for the money which we spend. The technology should only be used if it changes how we treat the patient, not just because we have the technology. Some would like to do MRI before any biopsy, as happens with mammography, but the comparison isn’t completely valid. In France for example, a mammography costs around €80, and whereas an MRI costs €350. In addition, the infrastructure needed is still significantly different.

Do not miss this today:
Posters & Videos - The Prize Winners
Special presentations on stage at the e-Poster Area at 11.00 hrs.

Best Paper on Fundamental Research: I. Ahmad (Glasgow, United Kingdom)
Best Paper on Clinical Research: J. Steinmetz (Muensster, Germany)
First Prize Best Abstract (Oncology): R. Seiler (Bern, Switzerland)
First Prize Best Abstract (Non-Oncology): H. Langenhuijsen (Nijmegen, The Netherlands)
Second Prize Best Abstract (Non-Oncology): M. Ilg (Chelmsford, United Kingdom)
Third Prize Best Abstract (Oncology): N. Fossati (Milan, Italy)
Best Scientific Paper on Fundamental Research in European Urology: A. Ross (Baltimore, United States of America) Sponsored by ELSEVIER
Best Scientific Paper Clinical Research in European Urology: J. Weinreb (New Haven, United States of America) and J. Barentsz (Nijmegen, The Netherlands) Sponsored by ELSEVIER

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Sunday, 26 March 2017

EANM/ESUI/ESUR Congress

Day 2 Award Gallery

Best Booth Award 2017: STEBA BIOTECH
Bertrand Gallias MD, Prof. Chris Chapple, Dr. Stefan Spaniol, John Rewcastle PhD, Silvestre de Lima Neto, Prof. Avigdor Scherz

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EUT Congress News
Sunday, 26 March 2017
The identification of germline mutations in hereditary cancer syndromes is an important finding. These mutations make it possible to identify individuals who are at high risk for developing the disease (e.g. BRCA2) in breast cancer. This has targeted therapeutic approaches directed at events that drive tumor initiation and progression (e.g. renal cancers).

For this reason, for the last three decades this has been an area of intense investigation at the Brady Institute. Two important conclusions have been drawn: the first is that prostate cancer is more heritable than other common cancers, including ovarian, kidney, breast and colon cancer. Paradoxically, although the genetics of these less heritable malignances is well established, there is still much that is unknown about the genetic pathogenesis of prostate cancer. For this reason, I selected this topic and thought I would tell the story of our search for the missing heritability of the disease.

Family history is a major risk factor

The story begins in 1987 when a 49-year-old man asked me if prostate cancer was hereditary. When I asked him why he wanted to know he responded that his father, his father’s three brothers, and his grandfather died from the disease. At that time, it was common knowledge that women with a mother or sister who had breast cancer had a two-fold higher risk for developing it. So why didn’t know the answer to his question. Because the available literature on prostate cancer was sparse. There was information from the Utah Mormon genealogical registry but it was unclear if these findings could be applied to the general population or whether they represented a rare founder mutation in a isolated population of men. To determine if the same were true in another population we undertook a case-control study of 572 consecutive men who underwent a radical prostatectomy at Hopkins using their spouses or female companions as a control. Our findings, which confirmed a 2.2 fold increased risk for men with one first-degree relative, was published in 1990 by four other studies that reported similar results.

Familial aggregation is genetic

The next step was to determine whether this familial aggregation was caused by inherited genetic factors or factors shared in the environment. Using the same population, we performed a segregation analysis that demonstrated the best model predictedautosomal dominant inheritance of a rare (0.5%) high penetrance risk allele in families with early age of diagnosis and multiple affected family members. This study demonstrated for the first time that prostate cancer is inherited in Mendelian fashion and provided a foundation for gene mapping studies of heritable prostate cancer. Finally, based on the segregation analysis we developed a definition for hereditary prostate cancer (HPC): three or more first-degree relatives (father, son, or brother); or three generations with prostate cancer in the maternal or paternal lineage; 2) early onset prostate cancer (age ≤55 years); or 3) prostate cancer with a family history of the BRCA2/mutation or other cancers (e.g. breast, ovarian, pancreatic).

Where is the missing heritability – rare variants?

So where is the missing heritability? Going back to the drawing board, but this time armed with high-throughput next-generation sequencing (NGS), we began to search for rare variants with the hope that there may be multiple rare variants that contribute a large effect.

Next, investigators became excited about the influence of SNPs, and the possibility that a large number with each having a very small effect would be the answer. These studies led to the successful identification of over 500 SNPs associated with prostate cancer risk. Although the relative increase in risk for any single SNP is small, the risk increases as the number of inherited risk SNPs increases but these appearances to explain only about 25% of the risk associated with a positive family history and the clinical utility of these findings remains uncertain.

BRCA1/2, DNA Repair, and Mismatch repair mutations

Twenty years ago BRCA2 was implicated as an important gene for prostate cancer by studies in Icelandic families and more recently Eeles and her research group at the Royal Marsden provided additional evidence that defective BRCA2 genes are associated with inherited risk of more aggressive prostate cancer. However, it was only within the last couple of years that we learned of their impact on the development of castration-resistant prostate cancer (CRPC).

A study by the Step up to Cancer research group, which carried out the first in-depth sequencing of men with CRPC, demonstrated that 6% of men with CRPC had deleterious germline mutations of BRCA2. When coupled with other genes involved in DNA repair (like ATM), and the mismatch repair genes in Lynch syndrome, e.g. MSSH, the total number of CRPC patients with inherited mutations rose to over 12%. In a study at Hopkins, together with our colleagues at NorthShore, we found that in men who were free from prostate cancer prior to age 65, 10 to 12% carried mutations in BRCA2/BRCA2 and ATM.

Have we been looking in the wrong place?

No one knows for sure, but based on the recent discovery that patients with lethal and aggressive prostate cancer who do not have a strong family history can carry DNA repair mutations in their germline, maybe we have been looking at the wrong patients. Our studies have always concentrated on men with multiple affected family members who are alive, instead, if future studies concentrate on patients with lethal and advanced disease it is possible we will uncover many previously unknown important pathways.

Clinical implications

BRCA1/2 is a major risk factor for development of the disease. The history should include age at diagnosis of prostate cancer in both paternal and maternal lineages and a complete list of other cancers. Factors suggestive of a genetic contribution to prostate cancer include the following: i) multiple affected first-degree relatives with prostate cancer, including three successive generations with prostate cancer in

Hereditary Prostate Cancer

Genome-wide association studies to search for complex disease

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Robot-assisted radical prostatectomy (RARP) is increasingly being performed for the surgical management of localized prostate cancer and, to some extent, some patients might have preoperatively undetected or intraoperatively identified inguinal hernias (IH) (Photo 1).

It was reported that 33% of the patients had incidental IHs during radical retropubic prostatectomy (RRP) (1). A study carried out at Karolinska University Hospital, however, revealed that no patient who underwent RRP or RALP were included (2). The cumulative risk of IH development at 18 months was 12.2% and 9.9% for RRP and RARP groups, respectively (p=0.05) suggesting that RARP leads to a decreased risk of IH development (2).

It is important to make a proper physical examination preoperatively to identify asymptomatic and subclinical inguinal hernias before the RARP procedure. A preoperative abdominal computed tomography or ultrasound might also be helpful in identifying asymptomatic inguinal hernias before surgery. It might be difficult to diagnose inguinal hernias preoperatively particularly in obese patients. It was suggested that men with preoperative lower urinary tract dysfunction have an increased risk of a hernia at RARP and should be counseled about the possibility of requiring hernia repair (3).

Therefore, due to the preoperative evaluation if the inguinal hernia(s) is/are diagnosed before RARP the patients could then also be preoperatively counseled and informed about the possibility of repairing hernia at the same session.

In published literature, many colleagues reported that inguinal hernias are a common intraoperative finding during RARP, and concurrent hernia repair with the use of a mesh material is a safe and effective additional procedure with reasonable increased operative time (4). If the inguinal hernia is not recognized in the same session following the completion of the RARP procedure, it might be more difficult to repair it via laparoscopic or robotic surgery in the following months after the RARP procedure since there might be severe intra-abdominal adhesions due to the RARP procedure. In addition, this would be a second surgical impact on the patient with additional anesthesia exposure.

A first-generation cephalosporin is administered for antibiotic prophylaxis. Following completion of the RARP procedure, a robotic trans-abdominal pre-peritoneal (TAPP) hernia repair procedure is performed by using a mesh material.

For those who are not experienced in performing a robotic/laparoscopic inguinal hernia repair, it might be useful to participate in hands-on training courses in order to acquire training and experience. In addition, it might be useful to have a general surgeon colleague to supervise the initial cases if needed.

Surgical anatomy

It is important to understand and know the surgical anatomy to properly repair the inguinal hernia. Inguinal canal is lined by the aponereoses of the abdominal oblique musculature that runs the lateral border (internal) inguinal ring to the superficial (external) inguinal ring. The deep inguinal ring is formed by an opening in the transversalis fascia. The superficial ring is formed by a pop in the external oblique aponeurosis.

Normally, inguinal canal includes spermatic cord (ves), deferential artery, testicular veins, genitral branch of the genitofemoral nerve) and ilioinguinal nerve. Hernia protruding through a weakness in the transversalis fascia lateral to the rectus abdominis, medial to the inferior epigastric vessels and above the inguinal ligament is named as direct inguinal hernia. The hernia protruding through the deep inguinal ring, lateral to the inferior epigastric vessels and anteromedial to the scrotal cord is regarded as indirect.

Before starting the TAPP procedure, it is important to obtain a water-tight urethro-vesical anastomosis that is confirmed by distending the bladder intraoperatively with sterile saline solution (Photo 2). In addition, it is also important to have a good hemostasis that could be tested by decreasing the intra-abdominal pressure to 5 mmHg before starting the hernia repair. Likewise, a preoperative sterile urine culture should also be confirmed.

Our technique of TAPP inguinal hernia repair was reported and presented previously at the EAU ERUS 2016 Meeting (5). During the transperitoneal TAPP procedure a large peritoneal incision is made on the lateral sides of both medial umbilical folds, below the level of umbilicus opening the preperitoneal space. If bilateral extended pelvic lymph node dissection is also performed then the lymphatic tissues around external iliac arteries and veins up to the ureters are all cleaned giving the console surgeon a good anatomical exposure of the important vascular structures. It is important to include the peritoneal dissection lateral to the internal inguinal ring. It is also important to particularly pay attention to vascular and pain triangles during dissection. Vascular triangle includes external iliac veins, external iliac arteries, femoral branch of genitofemoral nerve and femoral nerve, whereas pain triangle includes femoral branch of genitofemoral nerve, femoral nerve and lateral cutaneous nerve of thigh.

Mesh materials

Before repairing the inguinal hernia defect with a mesh material, lateral and superior edges of the peritoneum are freed creating a space to locate the mesh. There are different mesh types available on the market to use for hernia repair. In addition to the polypropylene mesh materials, bio-absorbable coated permanent mesh materials are also available to cover the defect. Mesh size could be adjusted according to the size of the defect. Before inserting the mesh material through the assistant port into the abdominal cavity, the bedside surgeon and the nurse always changes gloves before handling and manipulating the mesh material to decrease the risk of contamination. Thereafter, the mesh material is introduced into the abdomen through the 11 mm sized assistant port (Photo 3).

Roulet, omentum, bowel segments or even urinary bladder could be found as herniated into the hernia sac and these structures should be carefully deconstructed. Following the application of the mesh material over the defect, laparoscopic applied tacks (absorbable or non-absorbable) could be used to secure the mesh over the hernia defect (Photo 4). Alternatively, a suture material could also be used for this purpose. Attention should be paid to not injure spermatic cord, testicular artery, genitofemoral nerve, epigastric artery or external iliac vessels during mesh application and securing.

If a bio-absorbable coated permanent mesh is used, peritoneum could be left open otherwise it should be closed over the mesh by using a running absorbable suture (Photo 5). An abdominal drain is inserted and is removed during the postoperative follow-up. If postoperative Day 3, urethral catheter is removed following a confirmation of no leakage on cytostomy. Robotic repair of the inguinal hernias by using mesh materials following the completion of the RARP seems to be a safe and easy procedure to perform by taking specific precautions and having the proper training and knowledge to avoid a further operative procedure for the patient.

References


Monday 27 March
10.30-10.50: Thematic session 18, Masterclass RARP Semi-Live; Management of inguinal hernias during robot assisted radical prostatectomy

Prof. A. Erdem Canda
Yıldırım Beyazıt University
School of Medicine
Ankara Atatürk Training & Research Hospital
Department of Urology
Ankara (TR)
Fertility is an emotive topic. The strong desire to father a child and pass your family name and genes to the next generation is considered important culturally, epidemiologically, socially, and psychologically.

Factors is construed as a marker of masculinity in many cultures, and a source of shame to those who are unable to achieve it.

Fertility issues have shaken the corridors of power, and even changed the cultural landscape at the highest levels. The latest big event in this line of work was held in Europe in taking place in London, the occasion gives cause to remember the history of English royal households long since passed and the trials of King Henry VIII.

Henry VIII and his first wife, Catherine of Aragon, had problems with fertility. Their marriage bore six children, including three male heirs, but all were either stillborn or died in the first two months, except their daughter Mary. Catherine’s inability to produce a male heir led Henry to annul this marriage in favour of his wife’s lady-in-waiting, Anne Boleyn. This move led to a break with the Catholic Church, the development of the Church of England and the dissolution of the Monasteries.

Fortunately, issues with fertility don’t shape history and nations in the same way in the modern era! However, the impact of such problems can significantly affect relationships and lead to feelings of inadequacy and detachment in men unable to produce offspring.

Male factor infertility

Male factors account for approximately 50% of cases of a couple’s infertility. While many cases can arise from rare genetic conditions where a man may have no fertility potential at all, in the main, environmental factors and hormone factors are the common causes of male factor infertility. As such, a man’s fertility potential is often a barometer of his health, and infertility a symptom of underlying disease.

Developments in reproductive techniques have transformed the landscape of infertility management. The advent of intracytoplasmatic sperm injection (ICSI) just over two decades ago provided the greatest boost to our male factor fertility management. By allowing single sperm cells to be injected directly into viable oocytes, this technique opened up a world of possibility to those previously considered infertile. While this has been an undoubted success, it has led to a shift away from understanding and correcting the underlying causes of male factor infertility, to one that simply overcomes it with assisted reproductive techniques.

When considering the causes of male infertility, the problem can be primarily divided into:

1. Issues with spermogenesis, or spermatogenesis, and the production of sperm cells.
2. Issues with sperm delivery.

Detailed assessment of the patient including examination of the testes and scrotal contents, assessment of hormone profile and semen analysis allow the urologist to pinpoint where the underlying issue may be.

The most challenging situation is azoospermia, where no sperm are seen in the ejaculate. Azoospermia affects approximately 10–15% of fertile men. Even in this extreme, infertility can be effectively managed and restored. Not yet any man with azoospermia has delivered a child, but more have fertility potential than one would expect and they may achieve fatherhood using various other techniques.

Obstructive azoospermia

In approximately 40% of cases, azoospermia is due to a structural, or ‘functional’, obstruction of the sperm pathway. Problems may occur at any point from its inception in the seminiferous tubule to its delivery at the external urethral meatus. In obstructive cases, the tubular structure and function is normal, with normal hormonal parameters. The management strategy depends on the level and nature of the obstruction, as summarized in the figure below. Effective reversal of obstruction allows restoration of normal fertility, with the advantage of allowing natural conception for the first and subsequent children. Analyses have shown reconstructive techniques can achieve live birth rates comparable to ICSI, but with better cost-effectiveness. By avoiding the need for ICSI, correction of obstruction also has the advantage of avoiding the need to medically stimulate the female partner for egg retrieval, thereby avoiding some of the additional potential complications and costs associated with assisted conception techniques.

Reconstructive techniques may not be appropriate in cases where there have been operations to remove older female partners. Delays to return of sperm in the ejaculate after successful dis-obstruction in some cases have also meant that by the time the obstruction has been optimized, their female partners fertility potential may have reduced to a point where the couple overall fertility potential is worse. Management of the male partner must therefore always be in the context of the couple.

