Medicom International Conference Series in Urology

34th EAU Congress

European Association of Urology

15-19 MARCH 2019 • BARCELONA • SPAIN

PEER-REVIEWED CONFERENCE REPORT

Prostate Cancer
Enzalutamide reduced the risk of death and radiographic progression-free survival vs placebo in the PREVAIL study of patients with asymptomatic metastatic castration-resistant prostate cancer.

read more on PAGE 3

Bladder Cancer
A haematuria risk score offers good discriminatory accuracy, which is superior to existing guidelines. Pending further validation, the haematuria cancer risk score may become mainstream in primary care and urology clinics.

read more on PAGE 6

Urinary Tract Carcinoma
The largest prospective clinical trial of immunotherapy in advanced urinary tract carcinoma (SAUL, phase 3b) demonstrated that atezolizumab is a tolerable and effective treatment, even in complex comorbid populations.

read more on PAGE 12

MEDICOM MEDICAL PUBLISHERS

Editor Prof. Frank Van der Aa, University Hospital Leuven, Belgium

Contents

COLOPHON

Editor	Prof. Frank Van der Aa University Hospital Leuven, Belgium
Advisory Board	Prof. Axel Merseburger University Hospital Schleswig-Holstein, Germany
	Dr Saeed Dabestani Lund University, Sweden
Publishing Director	Paul Willers
Editorial Manager	Lisa Colson
Editorial Coordinators	Dr Joery Goossens Sanne Lauriks
Medical Writer	Dr Rachel Giles
Production Manager	Desiree Heijl
Graphic Design	MOOZ grafisch ontwerp
Graphics	Wim Kempink

MEDICOM MEDICAL PUBLISHERS

Head Office
Medicom Medical Publishers
Faas Eliaslaan 5
3742 AR Baarn
The Netherlands

Postal address
Medicom Medical Publishers
PO Box 90
3740 AB Baarn
The Netherlands

Telephone +31 85 4012 560
E-mail publishers@medicom.nl

ISSN 2468-8762 19:4

Letter from the Editor

Prof. Frank Van der Aa

Dear Reader,

The 34