Testis cancer and oncology

Approximately 40–50% of men with testis cancer have impaired fertility at presentation, of which up to 10% are azoospermic (NOA). Currently patients with testis cancer are recommended to consider fertility preservation prior to orchectomy, although this is not considered essential at this step. In most units, semen cryopreservation is performed after surgery, but prior to subsequent chemotherapy, despite the negative impact of surgery on overall fertility potential.

In our unit, we have taken a proactive approach to fertility preservation, assessing all patients’ testicular function and hormones prior to orchectomy, with cryopreservation of semen at presentation. This allows detection of those with unexpectedly NOA, in whom we offer an onco-microTESE (See above). This procedure allows the safe oncolgic removal of the testis via an inguinal approach, with subsequent ex-vivo microTESE dissection of sperm from the removed testis to allow maximal fertility preservation from adjacent tissue that would have been reserved to the ‘scrapsheap’ of the pathology specimen. This approach has allowed successful fertility preservation in 66% of cases without having to involve the contralateral testis.

A proactive drive to improve fertility preservation in cancer patients at first presentation may prevent the need for orchectomy and subsequently irreversible iatrogenic effect of treatment has been inflicted.

Varicoceles

This has been an area of controversy for many years, based on the flawed analysis of Evers and Collins published in the Lancet in 2001. Subsequent review of the original data a decade ago found that confining the analysis to those with clinically significant varicoceles and infertility resulted in a significant improvement in pregnancy rates after correction of the varicocele. Despite this, most reproductive medicine specialists still do not treat varicoceles proactively.

There are a number of ways in which a varicocele may affect fertility, from the effects of increased temperature, to its effect on hormones, spermatogenesis, and DNA fragmentation. Meta-analyses have shown correction of varicoceles can lead to significant improvements in sperm counts and motility. Other studies have shown reduced DNA fragmentation and spontaneous miscarriage rates after correction. Randomized control trials have also shown that treatment of clinically significant varicoceles can improve the chance of spontaneous pregnancy with an odds ratio of 3.04, and NNT 5.23 in men with oligozoospermia.

In those with NOA and clinically significant varicoceles, treatment can lead to sperm recovery in the ejaculate in up to 32%.

Oncological microsurgical testicular sperm extraction (Onco-microTESE)

Oncological and surgical ways to fertility in young men

Medical and Surgical Options for Obstructive Azoospermia (OA)

1. Ejaculatory duct obstruction - surgical management with Transurethral resection of the ejaculatory ducts (TURED).
2. Retrograde ejaculation - pharmacological (e.g. of libido, hypothalamus, or prostate stimulation).
3. Vasa or Epididymal obstruction - microsurgical reanastomosis by endoscopic or epididymo-vasostomy.
4. Testicular obstruction - sperm retrieval surgery (TESA).

Non-obstructive azoospermia

- Non-obstructive azoospermia accounts for approximately 60% of all azoospermic cases, and remains the most challenging scenario in male factor infertility. Apart from the few cases of hypogonadotrophic hypogonadism, who respond extremely well to hormonal stimulation to recover their fertility potential, this group of infertile men fare less well with medical and surgical intervention. Challenging and controversial areas of management are discussed below.

Surgical sperm retrieval- MicroTESE

Surgical sperm retrieval (SSR) is the primary option in those with irreversibly NOA. Of the available SSR techniques, microTESE has the greatest chance of success. Compared to conventional TESA, microTESE almost doubles the chance of successful SSR (weighted means 33% vs. 54% in meta-analysis), allowing considerably more men the chance to progress to ICSI. MicroTESE is also successful in those men with previously failed conventional TESA.

In our series, 65% of men deemed infertile by conventional TESA had sperm found on subsequent microTESE, including azoospermic men after previous chemotherapy. Similar findings have been described in other series. This finding has led to the conclusion that men should not be considered infertile until they have a microTESE and are found to be infertile. Using hormonal stimulation with HMG/HMG prior to redo surgery may further enhance these success rates, although the best regime and dosage of drugs remains unclear at present and an area that requires better coordinated multi-centre trials.

When one considers the significantly lower complication rates of microTESE compared to conventional TESA, despite its more invasive nature, it becomes clear that microTESE should be the gold standard SSR technique in NOA. Despite this, there are still more fertility centres worldwide undertaking a conventional rather than microscopic SSR.

New techniques and developments in the management of male factor infertility continue to allow us to reduce the proportion of infertile men who are considered beyond assistance. Thankfully, the fate of nations no longer hangs in the balance!

References


Saturday 25 March

Plenary Session 2, Hot topics in andrology
Photodynamic therapy for prostate cancer

Treatment strategy in low-risk PCa may change with photodynamic therapy

Prof. Arnulf Stenzl
Dept. of Urology
Eberhard-Karls-University Tuebingen
Tuebingen (DE)

The principles of photodynamics, i.e., light-induced activation of intracellular or extracellular photosensitizers which can be used for diagnostic and/or therapeutic purposes in non-muscle invasive bladder cancer have been well-known to urologists. It has also been used for many years in the treatment of neurosurgical tumors as well as upper respiratory tract, gynecologic and dermatologic lesions with variable success.

It's use for prostate cancer is relatively new. There have been many in-vitro and in-vivo studies using Padeliporfin as the sensitizer, activated by intraprostatic laser light emitting fibers. The wave length and dosage in humans was set at 753nm with a fixed power setting of 150mW/cm, leading to an energy dose of 200 J/cm². The time necessary to achieve this fixed dosage is 2mm (3-5 sec).

Many photosensitizers have been tested for photodynamic diagnosis and treatment. Some photosensitizers such as aminolaevulinic acid and its derivatives use an enzyme defect in the hem synthesis which only occurs in certain tumour cells. The subsequent accumulation of protoporphyrin IX can be made visible with monochromatic light at a wave length of 428 nm.

In a more concentrated form or by using different bacteriochlorophyll derivative. If activated with low-power monochromatic (laser) light at 753nm, a reactive oxygen species (ROS) is formed which then may lead to ROS-mediated necrosis.

Since Padeliporfin is a vascular-targeted photodynamic therapy it is restricted to well-vascularized tissues (such as parenchyma but not capsular or fascial structures). Furthermore, in a solid parenchymatous organ such as the prostate the sensitizer can only act where a monochromatic light source can reach it, which means the laser fibers have to be placed in or near lesions made visible by imaging.

Vascular-targeted photodynamic therapy

Several weeks ago a prospective randomized study including 433 patients from 47 institutions throughout Europe and a minimum follow-up of 24 months has been published, comparing vascular-targeted photodynamic therapy with active surveillance in patients with low-risk prostate cancer. This is to date the only prospective randomized study comparing any approved or experimental focal therapy with active surveillance.

“Nevertheless, the remarkable results of this study may change the strategy in low-risk and maybe even intermediate-risk patients with prostate cancer. It may be a tool for a tissue-sparing form of treating prostate cancer which will benefit patients...”

The majority of those patients included in this study (86% and 88% in the vascular-targeted photodynamic therapy and active surveillance group, respectively) were stage T1c. The two-hour treatment under general anesthesia consisted of an intraprostatic placement of optical fibres through a perineal raster followed by intravenous application of the photosensitizer Padeliporfin. After 12 and 24 months the prostate was re-biopsied. Twenty-four months after the initial treatment a negative biopsy result was observed in 49% of the vascular-targeted photodynamic therapy group versus 12% in the active surveillance group, being highly statistically significant.

Several facts have changed since this study was initiated several years ago. The technique and quality of a prostate MRI have improved and a multiparametric MRI is in some centers nowadays used as a selection criterion for the initial biopsy as well as a marker for active surveillance. Active surveillance is a more widely accepted strategy for low-risk prostate cancer despite the fact that under-staging may occur and some patients with a long life expectancy cannot accept the psychological burden. Nevertheless, the remarkable results of this study may change the strategy in low-risk and maybe even low-intermediate-risk patients with prostate cancer. It may be a tool for a tissue-sparing form of treating prostate cancer which will benefit patients that may have an “under-staged” disease, and the small number of patients that may develop metastases despite an initially proven Gleason 3+3 score disease. And it might help men who are seeking non-surgical treatment despite different advice because they can’t live with subjective uncertainty of living with a malignant disease.

Recent developments in imaging including multiparametric MRI, PSMA-PET- MRI and navigation-assisted tools/MRT biopsy will further make focal therapy more accurate by improving prediction of progression, better targeting of relevant tumor lesions, and aiming re-biopsies at the previous sites of biopsy put in storage.
This article will highlight some points in a state-of-the-art presentation on the importance of recognizing the role of inflammation in LUTS/BPH pathogenesis and treatment. Several key contributions to the programme. Plenary Session 4, will cover the understanding of LUTS/BPH, BPE and BPH: evaluation, presentation and treatment with slightly more emphasis on the newer surgical options rather than the drug treatments. It will be chaired by EAU Secretary General Chris Chapple and Piotr Radziszewski (PL).

1. The session will start with a state-of-the-art presentation on the importance of recognizing the role of inflammation in LUTS/BPH pathogenesis and treatment by one of the key investigators and authors in this field, Mauro Gacci (IT).

2. This is followed by a high-level debate on the role of urodynamics in LUTS/BPH evaluation and treatment planning, chaired by Henry Woo (AU) and debated by Matthew Olif (UK) and Nishik Thierschduelm (GR). This is a common debate position, respectively. This debate is likely to be ‘won’ by the better proponent of their case although it is hoped that the results of the ongoing UPSTREAM study will answer this uncertainty in the relatively near future.

3. Next there will be patient cases in three different clinical scenarios presented by Andrea Tabara (IT) and we hope to identify how to select appropriate surgical interventions and agree when it is not appropriate to offer surgical intervention. (Discussants Alexandre De La Taille [FR] and Mark Speakman, [UK]).

4. Most of us now fully accept the importance of high-quality Guidelines in the evaluation and management of our patients and particularly their various junior registrars, Dr. Stanov Gravas (GR) will present the essentials of what matters in these documents and educate us on the strengths and perhaps some of the weaknesses of their different forms.

5. Over the last few years there has been a plethora of new technologies in the surgical management of LUTS/BPH and the next section chaired by Christian Gratze (DE) describes the latest developments in surgical progress using three fundamental and different modalities: Electricity (portoextract of Thomas Herbert and Chris Griffin (Cesare Marco Scoppino, IT) and Water (Neil Barber, GB). This should be a highly illuminating programme.

6. Many of us have patients who are still bothered with symptoms even after what appears to be a good case selection, a seemingly complete work-up and apparently successful surgery. Therefore a state of the art presentation by Karel Everaert (BE) follows which will update us on the latest thinking and provide important tips about how to avoid or deal with these problems if they occur.

7. The session finishes with the ‘blockbuster’ presentation from Claus Roehrborn (US), the ‘Emperor’ of LUTS/BPE who will give us his valuable personal explanation of, to borrow from Donald Rumsfeld, ...the known and unknown (by many of us) unknowns of the diagnostic and therapeutic pathways.

Terminology
Since the seminal BPH paper by Paul Abrams over 20 years ago we have gradually moved away from ‘prostatic’ and hopefully everywhere, except the US, also stopped using the term ‘BPH’ as a clinical syndrome, as BPH is first and foremost a pathological definition. We now recognise that using LUTS is the correct terminology as it is neither gender nor organ-specific. The UK NICE guideline and that of the EAU and many others have correctly moved to this terminology to define the storage, voiding and post-micturition symptoms.

The majority of our patients still present because of bothersome LUTS although a significant and important minority present because of either acute or chronic retention. Most guidelines agree on the important issues for the clinical history, examination and evaluation and it is good to see that more and more guidelines are correctly promoting the frequency volume chart or bladder diary as equal, if not even more important than a symptom score such as the IPSS.

Benign Prostatic Enlargement (BPE): Evaluation, drugs, surgery or new interventional treatment

Inflammation
Several studies have demonstrated the activation of chronic inflammatory prostatic responses in the pathogenesis and progression of both benign and malignant prostate disease. Approximately half of our patients with LUTS who come to surgery have signs of chronic inflammation on histological analysis. It is possible that new therapeutic molecules may in the near future be targeted to modify these inflammatory pathways and could then delay or avoid symptom and disease progression. In a subset of the MDTPS study in patients who had a pre-study prostate biopsy, no patients without histologic inflammation developed retention and more recently in an analysis of the REDUCE trial it was shown that the presence of chronic inflammation was associated with both the severity and the progression of LUTS/BPH.

Urodynamics
Most of us would agree that formal urodynamics can add useful information to the comprehensive workup of patients with LUTS, particularly if they are being considered for surgical intervention. It is however an invasive test that some patients find unpleasant. The urodynamicians who do routine urodynamics tend to advocate that surgery should only be performed in those men with proven bladder outlet obstruction. Advocates for restricted use stress the lack of evidence of better outcomes after urodynamics and of course the associated costs. Do the benefits therefore outweigh the disadvantages? The UPSTREAM trial has addressed this very question in a systematic and randomised way and it is hoped that Marcus Drake (GB) and co-workers will provide us with a definitive answer in 2018.

When to operate?
This is not an easy decision and certainly not as easy as many of us thought it was when we were junior registrars. Surgery can often be very beneficial for patients but get patients with retention below those they had expected, or if they get complications they can subsequently be very difficult patients to manage. If at all possible therefore, patients should always be encouraged to have a trial of medical or conservative therapies before proceeding to surgery. The only strict exception would be high pressure chronic retention.

In reality patients need to ‘earn’ their operation and be demanding surgery before plans are made. They need to be made fully aware of all the possible alternative therapies and the potential complications and symptom failure for each of them. It can be better to do what we may believe is the second-best solution if that is what we have informed the choice of the patient. Understanding and managing patients’ expectations is now an important and time consuming part of our role.

We are now much more knowledgeable on which patients require more therapy with drugs and which require combination therapies, and Claus Roehrborn and others have highlighted the importance of identifying which of our patients are at a greater risk of LUTS progression and those more likely to develop complications of their disease. The reasonable question is, are we as thoughtful about which surgical modality to offer our patients as we are with the drugs? Should this be based on prostate size or on the type of LUTS that they suffer? Do storage and voiding symptoms behave differently after surgery? Is there a value in offering more minimally invasive therapies to our younger patients wishing to avoid ejaculatory problems? Whilst accepting that there is a greater probability that they will require further surgery in the future or should we promote a more definitive procedure as first choice? Clearly patient choice and the limitations of the local health care organisation will strongly influence these decisions.

Guidelines
Clinical Practice guidelines addressing the management of men with LUTS/BPH began appearing in the urological journals in the early 1990s and the number and quality of these have increased year on year. Most national urological associations publish their own guidelines and larger organisations like the EAU provide their high-quality guidelines free for members and non-members alike. In the early days these were often based on the ‘ex cathedra’ statements of senior urologists but they are now predominantly based on evidence-based medicine and therefore of a much higher quality, although there are methodological issues that vary between them and thereby affect the quality. In addition, the uptake and utilisation of these guidelines by their members is less than it should be; a good example would be the underutilisation of frequency volume charts (bladder diaries) even though they are recommended in all good guidelines.

Emerging technologies
Surgical interventions for LUTS/BPH have evolved considerably over the last 10 to 15 years and the pace of development is showing no signs of slowing. The principal surgical options have been resection, enucleation and/or vaporisation and these have led to generally acceptable long-term outcomes with reasonable safety. Most of these procedures are operator dependent and we tend to believe that success depends upon the degree of relief of obstruction of the bladder outlet.

Whilst some of these procedures have required hospitalisation the latest developments are focused on trying to achieve an outpatient / daycase or office-based procedure without the need for general anaesthesia. There has also been greater awareness amongst patients of some of the sexual and ejaculatory dysfunctions from some of the more traditional approaches. This has led to even more minimally invasive therapies such as intra-prostatic injections (still undergoing clinical trials) and innovations such as the Neotract Urolift™ device that has been introduced after a well-structured investigational clinical trials process (unlike some of the innovations in the past).

There have also been a variety of ablation techniques ranging from the use of high frequency ultrasound to water vapor (Rezum and Procept aquablation). Within the realm of interventional radiology there has also been increasing success with prostate artery embolisation. It is unlikely that robotic assisted simple prostatectomy will be cost-effective. A comprehensive list of treatments is provided in Table 1.

Table 1: Treatment Options for LUTS/BPH

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<td>Conservative measures</td>
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<td>• transurethral RF water vapor thermotherapy (Rezum™ system)</td>
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<td>• robot-guided water ablation</td>
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<td>• PROCEPT Aquablation®</td>
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<tr>
<td>• HistoTract</td>
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<tr>
<td>• Robotic assisted simple prostatectomy</td>
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**Cheers!**

Have an after-work brew with us at our **booth B43** and discover our truly defined urology solutions. First come, first served. Every evening as of 17.00!

EUT Congress News

Mark Speakman  
Taunton & Somerset  
NHS Foundation Trust  
Dept. of Urology  
Musgrove Park Hospital  
Taunton (GB)
The current EAU guidelines on non-muscle invasive bladder cancer (NMIBC) recommend cystoscopic follow-up for five years in patients with low-grade NMIBC but this is only a Grade C recommendation as there is little high-quality evidence in this area.

Indeed the EAU guidelines themselves state that ‘tumour recurrence in the low-risk group is nearly always low stage and LG/G1. Small, Ta LG/G1 papillary recurrence does not present an immediate danger to the patient and early detection is not essential for successful therapy’ (E1:E28).

The UK National Institute for Health and Care Excellence (NICE) develops practice guidelines for the National Health Service (NHS) in England and the NICE Bladder Cancer Guidelines were developed by a panel of 15 experts and published in 2015. One of the most notable recommendations was that patients with low-grade NMIBC could be discharged at one year as long as they had been free of recurrence at both their three and 12 month cystoscopies.

It is known that the outcome of cystoscopy at three months is a strong predictor for future recurrence and patients who are free at three months is a strong predictor for future recurrence and patients who are free at three and 12 month cystoscopies.

Based on this, NICE recommended that in the UK patients with low-risk NMIBC with no recurrence at 12 months should be discharged back to primary care and importantly their primary care physician should not perform regular investigations such as urine cytology to monitor for recurrence. However patients were to report any visible haematuria immediately. The guidelines were published in February 2015 and in the two years since, the majority of urology departments in the UK have adopted this strategy. Although as yet no scientific literature has been published on outcomes following this change, the British Association of Urological Surgeons (BAUS) have been monitoring the situation closely and as yet no concerns have been raised by UK urologists.

Many departments report a significant easing of their cystoscopic workload following the change which has enabled them to focus on faster cystoscopic investigation of new haematuria referrals. Interestingly, no concerns have been raised by UK urologists.

The rise of national socialism and fascism and the subsequent occupation of the continent during the Second World War dramatically influenced and destroyed the careers of urologists and the development of the young specialty of urology. This new publication by the EAU History Office documents the fates of urologists in this period and explores the effects of the war on our field.

Reference
Bladder cancer is the 15th most common diagnosed cancer and significant cause of tumour-related deaths worldwide. Although we observe global reduction of bladder cancer mortality in recent years, its occurrence remains a topic of concern.

**Improve efficacy of primary prevention**
Several endoscopy features, originally considered rare or non-existent, were identified and confirmed many decades ago, which brought unique opportunities for primary prevention and reduction of disease incidence and mortality. Unfortunately, not all expectations and promises were accomplished.

There is no doubt that the most important risk factor for bladder cancer development on a population basis is, at present, tobacco smoking. Recently published meta-analysis of cohort and case-control studies estimated pooled relative risk of bladder cancer between current and former smokers of 3.47 and 2.24, respectively. Moreover, both current smokers (RR 2.53) and former smokers (RR 1.44) have a higher risk of bladder cancer mortality compared to non-smokers.

According to recent data, global modeled age-standardized prevalence of daily tobacco smoking in the population older than 15 years decreased from 2.1% in 1980 to 31.1% in 2012 for men and from 41.2% in 1980 to 31.1% in 2012 for women. Because of population standardization of samples collection as our group presented in demonstrated studies. Appropriately, non-invasive bladder cancer detection remains a significant challenge for future research activities.**

**Improve results of transurethral resection (TURB)**

The treatment strategy of NMIBC is based on complete TURB, individually followed by intravesical chemotherapy or immunotherapy instillations. TURB represents the critical step in the management of NMIBC. The aim of the procedure is to establish the histological diagnosis, determine the tumor stage and grade, and remove complete resection of non-muscle-invasive tumors. Unfortunately although TURB is a frequently performed procedure which should be familiar to all urolgist, its results are far from optimal and both the diagnostic and therapeutic purposes are not always accomplished. Indeed, tumors are frequently overlooked and left behind during initial resection or, more importantly and dangerously, their depth of invasion can be underestimated.

To overcome these limitations, the second resection (second TURB) performed after two to six weeks is included in our treatment algorithms. The current version of European Association of Urology (EAU) Guidelines recommends considering a second TURB if initial resection was incomplete and when the pathologist reported no muscle tissue in the specimen, with exception of T0/T1a tumors. For muscle-invasive disease, second TURB should be performed when a T1a tumour was detected at the initial TURB. The second TURB can detect residual tumour in 33 to 55% of cases staged as T1 by initial resection. More importantly, the likelihood that muscle-invasive disease is detected by second resection of initial T1a tumour ranges from 1.3% to 25% and it increases to 34% if there was no muscle in the initial resection. It has been demonstrated that a second TURB can increase recurrence-free survival and improve outcomes after BCG treatment.

We should not forget, however, that a second TURB is just the “rescue” procedure. The recommendation to repeat surgery in a significant number of patients with NMIBC must be critically discussed and our effort should be concentrated on an improvement of the quality of the first TURB. How to perform the optimal initial TURB? The essential requirement is modern equipment and surgery performed by well trained surgeon. There were several modalities presented which could improve visualization of the tumour lesion and can be categorized as POD (Fluorescence cystoscopy), NBI (Near-Infrared Imaging) and SF-POD. Principle of POD is based on selective accumulation of protoporphyrin IX in tumour tissue after intravesical instillation of 5-aminolevulinic acid (5-ALA) or, preferably, hemoxenominolevulinate (HxAL). Protoperphyrin IX emits intensive red fluorescence after illumination with blue light.

**Improve efficacy of adjuvant treatment after TURB**

The principles of the adjuvant treatment are individually tailored intravesical chemotherapy or immunotherapy instillations. The indication is based on pathological risk stratification into three risk groups, which is specified in EAU guidelines (EAU guidelines on NMIBC).

Major problems present patients with high-risk tumours, which progress in a significant number of cases. The only treatment modality which can reduce the risk of tumour progression is BCG intravesical immunotherapy. We understand today that to achieve optimal efficacy, BCG must be used including the maintenance schedule.

In spite of that, we are aware of several limitations. BCG fails in a not negligible subgroup of patients - it was demonstrated that in T1G3 tumours the five-year disease-related death rate reaches 15% despite BCG therapy. BCG has several side-effects and is not tolerated by all recipients; moreover, we are facing today the enormous market shortage of the drug, worldwide. Moreover, after failure of BCG treatment there is no reliable bladder-sparing option which could prevent patients from radical cystectomy. Apparently, we need effective treatment for patients with BCG failures and, even more important, for patients with positive cytological or instilled MUC. We do not know which methods could replace BCG as a primary treatment option after TURB.

What is new in adjuvant treatment? Promising data have been presented on enhancing the efficacy of MUC and microwave-induced hyperthermia in patients with intermediate and high-risk bladder cancer, a reduced RFS at 24 months in the MMC group was demonstrated. There are several available technologies which could replace the treatment of instilled MUC. They are based on different principles than microwave-induced hyperthermia and must be evaluated separately. The data about these therapies in prevention of recurrences are however still lacking.

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Dr. Marko Babjuk
Department of Urology
Hospital Motol and
Faculty of Medicine
Charles University
Prague (CZ)

Figure 2-A: White Light

Figure 2-B: Narrow Band Imaging

Figure 2-C: White Light

Figure 2-D: Photoemission Diagnosis

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Hospital Motol and
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Prague (CZ)
Clinical Guidelines

Aren't we all stakeholders?

The EAU Guidelines Office (GO) has been expanding their activities over the past years, supported by a number of designated Committees including: the GO Methodology Committee, chaired by Prof. Dr. Richard Sylvester and the GO Guidelines Associates Committee, chaired by Prof. Dr. Thomas Knoll. The GO, together with both committees, have made great strides in improving the methodological quality of the EAU Guidelines.

However, one area that will require particular attention in future update cycles is stakeholder engagement in the EAU guidelines development process. Stakeholder participation is an established feature of high-quality clinical guidelines development. The GO’s anticipation is that inclusion of all key stakeholders in the development process will result in better guidelines, better adherence by patients and clinicians and improved care whilst potentially increasing cost-effectiveness.

What are ‘stakeholders’, a definition may be: ‘any group or individual who can affect or is affected by the achievement of the organisation’s objectives’. This involves all individuals and groups that ‘use’ clinical guidelines, are subjected to them, or are contributors to their content. Obviously, all of you, at EAU2017 are our stakeholders, without exception. Contributors to their content. Obviously, all of you, clinical guidelines, are subjected to them, or are involved in the EAU guidelines development process which includes:

- Guidelines topic selection;
- Panel development;
- Decision on the remit (the scope of a guideline – what needs addressing?);
- Development of recommendations; and
- Review of results.

The UK National Institute of Clinical Excellence (NICE) have a very robust methodology in place for stakeholder involvement, which serves as a model for many other guidelines developers. However, translating such models to an international setting is challenging. In particular, meaningful engagement of patients in clinical guidelines development has posed a challenge to the EAU GO. Some EAU Guidelines Panels include a patient advocate, but a sustainable method on how to progress this further across all of our Panels, has been lacking. However, with the assistance of Prof. Dr. Rachel Giles (Patient Advocate in the EAU Renal Cell Cancer Guidelines Panel on behalf of the International Kidney Cancer Coalition) a potential model has been developed. Recently, a scientific paper mapping out the various aspects of this process was accepted for publication. The authors consider that transparency, accountability and harmonisation of patient care based on the best available scientific evidence are core elements of this process.

In addition, the GO recently carried out a prioritisation exercise to identify and rank clinical topics that should be addressed in the 2018 EAU Guidelines. This was done through a process of structured consultation of a large stakeholder base. While it is still early days, this may become a standard element of EAU guidelines methodology.

Over the past two years, the EAU GO has heavily invested in the development of systematic reviews as a means to ensure that guidelines recommendations are based on the best available scientific evidence. Whilst this has been highly successful, and will continue into the future, a number of important clinical questions elude this process since either no high level evidence has been published, or the available publications do not allow for a clear conclusion because they present contradictory findings. Having a transparent process in place, which can address such questions in a structured fashion, will be hugely beneficial. In this situation formalised consensus finding will allow all stakeholders to reach agreement on such controversial subjects. For this reason an EAU consensus group, chaired by Prof. Dr. Axel Bex, has been set up to develop a protocol to guide this process. The GO firmly believes that in order to maximise outcomes for this consensus process, stakeholder engagement is key. Another future project for the GO is public review of all pre-publication guidelines documents. Other organisations are already following such an approach with highly positive result.

Ultimately, all these processes rely on transparency as well as the management of all stakeholders’ potential conflicts of interest (COI). To address the issue, Prof. Dr. Anders Bjartell and a team of EAU GO Panel Chairs have developed a policy document addressing the handling of potential conflicts.

The GO sincerely hope that when we reach out to you to learn your views, you will enthusiastically engage with us since all EAU members are key stakeholders in all of the activities of the organisation.

Reference

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Stop Guessing. Start Knowing.

PDD – flexibility in visualization with IMAGE1 S
The public awareness on prostate cancer has introduced individual screening on a large scale in many societies around the world. As a result, prostate cancer incidence has changed profoundly.

While the highest rates are still found in western societies (Terre 2012), statistics show the steepest incline in prostate cancer diagnoses in Asian countries (Figure 1). The widespread use of screening of healthy men has resulted in decreases in cancer-related mortality. However, any screening procedure carries a risk of over-diagnosis, i.e., the diagnosis of a clinically insignificant cancer that would not have been discovered in the absence of screening, and that would neither harm the patient. In turn, over-diagnosis has led to overtreatment, with the potential for unnecessary side effects. The amount of unavoidable over-diagnosed cancers is rising, as it is proportional to the intensity of screening. As in addition the population of many countries continue to age, not only the number of diagnosed cancers grows, but also the prevalence of men with cancers that need to be observed lifelong.

Active Surveillance (AS) of low risk prostate cancer therefore remains an important asset in the care of prostate cancer patients, until a reliable marker is found that will indicate the future development of symptomatic metastatic cancer in every man diagnosed. The key to making sure that AS is the appropriate treatment approach for the patient is determining as certainly as possible that the tumor is currently not life-threatening or is at a low-risk of spreading or getting worse, thereby avoiding unnecessary treatment. To do so, we rely on risk assessment methods for individual patients on AS. Traditionally, these include serial measurement of serum PSA levels, digital rectal examination and surveillance biopsy sampling.

But meanwhile, multiparametric magnetic resonance imaging is being increasingly mobilized to support patient selection for AS as well as for monitoring those already on AS. As this technology and outcome data are still improving, the now kid on the block is genetic profiling. All the technologies mentioned have their individual diagnostic and prognostic value, and their relative importance varies over time. Here we focus on MRI as part of a multiparametric risk evaluation in men with newly diagnosed and low risk cancers.

Wishful thinking

In a perfect world, there would be no over-diagnosis, and AS as a treatment option would not exist. However, as long as it is difficult to accurately determine the certainty of a man of 50 years, electing to undergo screening because he has a first-degree relative (a father, a brother) or a female relative with breast cancer, we need to live with the uncertainty that over time a symptomatic prostate cancer can surface. And the longer the period for our predictions is, the larger the uncertainty will be. This means that we will refrain from looking ahead more than 10 to 15 years (with the ’likely exception from having a serum PSA below the age of 50). So men will screen (and remain to be screened by physicians), and cancers will be diagnosed based on the histologic evaluation of biopsies.

Now we hope of course, that histologic biopsies will become unnecessary to diagnose prostate cancer, and if by non-invasive testing with imaging, urine and blood tests we can claim that a person will not be affected by symptomatic prostate cancer, that would be ideal. That, however, is unlikely to happen during our careers. What might happen is that an individual can be predicted with a likelihood of not having a relevant cancer for the next 10 years, based on urine and blood tests, enriched with information obtained by imaging workup. And this in combination with the individualised advice for re-screening in case there is a low-risk. Also it is reasonable to think that in case of an increasing prostate cancer an adjusted scheme for diagnostic biopsies will be provided, sometimes with systematic biopsies, sometimes with targeted biopsies only, to minimize the number of unnecessary diagnostic biopsies.

In fact it looks like the figure below, in which a regular care path for active surveillance is depicted, together with the option of additional MRI for targeted biopsies of usual PRIAD 3-5 lesions.

No gold standard

Because of the slow growth and metastatic potential, the follow-up of low-risk tumours takes many years. Therefore, at least for the next decade or so, we need to accept the surrogate endpoint of 14 predefined risk groups for treatment decisions (based on tumour stage, serum PSA levels, biopsy Gleason score and other risk parameters) at the time of diagnosis, at the time of radical prostatectomy specimens. It shows that MRI visualises relevant tumours, but not all, and that the PRIAD or Likert system does not completely parallel the Gleason grading (Homburg 2013, Sjogren 2015). We need imaging to confirm the nature of the MRI lesions observed.

Confirnatory MRI: Within one year after diagnosis

The fundamental question regarding MRI is whether we are able to see and distinguish the relevant and the irrelevant tumours by MRI, and whether we need histologic proof by biopsy. What do we know? So far, we have been exploring several things:

1) We have evaluated MRI by relating it to radical prostatectomy specimens. It shows that MRI visualises relevant tumours, but not all, and that the PRIAD or Likert system does not completely parallel the Gleason grading (Homburg 2013, Sjogren 2015). We need imaging to confirm the nature of the MRI lesions observed.

2) We have re-evaluated men, selected for AS by traditional criteria, with confirmatory MRI (after three years, five years, and ten years from time of diagnosis) to see if all diagnosed tumours were visible. It is clear that not all men on AS have visible lesions on MRI. The results of our analysis are shown in the table below.

<table>
<thead>
<tr>
<th>Year</th>
<th>MRI-positive</th>
<th>MRI-negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 yrs</td>
<td>70%</td>
<td>30%</td>
<td>100%</td>
</tr>
<tr>
<td>5 yrs</td>
<td>60%</td>
<td>40%</td>
<td>100%</td>
</tr>
<tr>
<td>10 yrs</td>
<td>50%</td>
<td>50%</td>
<td>100%</td>
</tr>
</tbody>
</table>

MRI may provide some additional information that improves the diagnosis by histopathological biopsies, and results in targeted biopsies and additional upgrading of low-risk tumours towards intermediate or even high-risk tumours in ca. 10% of cancers, not detected by the PRIAD system. MRI may provide a very good answer of the top of the value of repeated systematic TRUS-directed biopsies itself, which already corrects grading in ca. 20% at confirmatory biopsies. However, would the diagnosis be dependent on targeted MRI, then 10% or relevant tumours would be missed upfront due to the lack of systematic biopsies.

This means that MRI can reduce the upfront misclassification by correction of targeted biopsies in men that were not diagnosed with low-risk tumours (according to standard criteria) but did have an MRI before diagnostic biopsy. This is important as the main reason for reclassification within one year in AS protocols currently is an upgrading by confirmatory biopsies (due to missing the lesion index) or underestimation of the size of the lesion. Correction of this misclassification might correct for 20% of men being treated incorrectly by active surveillance according to current risk categories.

Unfortunately, current data shows that MRI also misses relevant tumours around 30% of the time. MRI may not be visible on MRI, so would be missed in any strategy that makes use of targeted biopsies only. We do not know how to correct for this failure of MRI apart from performing systematic biopsies. However, we may suspect these hidden non-visible tumours if we consider genetic factors, like an increased PSA density. Offering systematic biopsies only to those at higher risk, whether due to increased PSA-density or based on genomic profiling, may save a large number of unnecessary systematic biopsies (Figure 2).

MRI for Follow up

Men on AS have been followed with MRI (Feller 2016, Frye 2016), but the amount of consistent data appears to be sparse. We have no clue at this moment how often men on AS; and MRI or AS changes over time, and if so, which changes are relevant. We do not even have a reclassification system that is immediately available. There is still a lot of work to do, and it can only be done if the radiologic community will standardize reporting and production of MRI. Or we now develop polygons related to the density and contrast intensity of identified lesions. The international multidisciplinary PRECISE group of ESRO is working on the development of preliminary recommendations for reporting of individual MRI studies in men on AS and for researchers reporting the outcomes of reports of men on active surveillance.

Filling the gap: GAP3 (Bruinsma, 2015)

The reports of individual series on the value of MRI in the diagnostic process have been supportive for the use in active surveillance, but the proof is still pending. The problem is the eating. In the worldwide consortium initiated by the Movember Foundation, a global charity with a vision to change the face of men’s health, a database has been constructed over the last two years which comprises data on more than 15,000 men with prostate cancer treated by AS in 45 centers from the USA, Canada, Australasia, the UK and Europe. The Global Action Plan Prostate Cancer Active Surveillance (GAP3) initiative provides the means to analyse these data, including those men that underwent an MRI at some point during AS. These real-time clinical experiences, and also the further analysis of their MRI images, will provide answers that cannot be obtained from the low-volume studies so far. Still, the number of men being followed for at least five years needs to grow, since at the moment sufficient imaging data is available only for those men that have participated in the PRIAD-MRI study protocol. Confirmatory MRI with targeted biopsies within 12 months of diagnosis may add to the evidence. A new consortium of men with low-risk tumours (or even metastatic tumours with a prostate-specific antigen ≥ 20 ng/ml) with confirmatory conventional TRUS biopsies. Offering systematic biopsies in case of negative MRI to men with increased risk by PSA-density or genomic profiling may optimize the care path (blue path).

### Key points

1. Active surveillance for low-risk prostate cancer is an unavoidable treatment option to reduce or delay overtreatment

2. Multiparametric magnetic resonance imaging is being increasingly mobilized to support patient selection for AS as well as for monitoring those already on AS

3. Confirmatory biopsies as a combination of systematic and MRI-targeted biopsies substantially improve misclassification of men previously selected for AS compared to systematic biopsy findings only

4. The role of MRI for follow-up is still unclear due to lack of standardized evaluation of MRI, and lack of knowledge in the interpretation of findings

5. The Movember Foundation’s Global Action Plan Prostate Cancer Active Surveillance (GAP3) project represents a unique and extensive resource to assess the value of MRI for the future management of AS.

6. AS in the absence of MRI (involving traditional protocols) in underprivileged areas remains a safe treatment option.

Editorial Note: Due to space constraints the reference list has been omitted. Interested readers can email at EUT@roweunet.com for a complete listing.

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**Figure 1**: Incidence of prostate cancer per 100,000 in the world (Terre 2012)

**Figure 2**: The care path for active surveillance (J.A. Alberts, Eueness ME). The top blue line depicts current Active Surveillance PRIAD-MRI study protocol. Confirmatory MRI with targeted biopsies within 12 months of diagnosis may add to the evidence. A new consortium of men with low-risk tumours (or even metastatic tumours with PSA ≥ 20 ng/ml) with confirmatory conventional TRUS biopsies. Offering systematic biopsies in case of negative MRI to men with increased risk by PSA-density or genomic profiling may optimize the care path (blue path).
Biomarkers for immune checkpoint inhibitors

A key concern: Identify who may benefit from new strategies

The field of immuno-oncology has witnessed unprecedented success in recent years, with several tumor types such as bladder and kidney cancers. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer. Nivolumab has been FDA-approved for bladder cancer.

Unfortunately, to date, the search for robust and clinically validated biomarkers that can accurately and reliably predict response to immune checkpoint inhibitors has been without success. A specific problem for immune checkpoint inhibitors is that conventional treatment response criteria to immunotherapies using standard imaging techniques are not optimal assessment strategies. This may be misleading to the tumor microenvironment, which collectively influence the clinical response to CTLA-4 blockade in melanoma. A greater mutational load may thus translate to a higher number of neo-antigens, which may lead to greater T-cell dependent cytotoxic tumor production and cell kill when immune checkpoint blockade is lifted.

Multiple tumor factors contribute to the challenge of assessing PD-L1 expression of an isolated tumor specimen at a single time point as a critical indicator in determining if a patient may benefit from anti-PD1- or anti-PD-L1 therapy. Due to the adaptive nature of PD-L1 and its upregulation by pro-inflammatory conditions, PD-L1 expression levels tend to be dynamic rather than stagnant, raising questions as to whether a single tumor sample may have been taken at the time of a patient’s original diagnosis is truly reflective of the current state of disease, especially after multiple lines of antitumor therapy.

PD-L1 expression also tends to be focal, mainly bordering areas of tumor cells and lymphocytes, leading to concerns of sampling error by missing the tumor-immune interface and thereby rendering false negative results. Indeed, in a study that assessed matched patient samples from primary and secondary sites of disease from patients with RCC, there was discordant tumor cell PD-L1 staining in 20.8% of patients, raising concerns that inter-tumor heterogeneity may compromise the accuracy of overall tumor PD-L1 expression status. Additionally, PD-L1 is expressed not only on tumor cells but other components in the tumor microenvironment, such as macrophages and lymphocytes. Determining if positive PD-L1 expression is actually meaningful on such cells is currently an area of active research.

Candidate predictive biomarkers

Emerging alternative candidate predictive biomarkers include the tumor’s mutational load, neo-antigens, tumor infiltrating immune cells and the tumor microenvironment. While correlation of response to immune checkpoint inhibitors with driver mutations has been largely unsuccessful, there is mounting evidence that mutational load may be a proxy response to immune checkpoint inhibitors. Melanoma, lung and bladder cancers – malignancies in which PD-L1 expression is higher – are now approved – ranked as the tumors with the highest median mutational load.

Most recently, a Phase II study of atezolizumab in patients with advanced bladder cancer evaluated the mutational load of enrolled patients, and showed that the median mutational load was significantly higher in responders compared with non-responders (12.4 vs 6.4 per megabase; p < 0.001), independent of The Cancer Genome Atlas subtype or immune cell subgroup. While costs of genomic sequencing has been steadily decreasing over the past decade, whole exome and whole genome sequencing and their respective data analyses remain challenging in terms of the associated relative financial costs and time implications as well as bio-informatic challenges, limiting their large-scale application in the routine clinical setting.

While PD-L1 inhibitor trials in colorectal cancer have been disappointing, patients with mismatch-repair deficient tumors – determined by microsatellite instability analysis – had an improved objective response rate (82 vs 0%) and disease control rate (92 vs 9%), which is interesting for us urologists since upper tract urothelial carcinoma carries a significant alteration rate in mismatch repair genes. While further studies are needed, these data suggest that targeted next-generation sequencing panels or microsatellite instability analyses may potentially be a more time and cost-effective surrogate of the mutational load of tumors.

The link between mutational load and response to immune checkpoint inhibitors is likely to be due to the production of neo-antigens by tumor cells compared with somatic cells. Single nucleotide mutations may lead to changes in peptide sequences producing T-cell neo-antigens that are prone to immune attack. A greater mutational load may thus translate to a higher number of neo-antigens, which may potentially lead to greater T-cell dependent cytotoxic tumor production and cell kill when immune checkpoint blockade is lifted.

In advanced melanoma treated with ipilimumab, a neo-epitope signature was correlated with survival. In urologic cancers, there are no such studies yet. The inherent challenges in the study of neo-antigens are that not all will elicit a 7-cell response. While there may be shared antigens present in the majority of tumors, it may be the unique antigens present within each patient that are necessary to elicit an immune response. This, the complexity of mutational load and neo-antigens may be scientifically promising as a tool for the prediction of response to immune checkpoint inhibitors, further investigations is still required to confirm their clinical utility.

Finally, there is a complex host of factors in the tumor microenvironment, which collectively influence immunomodulatory effects to either promote or combat tumor growth. Strong lymphocytic infiltration has been shown to be associated with improved patient outcomes in bladder cancer. While the prognostic value of tumor-infiltrating immune cells has consistently been shown in various tumor types, its predictive role is still under investigation.

Today, the era of truly personalized immunotherapy is well within reach – heralding further acceleration and innovations in patient care. Two future areas that sound promising are molecular imaging with radionuclides tagged to antibodies like anti-cytotoxic T-lymphocyte antigen-4, and anti-PD-L1 and immune surveillance with monitoring of the T-cell receptor repertoire in both tumor tissue and peripheral blood samples. Building on the significant benefits that have already been demonstrated in multiple tumor types, the incorporation of state-of-the-art high-throughput predictive or response biomarkers will improve our ability to select patients for stratified immunotherapies, identifying those who are most likely to respond to treatment while minimizing the risks of immune-related toxicities.

References


Sunday 26 March 2017 11:01-12:15: Theme Session 6, Immunology: Changing treatment paradigms in real and urothelial cancer
Ureterocutaneostomy
UUCS is a good option for frail and elderly patients

There are two epidemiological phenomena, which are aging and gaining more and more importance. First, the population of western countries is ageing by an estimated threefold increase in the number of octogenarians within the next 30 years. Second, the peak incidence of bladder cancer is at 85 years (5,6).

Consequently, the incidence of invasive bladder cancer (BC) will increase, due to a stage shifting with age towards a more immuno-suppressiveness at first presentation (5) and simultaneously the registered comorbidity in newly diagnosed and aged BC patients will increase as well (6). In the future, we will be confronted more often with the need of radical cystectomy (RC) in aged and frail patients.

Radical cystectomy is a major procedure and associated with a significant rate of postoperative complications in up to 60% (7-9) and 90-day mortality rates of approximately 10-13% (9). Most of the complications develop in the early postoperative period and are derivation-related (8,9). Therefore, it is essential to tailor the right diversion correctly to the individual patient, minimising the risk and maximising the patient’s benefits. We present a modified technique of the ureterocutaneostomy (UUCS) which is an often used but rarely reported modified technique of the ureterocutaneostomy (10) and simultaneously the registered comorbidity in newly diagnosed and aged BC patients will increase as well (6). In the future, we will be confronted more often with the need of radical cystectomy (RC) in aged and frail patients.

Preoperative management
Consultation of the patient by an oncological therapist. The stoma has to be placed in the upper left (or right) abdominal quadrant (about the half way between umbilicus and xyphoid in a pararectal position). A subcutaneous prophylaxis for deep vein thrombosis is started the evening before surgery. Nowadays we do not use intestinal preparation. Antibiotics: Cephalosporines of third generation in combination with 1.5g of Metronidazole at beginning of surgery and after 6 hours.

Operative technique step by step:
- Landmarks are: xyphoid, 12th rib, umbilicus, superior anterior iliac spine and symphysis pubis.
- Normally during cystectomy, the distal part of the ureters is just divided and intubated by a ureteric catheter.
- The left ureter is mobilized sparing the testicular artery and respecting the mesoureter until the ureteropelvic junction.
- Mobilisation of the right ureter until 3 cm under the ureteropelvic junction.
- Cross over to the left site of the right ureter between the Treitz-Ligament and the inferior mesenteric artery. Do it as high as you can.
- Passing the mesocolon the ureter is brought to the retroperitoneum (cave: the mesocolon has to be large enough to avoid kinking).
- Placement of the stoma:
  - Removing of a suitable circular skin-flap (never smaller than 1.5 cm in diameter).
  - Removing of a circular button of subcutaneous fat until the anterior rectus sheath. It will later be substituted with greater omentum.
  - Cross incision of the anterior sheath.
  - Blunt creation of a gap in the rectus muscle.
  - Cross incision of the posterior rectus sheath and peritoneum on the tip of the underlying finger.
- Pull through both ureters at least 1.5 cm above ureterovesical junction.
- Observe arterial capillary bleeding from both ureteral stumps and spontaneous urine ejaculation.
- The greater omentum is brought through the gap, completely wrapping both ureters.
- The omentum is fixed with single stitches 5/0 Vicryl on the rectus fascia at the outer and the inner side.
- Both ureters are spatulated on a length of at least 1.5cm.
- A single stitch Monocryl 6/0 units both ureters in the middle on the deepest point (knot to the contralateral ureter).
- Check again if both ureters are showing capillary bleeding and if spontaneous urine ejaculation is present.
- Fixation of the ureter-ends in Butterfly technique to the skin-edges by single stitches of Monocryl 5/0.
- Stenting of the ureter with Mono-1 8 or Charr.
- Fixation of the ureteric stents with two single stitches 2/0.
- Placement of a urine bag.

Postoperative care
Fluid balance, blood count and creatinine control every day. Antibiotic treatment is continued until 10th postoperative day followed by a long term prophylaxis until the stents are removed. This happened normally after 90 days and was followed by an endovenous pyelogram. We start on Day 1 with the mobilisation of the patient and with the oral nutrition.

Results
Early postoperative complications following radical pelvic surgery are closely related to the type of urinary diversion. Intestinal complications after an end-to-end-anastomosis often start a chain reaction with a fatal outcome. Due to a bowel rest and overextension of the intestine the patient develops an intestinal compartment syndrome with secondary pulmonary and renal insufficiency (9).

In our published series of 150 high risk patient, we compared ileal conduit vs. colon conduit vs. ureterocutaneostomy (UUCS) (10). The highest intestinal complication rate showed the ileal conduit group with 34.5% the colon conduit group had 5.8% whereas the UUCS group had none of them. The UUCS group showed a 4.8% of stoma complications requiring surgical re-intervention and 19.5% of asymptomatic dilatation grade II following Emment (10). The use of omentum significantly reduced the risk of stoma stenosis. In the last years we prolonged the stent placement until Day 90 after surgery which decreased further stoma complications. In cases of stoma obstruction, mono-1 catheters can be reinserted and changed every three to six months. Stoma correction can be performed later using a buccal mucosa graft.

Final remarks
Quality of life (QoL) is an important outcome in all forms of cancer treatment and takes into account the physical, mental and social well-being of the patient. The goal of QoL, can be achieved through a curative approach, by palliation or in extreme cases through abstention of any therapy. One of the main problems of QoL, is the subjective experience and the difficulty of reproducibility.

However, patients with primary muscle invasive bladder cancer, who also suffer from high competing co-morbidity, rarely benefit from a conservative strategy (10). The high disease specific mortality and the high disease-related complication rate hardly compromise the remaining life span. Therefore, the standard policy in muscle invasive TCC is still RC with lymphadenectomy, which provides the best long-term results (13,18).

Nevertheless, we know that higher age and serious comorbidity were independent indications for abstinence from cystectomy (10). A way to minimize complications in RC is to avoid intestinal surgery. The modified UUCS is an alternative to the standard ileal conduit in high-risk patients as well as in elderly frail patients with bladder cancer. The epidemiologic trend will lead to an increased demand of RC in risky and frail patients. Creativity and innovations are required to face the upcoming challenges.

Ageing population
The western population is ageing and the mean age of cystectomised patient is increasing. Well-established continent diversions are mandatory in younger and healthier patients. For the old and oldest patients a ureterocutaneostomy is a good option and will experience a renaissance, as age alone can not be an exclusion criteria for cure or palliation. However, only simple and reproducible approaches will stand the test of time.

Editorial Note: Due to space constraints the reference list has been omitted. Interested readers can emall at EU7@uroweb.org for a complete listing.

Sunday 26 March 13:30-15:45: Thematic Session 8, Challenges in urinary tract reconstruction
Children born with congenital anomalies of the genitourinary tract receive the highest level of care in their paediatric life. This has led to a dramatic improvement in outcomes. Survival is now regarded as normal – even in the face of major anomalies.

This is as a result of surgical innovation and excellence in specialist centres combined with proactive care (such as intermittent self catheterisation) early in life. Surgical developments, alongside other specialties, such as intensive care have led to a realistic rise in expectations.

Parents and, latterly, patients now anticipate reasonable urinary function and as a profession we aim to offer this. These are combined with expectations relating to sexual and reproductive health. Parents and, latterly, patients now anticipate realistic rise in expectations.

Support with both from the European Society of Paediatric Urology and the European Association of Urology, we have formed a working group. The aim of this group is to promote the care of these patients by contributing to both annual meetings. The potential for further innovation such as joint meetings with specialist groups such as ESGURS, ESAU and ESFFU exists and the work of Prof. Piet Hoebeke and his team in organizing the first joint meeting between ESGURS and the ESFFU in 2015 demonstrated the potential to be found in such projects.

We have welcomed support from the ESPU, EAUL, SIU and BAUS in supporting educational sessions within their meetings. We have collaborated with colleagues, as part of the AUA, and contributed to sessions in the American meetings too.

The value of this is to establish a means by which these teenagers and young adults can receive lifelong care, even if needed. There is no one model that works in all settings. The principles are based on preparation and transition where the child develops their own understanding of their diagnosis, treatment and takes responsibility for their healthcare needs. As they develop this independence, the healthcare relationship shifts away from their parents or carers, taking responsibility to the patient themselves. This can be difficult for a variety of reasons relating patient, parents, politics and finance.

Above all, the service needs energy and expertise from a multidisciplinary team who have dedicated time for these patients. This allows investment and development of the service in the first instance and specialist clinics and surgery in the long-term.

We know that some conditions are vulnerable to late renal failure – these include posterior urethral valves – whilst important, early changes can be subtle and awareness is important to allow detection and understanding risk factors becomes important. Whilst many have worked hard to produce – these outcomes some conditions appear to have complication rates potentially worse than originally published. It is important to emphasise that this is not because of bad surgery – many factors appear to play a part – not least the underlying disease and puberty. However, to take hypoplasias as an example we have no clear understanding about the denominator, standardization of the condition and the surgery. This means that in the current environment it is a huge challenge to produce data that gives the real outcomes for complications such as structure, fistulae and re-operation rates.

Other patients need monitoring following complex reconstruction – looking for factors such as metabolic change, stones and infection. Others will need reconstruction in adolescence and adulthood whilst around 60% of those who have had bowel incorporated into their urinary tract in childhood will need further surgery in adulthood. There is a huge range of potential interest. This is a field that is early in its development and the population of patients needing care will inevitably grow - creating a wide range of clinical and academic opportunities.

Some of the work will involve controversial decisions and thus needs to be dealt with as part of multidisciplinary teams. In some groups the timing and nature of surgery or the increasing development of patient understanding and their own questions around existing standards of care provide clinical, surgical, moral, ethical and intellectual challenges that clinicians must confront.

By definition, paediatric urologists are passionate about these patients and have a strong desire to see that they have good ongoing care. This needs to be comparable to their previous care. Whilst there are pockets of interest – the aim of the working group is to educate and encourage adult urologists to develop an interest in these patients and provide specialist care as part of their practice. We hope that this stimulus will enliven interest in the adult urological community.

In the long-term the working group hopes to see the development of wider academic work, the ability for interested clinicians to communicate and network with similarly interested colleagues. This can only help with providing clinical support for those working in this field and, as a result, improve care for all patients across the board.

Ultimately, with the engagement of a wider group of clinicians all will benefit. In the long-term the development of educational programs, fellowships and guidelines may ensue. We would welcome interest from any clinicians and would be delighted to support those who have interest and aptitude for the care of these patients.

Editorial Note: Due to space constraints the reference list has been omitted. Interested readers can email EUT@uroweb.org for a complete listing.

Sunday 26 March 11:30-11:45: Thematic Session 3, Paediatric Urology
Clinical trials have shown that hexaminolevulinate (HxL) fluorescence cystoscopy has improved detection of bladder tumours compared with standard white-light cystoscopy (WLC), resulting in more efficacious treatment. A meta-analysis of raw data had previously revealed an increase in the detection rate of carcinoma in situ (CIS) by 49%, and there were almost 25% patients with at least one additional T1 tumour identified with WLC only (p < 0.05). Despite improved detectability of bladder cancer with HxL, literature has not reported a beneficial impact on progression or survival of muscle-invasive bladder cancer (MIBC). However, progression is one of the most important clinical outcomes in non-muscle-invasive bladder cancer as it indicates a worsening of disease.

A working group compared the results of HxL- vs. white-light guided TURB and found out that rate of progression was significantly lower in patients in whom a TURB was performed with HxL versus WLC alone. This recently published meta-analysis by Gakis et al. included NMIBC studies published between 2000 and 2016 reporting on progression after HxL- and WL-based TURB. Eligible studies were identified via PubMed search and a manual search of publications in journals not listed in PubMed. The selection excluded non-English articles, non-original articles (i.e. review articles with or without systematic review or meta-analysis), editorials or case reports, studies on non-papillary/bladder tumours, acid (ALA)-based TURB, and repeated publications on the same cohort to avoid publication bias.

Overall more than 3,200 patients studied

The review covered a total of 29 studies, of which five were controlled clinical trials. The majority of patients were included for bladder cancer (74%). The 1,301 patients in these five studies, 49.5% (n=644) after HxL and 50.5% (n=667) with WLC, p = 0.02. Progression-free survival was reported in a single study and was longer after BLC and showed a trend towards increased survival (p = 0.05).

The primary objective of the analysis was the rate of progression due to the fact that a beneficial impact of HxL-guided TURB on progression of NMIBC has not been confirmed in meta-analyses until now. These results may be due to the clinical trials using varying definitions or have failed to define disease progression altogether. Therefore, the International Bladder Cancer Group (IBCG) suggests a new definition that goes beyond the commonly used increase in stage from non-muscle-invasive to muscle-invasive bladder cancer: The largest and most recent publication included in the review re-analysed data of a phase III randomised trial on HxL- vs. WL-TURB with regard to progression using the new IBCG definition.

“This is the first meta-analysis which shows a significant beneficial impact of HxL-guided TURB on progression compared with HxL-guided TURB on progression. Patients should therefore receive hexaminolevulinate-rather than white-light-guided TURB (alone) at their first resection, which might ultimately result in a significant delay of progression to be treated timely and adequately.” Professor Gakis from the Department of Urology, Medical University of Graz, Austria, summarised the result of the review.

Diagnostics with HxL was also associated with decreased risk of recurrence of non-muscle-invasive bladder cancer versus WLC in another recently published meta-analysis. This published data and stratified analysis by use of 5-ALA and HAL. Findings were similar when looking at short-term, intermediate-term and long-term recurrence risk. Efficiency on short-term and long-term recurrence were statistically significant in trials that used HAL, and were not statistically significant in trials that used 5-ALA.

Diagnostic with Blue-light cystoscopy for the first resection

Today, HxL is mentioned and recommended in the majority of Guidelines (Figure 2), including the recently updated American Urological Association (AUA), Association Française d’Urologie (AFU) and Deutsche Gesellschaft für Urologie (DGU) Guidelines from 2016. On November 29th, 2016, during the national meeting of the Association of French Urologists (AFU) in Paris, France, the new 2016 French National Guidelines for the management of Bladder Cancer were presented. The purpose of the Comité de Cancérologie of the AFU (CCAFU) was to propose updated French Guidelines for non-muscle-invasive and muscle-invasive NMIBC bladder cancers. In order to evaluate references and their levels of evidence, a Medline search was been conducted covering diagnosis, treatment and follow-up of bladder cancer between 2015 and 2016.

The new French Guidelines recommend blue-light cystoscopy for the first bladder cancer resection in the majority of patients and for consecutive TURB in nonmuscle-invasive bladder cancer. This facilitates the most rect stress and grading, which is crucial for the optimal follow-up and management of the patient. In contrast to the former version of the Guidelines the new edition includes the situations in which diagnosis with BLC can reduce the risk of recurrence. A cost-effectiveness study applied to the French system revealed a QALY gain (an economic indicator aiming to estimate the value of life) for the use of fluorescence guided TURB with HAL starting with the first TURB of any NMIBC.

According to Morgen Rouprêt, Professor of Urology at the Pitie-Salpêtrière Hospital, University Paris, and one of the authors of the Guidelines, “the strong level of evidence associated with the newest data incorporates into the European Guidelines for the use of blue light cystoscopy will result in an increased in urological care for the management of patients with bladder cancer in France.”

References

Adverse events should also be reported to the Ipsen Medical Information Department on 01753 627777 or medical information@ipsen.com. Hexvix® is the property of Photocure.
Adreno-cortical carcinoma (ACC) is a rare malignancy with an estimated incidence of 0.5–2 cases per million per year. It has two peaks of incidence: the first in the first decade and the second one between 60 and 50 years.

Women are the most frequently affected (55–60%). ACC is associated with poor prognosis, with a 5-year survival rate of 24% for men and 7% for women.

**Proliferation index as Ki-67**

Invasive tumors and metastases may help the clinicians to differentiate low-grade (Ki-67 <10%) and high-grade ACC (Ki-67 >10%) and to guide clinical decision. Indeed, Ki-67 index is a prognostic marker in both localized and metastatic disease.

**Sequence of treatments**

- Surgery and medical treatments to improve oncological outcomes

**Adreno-cortical carcinoma of distant metastases**

- Adjacent organs or venous tumor thrombus in vena cava or hilar nodes, lung, liver and bone.

- Commonly at regional or paraortic/paracaval lymph nodes, lung, liver and bone.

- Usually ACCs are large at presentation, being more than 8 cm in diameter in most of the cases (Figures 1). Haemorrhage and necrosis are often reported; vascular invasion with a tumour thrombus extending into the inferior vena cava (IVC) is not uncommon; metastases are frequently found at the baseline staging, most commonly at regional or paraortic/paraclavicular lymph nodes, lung, liver and bone.

- Gadoinium-enhanced Magnetic Resonance Imaging (MRI) and chemical shift MRI may give the same information as the CTA scan but may better define an eventual neoangiogenesis. Concerning the functional imaging, ACC showed a high 18F-fluorodeoxyglucose (FDG) uptake but the routine use of FDG-PET still needs validation. Recently, the metabolite (18F-MET) proved to be useful in identifying the adenocortical origin of the tumours because it specifically binds to adrenocortical CYPIB1 enzymatic activity, which is a key role in the synthesis of steroids. This new tracer seems to be promising but is still under evaluation.

**Pathology**

Macroscopy revealed a usually large, heterogeneous lesion with a colour surface that ranges from brown to yellow depending on the lipid content of the cell; gross necrosis is virtually always present. Necrosis, microcalcification, invasion of contiguous organs, extra-adrenal tissue, lymphatic or blood vessels are the typical features of ACC. The Weiss score is commonly used: it is composed of three components (three concerning the architecture, the three nucleus and the three concerning any type of invasion). The sum of the positive items (each one scores 0 if positive) defines the final score and a Weiss score > 8 defines an ACC.

**Staging**

Several classification systems have been proposed for ACC: the ENST staging system and the Union Internationale Contre Le Cancer (UICC). The former is based on the tumor size and the presence of any type of invasion. The sum of the points is used for the total staging. Overall survival in patients with stage II was significantly lower than stage I. **Table 1: ENS@T stage classification.**

**Surgery**

Laparoscopic specific techniques are increasingly being used for the treatment of ACC. Several authors have emphasized the importance of the principles of oncologic surgery have to be respected and the threshold for conversion to an open surgery should be low.

**LND**

In a single retrospective study, some authors suggested the need of neoadjuvant chemotherapy (mitotane alone or mitotane + etoposide/cisplatin or etoposide/cisplatin + mitotane) in patients with BRAIC, defined as imaging suggesting a need for multi-organ/vascular resection; imaging suggesting potentially resectable gliomatosis peritonei; and patients having marginal performance status/ morbidities precluding immediate surgery. These authors concluded that the favorable outcome of these patients, despite more advanced stage of disease compared to those treated with surgery as first step, suggests a benefit of neoadjuvant treatment (followed by surgery) in patients with BRAIC.
AUTOCON® III 400
Cutting edge technology for your transurethral treatment
**EAU-RF PRECISION** study recruits ahead of schedule

**Comparing MRI-targeted biopsy to standard trans-rectal ultrasound guided biopsy for the diagnosis of prostate cancer in men without prior biopsy.**

**Study status**

The study is recruiting ahead of schedule with 267 men recruited in 12 months at 28 sites (data correct as of 12 January 2017). Anticipated recruitment end date is October 2017.

**Background**

The classical pathway for the diagnosis of prostate cancer is TRUS biopsy of the prostate following a raised PSA. TRUS guidance is performed primarily for anatomic guidance and the ultrasound discriminates poorly between cancerous and non-cancerous tissue. Biopsies are concentrated in areas of the peripheral zone, which harbours the majority of cancer.

An alternative pathway for the diagnosis of prostate cancer in men with raised PSA is to perform a multi-parametric magnetic resonance imaging (MPMRI) to localise cancer and to use this information to influence conduct of a subsequent biopsy, known as an MPMRI-targeted biopsy. This pathway may offer advantages over the classical pathway.

**Study design**

The study is an international multi-centre randomised controlled trial, with 472 men randomised 1:1 to one of two arms. Men will either undergo TRUS biopsy, or will undergo an MPMRI and targeted biopsy of suspicious areas.

**Hypothesis**

The proportion of men with clinically significant cancer detected by MPMRI-targeted biopsy will be no less than that detected by standard 12-core TRUS biopsy.

**Methods**

Men referred with clinical suspicion of prostate cancer who have had no prior biopsy are randomised to either standard 12-core TRUS biopsy or to an MPMRI arm. In the MPMRI arm, areas of the prostate are scored on a five-point scale of suspicion for clinically significant cancer:

1. Highly unlikely to be clinically significant cancer
2. Unlikely to be clinically significant cancer
3. The presence of clinically significant cancer is equivocal
4. Likely to be clinically significant cancer
5. Highly likely to be clinically significant cancer

Areas scoring 3, 4 or 5 will undergo targeted biopsy, only. Up to three MPMRI-suspicious areas will be targeted with a maximum of 4 cores per patient leading to a maximum of up to 12 cores per patient. Visual registration or software-assisted registration may be used. Pathologic findings from all biopsies will be recorded and compared between arms.

**Primary Outcome**

Proportion of men with clinically significant cancer detected

**Secondary Outcomes include:**

1. Proportion of men with clinically insignificant cancer detected
2. Proportion of men with negative MPMRI who avoid biopsy
3. Maximum cancer core length of most involved biopsy core

**Key patient inclusion criteria**

1. Men at least 38 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy
2. Serum PSA ≤20ng/ml
3. Suspected stage ≤T2 on rectal examination (organ-confined prostate cancer)

**Key patient exclusion criteria**

1. Prior prostate biopsy
2. Prior treatment for prostate cancer
3. Contraindication to MRI or prostate biopsy

**The potential implications of this trial:**

- Introduction of an alternative prostate cancer diagnostic pathway
- A reduction in the number of patients undergoing prostate biopsy
- A reduction in the number of biopsy cores taken per patient
- A reduction in biopsy-related sepsis, pain and other side effects
- A reduction in the over-diagnosis of clinically insignificant prostate cancer

**Funding**

The EAU Research Foundation provides their web-based database management system for collection of patient data and provides all sites per patient recruited funded. The study coordinator, Veeru Kasivisvanathan, is funded by a UK NIHR Doctoral Research Fellowship (DRF-2014-07-146) and UK sites are funded by the NMRC Clinical Research Network.

**Participating centres**

- Argentina
  - Centro de Urología
- Belgium
  - Ghent University Hospital
- Canada
  - Jewish General Hospital
- Finland
  - Helsinki University Central Hospital
- Greece
  - Athens University Hospital
- France
  - Bordeaux University Hospital
  - CHU Lille, University Lille Nord de France
  - Lyon HÉV and Lyon Sud
  - Paris Pitie
- Italy
  - Sapienza University of Rome, Italy
  - San Raffaele Hospital, Milan
- Germany
  - University Hospital Heidelberg
- Netherlands
  - Erasmus University Medical Centre
  - Radboud University, Nijmegen Medical Centre
- Sweden
  - University of Gothenburg
  - Uppsala University, Sweden
  - Basingstoke and North Hampshire Hospital
  - Northwick Park Hospital
  - Princess Alexandra Hospital
  - Royal Free Hospital NHS Foundation Trust
  - University College London Hospitals
  - Whittington Health Trust
- USA
  - Chicago University Hospital
  - Mayo Clinic Rochester
  - Weill Cornell Medical Centre
  - UCS Institute of Urology

*Note: For details on the project, visit [https://uroweb.org/research/projects](https://uroweb.org/research/projects) or contact the author at veeru.kasi@ucl.ac.uk*
Urothelial cancer

How will immunotherapy change the treatment paradigm?

Urothelial cancer, though common, is a very diverse disease. Despite urothelial cancer spent many years as a poor relation amongst drug developers and the pharmaceutical industry with only minimal programs, there are now developing outcomes for patients in the last two decades.

But this is changing. Checkpoint inhibitors have shown clear evidence of activity in this disease and are already impacting on outcomes for some patients. The advent of these technologies brings the opportunity to drive even better outcomes, but also brings the threat of new toxicities and the risk that other active treatments become inappropriately sidelined.

Current paradigm

Advanced urothelial cancer is generally regarded as an inevitably fatal condition where the aim of treatment is palliation and disease control with little or no chance of cure. This is the observation that, even before the advent of immunotherapy, there was a small percentage of patients who were long-term survivors following chemotherapy (von der Maase et al. 2005; Bellmunt et al. 2012).

It is widely acknowledged that a significant proportion of patients will never be suitable for palliative chemotherapy due to comorbidities and performance status and that many of those who do receive chemotherapy suffer significant toxicity with little benefit. Despite relatively high-response rates to first-line chemotherapy, the duration of benefit, for most, is distressingly short, and prognosis after failure of chemotherapy is exceedingly poor. Whilst the broad concept of sequential ‘lines’ of palliative chemotherapy is applied as much to urothelial cancer as other solid tumours.

In urothelial cancer, there are now ongoing phase III trials of anti-PD-1 and anti-CTLA4-based combination chemotherapy which may drive a change in practice whereby the initial treatment of advanced urothelial cancer remains much as it is present but with the addition of mono-agent checkpoint inhibitor for all patients where it is safe to do so (in combination with cisplatin or cisplatin-based regimens and, conceivably, alone for those unsuitable for chemotherapy).

Patient stratification with regards to palliative chemotherapy is relatively simple with three groups defined: those who are suitable for cisplatin chemotherapy, those who are suitable for chemotherapy but not cisplatin, and those who are unsuitable for any type of chemotherapy. By and large, there is no significant group of patients who were not considered for cisplatin chemotherapy as there is, for example, in advanced renal or prostate cancer. The chemotherapy drugs that are used are all broad-spectrum cytotoxics and all, with the exception of vinflunine, have broad application across a range of different solid tumours. As a result, most clinics with capabilities to use chemotherapy will be capable of administering chemotherapy to patients with advanced urothelial cancer and many patients are treated in centres with low volumes of patients with advanced urothelial cancer.

What can we learn from other diseases? (melanoma and lung)

Immunotherapy, in particular the checkpoint inhibitors, is changing the way patients with a variety of advanced solid tumours are managed. They have made their biggest impacts in melanoma skin cancer, where combination anti-PD-1 and anti-CTLA4 therapy has become the mainstream of treatment for those fit enough to receive it (Larkin et al. 2015) and, increasingly, non-small cell lung cancer where anti-PD-1 therapy is now used as a salvage treatment after failure of first-line chemotherapy (Borghede et al. 2015) and in front-line treatment of selected patients (Reck et al. 2016).

In renal cancer, anti-PD-1 therapy is widely used to treat patients who have failed at least one prior tyrosine kinase inhibitor (Motzer et al. 2015). Whilst the treatment paradigms in these diseases are also still evolving, it is likely that the uro-oncology community will learn and adapt from experiences in these other disease areas.

Combination therapy and patient stratification

Data regarding the efficacy of mono-agent anti-PD-1/PDL-1 therapy strongly suggest that there are substantial benefits which are, nonetheless, afforded to only a minority of patients. This is evidenced by the prolonged duration of response seen in only around 20 –25% of patients regardless of line of therapy (Balar et al. 2015a; Balar et al. 2015b; Bellmunt et al. 2016; Galsky et al. 2016; Rosenberg et al. 2016). This contrasts with first-line response rates to chemotherapy of 16 –19% in first-line (von der Maase et al. 2005).

Efforts, so far, to define predictive markers which might allow the selection of patients for primary immunotherapy, or, moreover, those for whom chemotherapy may be a preferable alternative, have failed to deliver a marker which could be used in the clinic. Therefore, current knowledge would suggest that there are risks in the wholesale replacement of primary chemotherapy with mono-agent immunotherapy. Indeed, even in the second-line setting, where, in unselected populations, immunotherapy clearly performs better on average than chemotherapy (Bellmunt et al. 2016), it is possible that some patients would in fact derive more benefit from chemotherapy.

Thus, the inability to stratify patients who should receive immunotherapy and those who should receive chemotherapy is a pressing concern. One solution to this concern could be offer patients combined therapy with chemotherapy and immunotherapy which is delivered either in combination or in a sequential regimen. In urothelial cancer, there are now ongoing phase III trials of anti-PD-1 and anti-CTLA4-based combination chemotherapy which may drive a change in practice whereby the initial treatment of advanced urothelial cancer remains much as it is present but with the addition of mono-agent checkpoint inhibitor for all patients where it is safe to do so (in combination with cisplatin or cisplatin-based regimens and, conceivably, alone for those unsuitable for chemotherapy).

The Immuno-oncology (IO) Tail and urothelial cancer

The checkpoint inhibitors have, to date, had more impact in advanced melanoma than in any other disease. The excitement here is largely generated by a substantial minority of recipients who appear to experience long-term, durable disease control. With mono-agent anti-CTLA4 therapy, it appears that around 20% of patients assume a risk of all-cause death which is little different from that of the age-matched, cancer-free population (Hodi et al. 2010).

When treated with combination anti-CTLA4 and anti-PD-1, the proportion of long-term beneficiaries is even greater (Larkin et al. 2015). Whether this effect holds true in patients with urothelial cancer remains to be seen in long-term follow-up of recent and ongoing trials, but there is already a suggestion that this might also be the case in renal cancer patients treated with anti-PD-1, an effect which was previously well-described in patients treated with high dose Interleukin-2 (Coppin et al. 2015). The long duration of responses seen in some patients with urothelial cancer may be an early sign.

This so-called ‘IO tail’ will impact on the way in which we regard systemic treatment for urothelial cancer. For some patients, at least, the primary objective of treatment will no longer be symptom control, but long-term disease control with the expectation that these patients may die of unrelated causes. The fact that this benefit is only afforded to a minority further reinforces the need for predictive markers, if only to establish the treatment objective for the individual patient.

Long-term treatment

One significant unknown is whether those that respond to checkpoint inhibitors need to continue treatment indefinitely. What is clear is that many patients will be spending longer on treatment than has been the case with chemotherapy for example in the ‘cytotoxic era’. This has significant implications for patients – for some of whom the morbidity associated with long-term treatment will become more significant than that associated with the disease – but also for clinical services which will need to increase capacity to provide treatment.

Toxicity management and service organisation

Immuno-therapy toxicity is dominated by autoimmune events, many of which are tolerable and experience major immune-related toxicities which require a degree of clinical acumen and a high level of awareness if they are to be identified at a point where effective intervention can be made. When managed in the context of broader oncology services, the advent of immunotherapy in urothelial cancer will present no additional challenge (as the issues are no different than for other cancers).

However, where these patients are to be managed in isolation from other diseases, then the clinical challenges associated with diagnosis and management of immune toxicity may be considerable. It is likely that some centres will opt to develop specific ‘immuno-oncology’ services (encompassing the necessary skills and specialisms to deal with the toxicities of these drugs for example gastroenterology, respiratory medicine, endocrinology and critical care) to support the expected tidal wave of use of these drugs across multiple tumour types.

Place alongside stratified medicine

As we get swept up by this important new class of drugs in urothelial cancer, it is important to consider that, for many, there is still high unmet need for better systemic therapies, and we must not allow momentum to be lost in the search for new targets and new drugs in urothelial cancer.

The current focus of drug discovery and drug development is to combine targeted therapy with predictive biomarkers to deliver precision medicine. Whilst it is possible that some patients needs will be completely met by immunotherapy, it is certain that for many they will not.

Trials are continuing to develop precision medicines in urothelial cancers (for example the ongoing development of the fibroblast growth factor receptor inhibitors, or the UK ‘ATLANTIS’ trial (www.clinicaltrials.gov) but also to explore the role of targeted therapies in combination with immunotherapy (for example in the ‘BISCAY’ trial (www.clinicaltrials.gov)).

Beyond advanced disease

The focus of this discussion has been on the immediate applications of immunotherapy inhibitors in advanced urothelial cancer. However, trials are already underway to explore their role in settings other than advanced disease. These include trials in the post-cytoreduction setting, the neo-adjuvant setting, and in combination with radical radiotherapy in muscle invasive bladder cancer and also in high risk non-muscle invasive bladder cancer (NMIBC).

Whilst it is premature to speculate how these trials will change treatment in the future, it is likely that immunotherapy will, in the future, be seen as an additional modality of care (rather than simply as a substitute for chemotherapy) in the multi-modality treatment of urothelial cancer.

Editorial Note: Due to space constraints the reference list has been omitted. Interested readers can email at EUT@uroweb.org for a complete listing.

Sunday 26 March 11.00 –12.30: Thematic Session 6, Changing treatment landscape of renal and urothelial cancer: The impact of immunotherapy

For many patients, there is still a high unmet need for better systemic therapies.

Urothelial cancer
On behalf of the BECG (Andreas Boechle, Maurizio Brandi, Roger Buckeryard, Colombo, Ashish M. Kamat, Donald Lamm, Raj Persad, Joan Palou, Mark Soloway and J. Alfred Wilcox)

It is an inescapable fact that some patients treated with intravesical immunotherapy using Bacillus Calmette-Guerin (BCG) have an ‘enduring response’. However, not all such recurrences are cause for concern and the definition of what truly defines failure of BCG therapy is critical when evaluating patients.

For example, the prognosis of patients with a low-grade recurrence is, as a rule, better than those who develop a high-grade tumour, to the extent that this is considered a ‘non-event’ by regulatory bodies.

What are the factors that we must remember when considering patient management? First, it is essential to verify that the patient has indeed received optimal BCG therapy. BCG therapy must be given with a six-week induction course followed by a three-week maintenance given at 3, 6, 12, 18, 24, 36 and 36 months SSWG maintenance11,12. While other maintenance regimens (monthly or quarterly instillation) have been studied; these have been shown to be no better than induction alone and hence do not constitute optimal therapy12,13.

Next it should be determined as to which category of patients the recurrent tumour belongs. The recommendations stems from the observation when a patient cannot tolerate an induction course or maintenance BCG15.

When we consider this subgroup of patients - the BCG unresponsive category - radical cystectomy is the only treatment option and other treatment strategies are considered inferior13. However, it does allow for consideration of a repeat BCG induction course or intravesical chemotherapy for intermediate-risk (low-grade) tumours14. Similarly, the American Urological Association (AUA) guidelines state that BCG-unresponsive patients should be offered radical cystectomy but if patients have not received adequate BCG treatment, they can be offered either a second induction course or maintenance BCG15.

This recommendations stems from the observation that if a patient has persistent disease after a single induction course of BCG, a second induction course is associated with a 35% response rate17. However, for patients with persistent disease after two or more than two BCG courses - or with progression of disease - there is minimal response expected and the risk of invasive and even metastatic disease outweighs the minimal potential benefit. Thus, if a patient is truly BCG-unresponsive and their high-grade bladder cancer persists after one or two courses of BCG, additional BCG is not recommended.

Current Options

Of course, patients are always seeking alternatives to radical cystectomy, as it behoves us to objectively consider and offer them such options. Prior to offering bladder-sparing therapies, thorough evaluation of the criteria is paramount, including: evaluation of the prostatic urethra and upper urinary tract. Enhanced optical imaging of the urethrum with a combination of indocyanine green (ICG) and near infrared (NIR) imaging should ideally be used to provide for a more complete tumor resection.

Electrodes current administration (EMADMA) enables optimization and deep penetration of chemotherapeutics. EMADMA with mitomycin has been extensively studied including in the pre-TURBT setting, where it was shown to significantly increase disease specific survival22. Other studies have evaluated sequential BCG + EMADMA MMC in treatment-naive T NMIBC disease by data regarding efficacy in this paradigm in BCG-unresponsive patients is lacking. Chemopheratherapy (CHT) is another strategy that has been used with MMC or epirubicin23. In one retrospective report of 111 BCG-unresponsive patients with a median follow-up duration ranging from two to 72 months, CHT was associated with one-year and two-year RFS of 89% and 56%, respectively. Other studies have similarly demonstrated activity for CHT in CIS patients as well as high-grade T stages, with similar efficacy among patients classified as BCG-failures and non-failures6. Thus, results are encouraging.

A large multicentre phase II trial initially suggested that BCG plus IFN-α might be effective in patients with prior BCG exposure. Long term follow-up and detailed analysis eventually demonstrated that among truly BCG-unresponsive patients, the response rate to BCG + IFN-α at 24 months is around 20%, similar to many other agents. Among the IFN paradigm, gene therapy with an adenovirus that expresses an IFN-α gene has demonstrated a 35% 12 month response rate at 12 months in the BCG unresponsive setting17 and is currently being evaluated in a single-arm phase III trial (NC17273349).

Other strategies

Fortunately for our patients, there are several ongoing clinical trials, and more in development, to address the problem of BCG unresponsive disease. These are summarized in our recent review and include studies with immune checkpoint blockade (anti-PD1 agents), growth factor receptor agonists, photodynamic therapy, viral gene therapy, viral oncologic therapy, as well as novel chemotherapeutics and chemotherapy-delivery technology. In addition, there are strategies being developed to enhance the efficacy of BCG itself — for example, BCG intradunal priming to augment responses vs antigen specific memory T cell response will be the subject of the randomized PRIME trial (NCT02736368).

While we remain optimistic and supportive of such efforts, a word of caution is due. These clinical trials must adhere to strict principles outlined earlier and adherence to well-defined disease states, plus well-defined and clinically meaningful endpoints. Otherwise, the results of these trials will result in data that is uninterpretable in the context of not only regulatory approval but especially with regards to benefit for our patients.

References

5. Paljevic L, Lagana P, Millier-Rodriguez F, Hall R, Salvador-Bayer J, Vicente-Rodriguez J. Control group and maintenance demonstrated activity as high-grade immunotherapy by data regarding efficacy in this paradigm in BCG-unresponsive patients is lacking. Chemopheratherapy (CHT) is another strategy that has been used with MMC or epirubicin23. In one retrospective report of 111 BCG-unresponsive patients with a median follow-up duration ranging from two to 72 months, CHT was associated with one-year and two-year RFS of 89% and 56%, respectively. Other studies have similarly demonstrated activity for CHT in CIS patients as well as high-grade T stages, with similar efficacy among patients classified as BCG-failures and non-failures6. Thus, results are encouraging.

BCG-unresponsive bladder cancer

Recommendations from the International Bladder Cancer Group (IBCG)
Cancer of the prostate is a leading cause of cancer death in men worldwide. While localized prostate cancer is highly curable, nearly all patients with metastatic disease progress to castration-resistant prostate cancer for which there are presently limited treatment options.

There is a high need to develop selective, context-dependent therapeutic strategies to manage metastatic prostate cancer. The identification of the pathways that drive a specific tumor cell to disease progression and metastasis is an important step in developing more effective treatments based on the tumor molecular and biological characteristics.

E6 transformation-specific (ETS) transcription factors constitute a family of signal-dependent transcription regulators with important roles in cell differentiation and carcinogenesis. The ETS gene family includes 28 members in the human genome. ETS factors share dimerization properties and recognize similar ETS binding motifs in the promoter regions of their target genes. Nevertheless, individual ETS factors activate or repress transcription of a large number of genes.

Furthermore, ETS factors interact with distinct protein partners inducing transcription and biological responses. These differences among ETS factors contribute to their specific properties and regulatory functions and are reflected in their diverse roles in tumorigenesis. In normal development, the ETS transcription factor ERG has a critical role in the formation of the vascular system, urogenital tract and prostate. ERG is also expressed at high levels in embryonic neural crest cells during migratory phase.

ERG expression regulates the pluripotency of hematopoietic stem cells, endothelial cell homeostasis and angiogenesis. In the adult mouse ERG is expressed in endothelial tissue including adrenal, cartilage, heart, spleen, lymphatic endothelial and eosinophil cells. ERG has been shown to have a major role in cell response to vascular inflammation and cell adhesion, normal homotypic cell-cell function and the maintenance of normal peripheral blood platelet numbers.

Gene rearrangements involving ETS are very frequent in prostate cancers. These events link the ETS gene to the promoter of the androgen-regulated gene TMPRSS2. This mechanism for overexpression of ERG in androgen-stimulated prostate epithelial cells. Aberrant overexpression of ERG due to the TMPRSS2 translocation in prostate epithelial cells, a cell context inappropriate for ERG expression, results in significant alterations and broad transcriptional reprogramming.

However, more than 10 years after the discovery of the TMPRSS2-ERG gene fusion and the role of ERG and EZH2 in prostate cancer progression, there is limited understanding of how these interactions may cooperate to fully exert its oncogenic effects and differentiation program. More recent work highlighted the important role of ERG ability to interact with other epigenetic and transcriptional regulatory proteins, such as the epigenetic effector BRD4 and the RNA helicase and translation initiation factor EIF4G2. Notably, the discovery of this complex ERG interface, along with our novel finding of the ERG/EZH2 crosstalk, opens new opportunities for understanding the molecular mechanisms of ERG induced oncogenesis and for development of targeted therapeutic strategies to reverse prostate cancer progression.

Collectively, our data provide advanced understanding of the epigenetic network connected with TMPRSS2-ERG gene fusion and the role of ERG and EZH2 in prostate cancer progression. Importantly, these findings define a therapeutically actionable pathway, modulation of EZH2 and BRD4 that would be expected to have broad impact on the treatment of ERG-positive prostate cancer.

References
New Endoscopic Stone Treatment

EST-s1: A “Made in the EAU” novel basic training curriculum for endoscopic stone therapy

Dr. Domenico Veneziano
Member, EAU Working Group
Endourology & Urolithiasis
Ospedali Riuniti
Dept. of Urology & Kidney Transplant
Reggio Calabria (IT)

The last few years have seen a fast growth in the field of urological education and simulation, particularly with the aid of hands-on training. In 2013, the E-BLUS exam was delivered for the first time during the European Urology Residents Education Program (EUREP). This year, we are finally ready to deliver the novel EST-s1.

E-BLUS, the renowned basic laparoscopy exam, was born from an analysis and integration of the American FLS (Fundamentals of Laparoscopic Surgery) project. In time, the curriculum was slightly modified to meet the specific needs of urology. Over the last few years, E-BLUS has spread the European teaching standards to even outside European borders, reaching as far as Indonesia and beyond.

With a recent surge in endourology and stone treatment, a development of dedicated protocol-based training and assessment relating to endourological techniques was essential. As opposed to E-BLUS, the EST-s1 (Endoscopic Stone Stone Treatment) step 3 protocol has been completely developed in the European Association of Urology, under the coordination of the European School of Urology (EUSU) and the EAU Section of Urolithiasis (EULIS). The team involved experts in simulation and stone treatment: Domenico Veneziano, Bhaskar Somani, Kamran Ahmed, Alberto Breda and many others. The “full life cycle curriculum development” template, as described by Richard Satava was followed along the process, which started in 2014 with a Cognitive Task Analysis of the RIRS (Retrograde Intrarenal Surgery) procedure, performed by the VNUWP (Young Academic Urologist Working Party) Endourology & Stone Treatment group. This initial research, based on a broad literature review, was the solid base behind the development process.

EST-s1, as suggested by its name, is the first of a series of courses to focus on the specific skills of endoscopic stone treatment: navigation and basic use of the operative channels. After several consensus meetings and test sessions, the preliminary trials took place in Athens, during the EUTedH congress. Data collection for validation took place during EUREPVI in Prague and involved 134 participants with different expertise. All trials have been DVD-recorded for re-evaluation and quality feedback sheets have been used to score several aspects of the procedure.

The training curriculum is composed of four tasks: a) navigating the stone, b) detecting the stone, c) localising the stone, and d) removing the stone. The four tasks are presented to the trainee in a standardised fashion. The ability to master all four tasks has to be demonstrated before a trainee can pass the EST-s1 validation.

During this congress, while the first official exam validation took place in Athens, during the EUTedH congress, the EST-s1 curriculum was approved by the EAU Education Program (EUREP). This year, we are finally ready to deliver the novel EST-s1. As suggested by its name, the curriculum is the first of a series of courses to focus on the specific skills of endoscopic stone treatment: navigation and basic use of the operative channels. After several consensus meetings and test sessions, the preliminary trials took place in Athens, during the EUTedH congress. Data collection for validation took place during EUREPVI in Prague and involved 134 participants with different expertise. All trials have been DVD-recorded for re-evaluation and quality feedback sheets have been used to score several aspects of the procedure.

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Assessment has been designed to rely not only on time taken, but also on a questionnaire on the quality of trainee performance, to be filled out by the proctor. Based on the literature research made upfront, the examination sheet contains a list of critical aspects related to basic endourological skills, such as positioning and use of the scope, handling the access sheath, and correct navigation based on technical needs. All tasks will be available for hands-on training sessions during this congress, while the first official exam session is planned for September this year, during the EUREPVI course.

With step 2 already in the works, we are sure that the EST-s1 curriculum will allow once again the sharing of surgical standards, contributing to an improved educational system for residents and better healthcare.

ADVERTORIAL

New Compact SWL Solutions for Urological Workstations

STORZ MEDICAL presents a new versatile lithotripter: The MODULITH® SLK »intelect«

Since more than 25 years STORZ MEDICAL is enhancing the technology of shock waves. With the new compact MODULITH® SLK »intelect« a lithotripter has been developed which can be perfectly adapted to different imaging modalities and used away from the urological workstation and be stored without using much space. The MODULITH® SLK »intelect« allows easy future updates at any time.

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The versatile shock wave solution.

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In combination the superior image quality of the workstation’s X-ray can be used for localising the stone and in-in X-ray control of the therapy success during the treatment.

After the therapy the lithotripter can easily be moved away from the urological workstation and be stored without using much space.

The MODULITH® SLK »intelect« is the ideal complement to urological workstations like the PRIMERA ST360®.

LITHOTRACK® Navigation System

LITHOTRACK® is an optical navigation system comfortably linking the MODULITH® SLK »intelect« to an urological workstation, C-arc or ultrasound device. The navigation up to a high-end setup with LITHOTRACK® and budget, from the economic solution without mechanical modifications for localisation. Virtually no installation is necessary and to correctly manoeuvre the cystoscope.

After Task 2, the safety guidewire is left in one of the ureters. Task 3 consists of simulating a semi-rigid ureteroscopy, with a working guidewire placement. This task ends with a successful placement of an access sheath. Task 4 takes place on the K-Box, a low-fidelity simulator designed by Olivier Traver, and tests trainees’ ability with the flexible ureteroscope. The original K-Box was slightly modified to correctly meet the assessment requirements. During the task the scope needs to be navigated to 10 numbered pre-marked points in the simulator, mimicking rotation, deflexion and in-out movements, in a standardised fashion.

Since more than 25 years STORZ MEDICAL is enhancing the technology of shock waves. With the new compact MODULITH® SLK »intelect« a lithotripter has been developed which can be perfectly adapted to different imaging modalities. The device features a fully motorized positioning of the therapy source making it easy to set up the lithotripter or to target stones in the urinary tract.

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LITHOTRACK® is an optical navigation system comfortably linking the MODULITH® SLK »intelect« to an urological workstation, C-arc or ultrasound device. The set-up of the lithotripter in combination with an X-ray system and the focus adjustment during the therapy are assisted by this navigation system. Once the stone is visualised, it only has to be marked in the ultrasound image and the automatic positioning system LITHOTRACK® moves the shock wave focus on the stone for the treatment. The same smart function works with X-ray systems as well.

The Lithotripsy Module for C-Cars

The MODULITH® SLK »intelect« in its basic version can be combined with several surgical C-Cars and OR-tables with lateral cut-out. The motorised movements of the therapy source facilitate the focus alignment for a fixed therapy head position. In-line ultrasound can be used for targeting radiolucent stones.

The MODULITH® SLK »intelect« can optionally be linked to C-Cars and ultrasound device via the optical navigation system LITHOTRACK®. This version allows maximum flexibility in set-up and use. No dedicated table is needed to perform a SWL, normal surgical OR-tables are sufficient.

Smart Features

The lithotripter can be folded easily to a space saving transport position for storage or transport. Safe and simple handling is ensured through the integrated brake which fixes the device securely for operations. The integrated focal gauge allows re-aligning the system or checking the focus alignment within seconds. It's appealing design was already awarded twice, once by the International Design Award and latest by the iF Design Award.

Economic Solution

The long service life of the proven shock wave technology of the MODULITH® SLK »intelect« allows easy future updates at any time. The lithotripter can be configured according to needs and budget, from the economic solution without navigation up to a high-end setup with LITHOTRACK® navigation system. It can be used with C-Cars and urological workstations like the PRIMERA ST360®.

The MODULITH® SLK »intelect« - Great flexibility has never been so easy.

Olaf Gleibe
Department Manager Urology
Male contraception: Where are we going?

Future genomics can lead to new and innovative fertility products

testosterone alone showed that it is very effective with few adverse effects. Addition of a progesterone synergically increases the rate and extent of suppression of spermatogenesis. However, the fact that superovulatory testosterone levels are necessary to achieve the desirable suppression of spermatogenesis has raised concern over the long-term effects of contraception on men’s health, especially as concerns the cardiovascular system and prostate associated morbidity. The focus of MHC development in recent years has been the development of novel androgens that may be more potent than testosterone in the suppression of gonadotropins and with fewer potential side effects.

The ideal steroid for therapeutic androgen replacement would be a potent testosterone agonist that does not undergo 5α-reduction to DHT but can be aromatized to an estrogen. In this regard, the synthetic androgen, 5α-dihydrotestosterone (DHT), has been developed. MENT cannot be δα-reduced to dihydrotestosterone like steroids and may have less stimulating effects on the prostate gland. Initial studies using MENT as an implant in men showed very effective suppression of spermatogenesis with four MENT implants.

Another androgen, dimethandrolone undecanoate (DMAU), is being developed as an oral preparation as well as an intramuscular injection. In the body, DMAU is converted to dimethandrolone (DMA) which is the active entity. In in vitro studies, DMA showed dose-dependent androgenic and progestational activities. The dual activities on the androgen and progesterone receptors may create a single agent capable of suppressing spermatogenesis while maintaining androgenic activity in men. A single-dose escalation study in healthy male volunteers has shown that DMAU appears to be a safe and well-tolerated contraceptive agent.

Role of anti-androgens

Cyproterone acetate (CPA), an antiandrogen with progestational action, in men, CPA has been widely used for the treatment of hypersexuality and prostatic cancer. Moderate dose cyproterone acetate (CPA) induces progestational/anti-gonadotropin effects at the hypothalamic-pituitary level in addition to its antiandrogenic action at the testicular level.

Addition of cyproterone acetate to testosterone is considered effective to suppress spermatogenesis and is based on the hypothesis that the synergistic action of these compounds can induce a more profound suppression of gonadotropins than either compound administered alone and that cyproterone acetate can act directly at the gonadal level to block the stimulation effect of androgens on spermatogenesis.

Role of pregestins

Nortestosterone is a potent pregestin that has minimal Androgenic or estrogenic activity. Nortestosterone applied transdermally has been used in combination with testosterone gel for hormonal contraception clinical trials in men. In a six-month study, a combined gel (testosterone 200 mg/day and nortestosterone 8 mg/day on skin) suppressed sperm output to <1 million/ml in 89% of men compared to 29% of those who applied placebo gel alone. There were minimal adverse effects.

Role of GNRH analogues or GNRH antagonists

There are two different approaches to male contraception that are presently based on two distinct types of derivatives of luteinizing hormone releasing hormone (LHRH), the antagonistic and agonistic analogues. GNRH agonistic analogues were originally developed as longer acting therapeutic agents to treat GNRH deficient patients, and given chronically, they had paradoxical inhibitory action on LH and FSH secretion. GNRH antagonists, block the pituitary GNRH receptors, and have been shown to be among the promising additives to testosterone. The overall effect of the administration of either GNRH agonists or GNRH antagonists on male reproductive tract is the development of azoospermia. However, the requirement of daily or weekly injections and the high costs of the currently available preparations have hindered the further development of GNRH antagonists for hormonal male contraception.

Non-hormonal contraception methods

Non-hormonal targets of contraception include sperm production at the testicular level, sperm maturation at the level of epididymis and development of sperm motility. Selectivity, specificity and lesser side effects compared to hormonal methods make these approaches attractive as non-hormonal contraception methods.

The ultimate goal of MHC is to reduce the number of sperm in the ejaculate so drastically that it is impossible to achieve fertilization. Studies using Gossypol is a compound found in cotton seed oil. Effectively suppresses spermatogenesis. In a clinical study carried out in China, gossypol rendered 98.5% of volunteers infertile at an oral dose of 20 mg per day for 75 days as the initial dose, followed by a maintenance dose of 15-50 mg per week, but its effects are not consistently reversible, and it causes hypokalemic and myopathy.

Immunization

GnRH vaccination involves the injection of GnRH conjugated to a foreign protein such as ovalbumin, and combined with an adjuvant, to induce anti-GnRH antibody formation. The antibodies bind to endogenous GnRH within the hypothalamic-pituitary-gonadal axis and prevent the release of GnRH on the pituitary gonadotropes, thereby removing the stimulus to gonadotropin secretion. As a result, they decrease steroid hormone secretion and reduced spermatogenesis in the male.

Spermaticgenic germ cell-specific proteins

Several agents that inhibit the sperm-specific or testis-specific targets have been identified and studies in animals have shown promising results. To date, however, most methods are still in experimental stages, since both toxicity and reversibility data are discouraging. Bromodomains, testis-specific (BRDT) is a tissue-restricted, chromatin-associated protein expressed in spermatozoa and round spermatids. The feasibility of targeting human BRDT with acrylamide peptidomimetics (12), which blocks the interactions of bromo and extra terminal (BET) proteins (BRD2, BRD3, BRD4 and BRD7) with histones has been tested. Sperm-specific calcium channel inhibitors (13) are short-term in vivo pharmacological inhibition with calciuncin inhibitors (cyclosporine A or FK506) leads to complete male infertility, with reduced sperm motility owing to an inflexible midpiece during sperm maturation in the epididymis. Inhibitors of sperm-specific calciumion could act on male fertility both effectively and reversibly because inhibition of PPIF/JC/PPR2 targets spermatozoa in the epididymis.

Manipulation of cellular junctions in the seminiferous epithelium

The testis is a unique organ with complex junction arrangements in the seminiferous epithelium. Cell junction dysfunction in the seminiferous epithelium is one of the many causes of male infertility. Recent findings in different animal models support the hypothesis that cell junction may be one of the prime targets for male fertility regulation. Adjulin, for example, a compound able to perturb cell-cell adhesion in the seminiferous epithelium.

The epididymis as a contraceptive target

When the maturing spermatocyte leave the testis, they are non-motile and unable to fertilize the oocyte in vivo. Their full maturation, including potential to display motility, takes place during transit through the epididymis. The use of small molecule pharmacological inhibitors to target epidydimal proteins necessary for the sperm maturation process represent an attractive choice for non-hormonal male contraception. Despite the existence of multiple potential epidydimal targets, the major difficulty in delivering the drugs to epididymis is represented by the blood–epididymis barrier.

New and innovative products will come from our knowledge of the unique physiology and genetics of reproduction, as well as by exploiting existing and future genomics, proteomics and protein network platforms.

Saturday 25 March
09.45-10.00: Plenary Session 2, Hot topics in Andrology
Testosterone therapy in men with prostate cancer

Long-term safety is uncertain but TRT is an option for well-informed patients

**Testosterone replacement therapy**

Testosterone replacement therapy after curative-intended treatment

It is intuitive to state that if the patient is cured from his PCa, i.e., the patient does not harbor any cancer cells, then TRT is as safe for the man with previous PCa as it is in any other man. However, a considerable proportion of men, undergoing curative treatment (radiotherapy or radical prostatectomy) will have residual disease. For these patients it is unknown if TRT affects time-to-metastatic disease or cancer-specific survival.

Only a few studies have addressed this issue and the available studies have all been small with short follow-up. One cohort study reported on 83 hypogonadal men undergoing TRT after radical prostatectomy and found no increased risk of PCa recurrence compared to age-matched men. Both men with high and low-risk PCa were included in the analyses. A second retrospective study of 7 hypogonadal men with mainly low-risk PCa (4 men had Gleason 8–10) treated with radical prostatectomy and subsequent TRT found no increases in PSA during a median follow-up of 18 months from TRT commencement. Similarly, no increased risk of disease recurrence has been demonstrated after radiotherapy in the currently available small retrospective cohort studies. However, TRT seems contra-intuitive after radiotherapy at least in men with locally advanced PCa. In this setting there is some evidence demonstrating improved survival when combining androgen deprivation therapy with external beam radiotherapy.

“The long-term safety of TRT is uncertain. Current evidence does not support an association between high levels of endogenous serum testosterone and the risk of developing PCa."

**References**


**Editorial Note:** Due to space constraints the reference list has been shortened. Interested readers can email us at communications@euroweb.org to request for the full list.

**Saturday 25 March**

**Plenary Session 2, Hot Topics in Andrology**

**Badder EpiCheck**

Epigenetic Bladder Cancer Detection with Superior Performance

A Test Urologists Can Act Upon

Visit us in booth A07 and win an iPad
Dornier Delta III blends the proven Delta lithotripter concept with new elements to optimize lithotripsy and workflow.

- New EMSE with shockwave penetration depth of 170 mm
- OptiCouple® for higher efficiency
- Optimized outline isocentric ultrasound arm
- Powerful X-ray
Today’s European Urology Events

Social Media Course

- Introduction by Jim Catto
- Source for scientific research by Stacy Loeb
- Dissemination of content by Stacy Loeb
- Measurement & Analytics by Hendrik Borgmann
- Reputation Management by Matt Cooperberg
- Guidelines in the use of social media by Inge van Ooort
- Interaction with patients - discussion

To be held in room 13 from 11.45 - 14.15

Surgery in Motion

- Male cystectomy
- Female cystectomy
- Ileal conduit
- Neobladder

March 26th

- Peter Wiklund, Stockholm (SE), Jim Catto, Sheffield (GB), Alex Mottrie, Aalst (BE), Joan Palou, Barcelona (ES)
- To be held in Room Copenhagen, North Hall (Level 1), 10.45 to 12.45

Platinum hour

- To be held at the European Urology booth #B02. Daily from 17.00

We would like to invite you to attend the Platinum Hour drinks reception to meet and greet the Editors, Authors and Reviewers of The Platinum Journal. Please join us daily to toast the success of European Urology, “Your” Platinum Journal.
Bladder cancer is the ninth leading cause of cancer in the world, being a common disease in Europe, North and South America and the eight leading cause of cancer death1. While most cancers have an incidence that is increasing or decreasing, bladder cancer has a very stable epidemiology in incidence and mortality2.

Another data that does not evolve over time is the tumor stage at the time of the diagnosis, with some data showing that non-muscle-invasive bladder cancer (NMIBC) remaining the most frequent (80%) as compared to muscle invasive disease3. The main risk of NMIBC is recurrence which occurs up to 60% of patients within five years of the primary tumor resection. On the medicoeconomic–level, this translates into a high cost of care4, and impairment of quality of life with a psychological impact5.

The decreasing recurrence rate should therefore be the main objective in the management of NMIBC. This depends on the histologic–prognostic group that determines the rate of endoscopic monitoring and the indication of an adjuvant treatment that includes chemotherapy (MMC) or BCG intravesical therapy6. Today, urololgical societies recommend adjuvant treatment by intravesical instillation for intermediate and high-risk patients. For both groups, randomized studies have confirmed the superiority of BCG therapy as long as the induction course continues with maintenance7. The alternative in case of contraindication or intolerance is intravesical chemotherapy8. In the absence of maintenance with BCG, treatments are comparable, with a risk of recurrence equivalent to 50 to 66% at two years.

Despite recommendations, it is estimated that 30% of patients will not be treated9. The non-prescription factors are numerous; they include the reluctance of the practitioners to carry out the treatment for fear of complications, lack of confidence in BCG efficacy, financial issues given the low valorization of BCG instillations. Another non-prescription factor is the refusal of the patient to receive treatment that requires repeated weekly instillations and exposure to serious adverse events.

Previous studies have shown that non-prescription or discontinuation of treatment is a factor in recurrence with significant socio-economic consequences10; the cost of recurrence or progression of cancer being much higher than the cost of bladinstillations11.

The effectiveness of adjuvant therapy for bladder cancer is even more impaired by the poor adherence and adopted timing to start bladder instillations. At the level of a urological unit, this means that a dedicated nurse will have a central role to informing the patient, organizing and delivering treatments, and detecting adverse events. In our case, a meticulous monitoring considerably decreased the rate of treatment drop-out and grade III toxicity.

Patient selection
Apart from patients with allergies or with a contraindication to BCG therapy (persistent hematuria, active tuberculosis, history of complication with BCG therapy) and for whom conservative treatments must be adapted, patients at very high-risk of progression must be rapidly identified and oriented towards radical treatment12. Several BCG regimens have been tested in randomized studies, including the decrease of BCG dose or the introduction of nonbacillus to our immunotherapy2. Several recently the rate of instillations and types of maintenance treatment13-15. The NIMBUS study, published by the EAU research foundation, proposes the reduction in the number of instillations, keeping the general schedule of induction and one-year maintenance16 (Figure). The hypothesis of this study is that the supression of instillations of weeks 3,4,5 during induction and of week 2 during maintenance does not alter the frequency of recurrence.

We believe this is an important study for several reasons: a reduction in the number of instillations will improve tolerance and therefore treatment adherence; this treatment will be prescribed and followed by a greater number of patients. On the other hand, in the current contex of BCG shortage a decreased number of instillations will improve our capacity to treat a larger number of patients, and finally, this European study is a good opportunity for a new cost efficacy study.

References
11. Shahin, O., et al., A retrospective analysis of 63 patients with non-muscle invasive bladder cancer...
Communication between patients and health professionals is one of the most important aspects of the support given to the patients and contributes to the high quality of healthcare.

This fact has led to the introduction of courses at medical schools and universities to improve the communication skills of medical students. Future physicians learn techniques in listening, explaining, questioning, counseling, and motivating. Compared to previous decades, patients today are less passive than 50 years ago. They want to be informed, they play an active role in their health process, they use the internet to seek medical information about their symptoms, illness, etc. But still there are things that patients do not ask or do not dare to ask their doctors. The question is not only what they do not ask the doctor but why.

As a clinical nurse specialist, I am a contact person for patients. It happens very often (almost daily) that patients call me the day after the consultation with the urologist to ask things they didn’t ask to the doctor. When I question them about the reason not asking the doctor, I hear several reasons, such as:

• After the consultation with the urologist the patient realized that he/she should have asked more details. It could be about the diagnosis, treatment or about results of the pathology report.
• Patient’s perception of the physician’s being rushed or busy.
• The information given by the urologist is misinterpreted by the patient;
• A medical treatment or surgery was proposed to the patient but the consequences or side effects of the treatment were not clear to the patient. In case of minor surgery or prostate biopsies, the procedure and the possible complications were vague to the patient; and
• The patient didn’t understand/forget the information given by the urologist about a new prescription.

Patients remember about 20% of the verbal medical information the physician gives2. Different reasons could explain this issue: the physician use medical terms the patient does not understand, the mode of information given (spoken or written) and factors related to the patient such as low level of education3. But since patients are more confident and become more active or involved in their own health issues, the physician gives more and more information.

The patient cannot assimilate the great amount of information given during the consultation. It is also difficult for the patient to have an objective view of a situation that involves him directly. Emotion and stress play an important role during the consultation and the level of distress increases if the physician makes a wrong impression; hence patients will remember less information1.

Older adults have more difficulty to encode and remember medical information and their memory also fades more rapidly. We have to consider this fact that majority of urology patients are older than 70 years.

Consultation hours

To help patients to remember the information, we can invite the patient to record the conversation with the doctor, which is now very easy with a mobile phone. Or the physician can give written information to complete or support the spoken information given. Patients often indicate that the reason for them not asking the urologist is the impression they have that the doctor was too busy or there is the lack of consultation’s time. The average visit length for general practitioners is between five to eight minutes4 in Great Britain and 10 to 20 minutes in Sweden5.

Visit length can vary by specialist. A new patient visit with an internet takes between 29 and 27 minutes and a follow up visit between 19 and 36 minutes.

Patients are satisfied when they estimate the length of the visit < 20 minutes. In the institute where I work, the visit length for new patients is 20 minutes for the urologist and for a follow-up visit, 10 minutes. When patients complain over the fact that the urologist was too busy or had to rush, it concerns usually follow-up and routine visits. They indicate that the time they have is too short for asking questions. I am convinced that the solution is not in giving more time for each patient but in making consultations more efficient, thanks to a time management course for doctors.

There are some disturbing factors as a phone call to the urologist during the consultation. It is very annoying for the patient when the conversation with the urologist is interrupted by a phone call. Another disturbing factor could be the attitude of some physicians during the consultation. Some physicians are so busy to type in the digital file that there is no eye contact with the patient. This attitude doesn’t encourage patients to ask questions.

In addition, there are things patients don’t dare to ask the doctor. It concerns psychological needs or the use of complementary and alternative therapies. Patients very often think that doctors are disinterested in psychological matters and only talk about medical matters. Patients talk easily with the nurse about non-medical matters. Nurses play a unique role by monitoring patients and can provide psychological support in adult oncology patients6. More and more hospitals or institutions have understood this unique role of nurses and provide nurse consultations beside the doctor consultations.

A bridge

Nurses are a privileged interlocutor. Patients often do not dare to say that they use natural products or complementary therapies to their doctor, but dare to tell the nurse. Seventy-five percent of cancer patients using complementary and alternative medicine (CAM) do not inform the physician about their CAM use7. It could have some serious consequences, as we know that that some herbal remedies or vitamins interact with traditional medications. For example, there are possible harmful interactions between vitamin C and anticoagulants and contraceptives. Furthermore, the physician and the nurse should know the scientific evidence of natural products and vitamins8.

Other factors which can influence the patient not asking the doctor are:
• Uncomfortable or intimate subjects in the presence of a conjoint or accompanying person, as the patient didn’t understand what the doctor said and didn’t dare to ask more explanations.

Patients come very often to the doctor with an attendant. The accompanying person gives support to the patient during the consultation, can ask questions but your person present can influence the communication between the patient and the doctor. Patients then don’t dare to ask the doctor particularly about sexual issues or uncomfortable subjects.

Finally, without paying attention the doctor can use medical jargon the patient does not understand. It happens that the patient doesn’t dare to ask what the doctor means. As healthcare providers we have to be careful to use vocabulary the patient can understand.

In conclusion, the doctor still has to make efforts to improve the communication with the patient to encourage the patient to ask questions. At the end of the consultation, it is often sufficient to just ask patients if everything was clear, or if they have other questions. With the permission of the physician the patient can record the consultation. Doctors and nurses have complementary roles with regards the communication with patients, and they can both motivate patients to ask questions.

References
7. Quilliam, Susan (April 2011). “The Cringe Report”: why patients don’t dare ask questions, and what we can do about that.” Fam Plann Reprod Health Friday, 24 March
8. Patients still have to make efforts to improve communication with the patient by encouraging the patient to ask questions.

EUT Congress News

Overcoming obstacles in patient communication

Things patients do not ask or do not dare to ask their doctors

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Current issues in urological nursing care
Changes in urological nursing include diversity in roles and practices

Nursing is evolving at an accelerated pace. In some countries this is happening more quickly than others and the EAUN is making sure that it can encourage and support advanced nursing practitioners at the forefront of change as well as the many urological nurses undertaking more traditional roles.

It is now seen in many countries as ‘normal’ for urology nurse specialists to undertake advanced practices in diagnostics such as urodynamics, flexible cystoscopies and transrectal and transperineal biopsies. As well as developing nurse-led follow-up in outpatient clinics, and treating patients using flexible laser cystoscopy, intravesical therapy and port insertion in laparoscopy.

This collaborative session at the EAUN conference will describe nursing developments in many areas of urology using presentations from the British Association of Urology Nursing (BAUN) in the UK, Denmark and the Netherlands.

The majority of healthcare models endorse collaborative approaches to delivering care to patients and multidisciplinary team-working is accepted as the gold standard in the majority of specialties.

As each different discipline (surgeons, pathologists, radiologists, nurses and allied healthcare professionals) bring its own unique skill set, the effect of each individual is cumulative, so that ‘The whole is greater than the sum of its parts’ and the patient benefits as a result. There is also increasing evidence that nurses bring a different dimension to patient care that other clinicians are unable to provide, as nurses are more holistic in their approach to a patient’s problems.

This is amply demonstrated in a UK initiative discussed in the session which prepares patients better for survival after cancer treatment. The “Recovery Package” aims to identify all the patients’ needs that develop either as a result of the cancer or as sequelae of the cancer treatment that has taken place. These holistic needs are assessed by the specialist cancer nurses during various stages of a patient’s treatment pathway and then are addressed in a timely manner, allowing earlier discharge to primary care.

National concerns

Most of us have our own national concerns with regards to healthcare, economic constraints, workforce shortages and an increasing demand in patient activity. Assigning nurses in advanced roles can be cost-efficient, effective, patient-centred and provide much needed continuity of care to patients. But nurses undertaking these roles still need the support of urological colleagues and work in a department that encourages innovation and the attainment of high standards.

Realising the important contribution that nursing makes to urology, the Secretary General of the EAU and the EAUN launched the Plus One campaign to promote membership of the EAUN; an initiative to encourage every department across Europe to support urological nurses in their locality by sponsoring at least one urology nurse in their department to become a member of the EAUN.

The main reason behind this was that although the EAU membership across Europe was very varied. But slowly by exemplary leadership, by setting attainable standards and by publishing evidence-based guidance, urological surgery has grown from strength to strength across all countries of Europe. Urology nursing, however, is in a similar situation to urological surgery decades ago. There often appears to be diversity in roles and practice in different European countries. Encouraging a nurse from each department to join the EAUN would allow the standardisation of urological nursing within the EU and nursing innovation to be shared more easily and more quickly through the regions. We welcome you to the collaborative EAUN-BAUN session to get a glimpse of what are the current issues in Urological Nursing and what is achievable with a bit of vision, support, enthusiasm and hard work.

Sunday 26 March

16.30 – 17.30: 18th International EAUN Meeting, Thematic Session 3: Joint EAUN-BAUN session: Current issues in urological care

Location: Room 1 (Level 3)
TOOKAD®
Vascular Targeted Photodynamic Therapy (VTP)

Symposium Chairman  Prof. Nicolas Mottet (France)

Should we treat Gleason 6 prostate cancer?

Data on phase 3 pivotal trials of TOOKAD Soluble vascular-targeted photodynamic therapy versus active surveillance in men with low-risk prostate cancer

PCA guidelines on focal therapy: where are we in 2017? What do we need?

Technical aspect of VTP surgery

Introduction into mechanism of action of vascular-targeted photodynamic therapy – TOOKAD Soluble

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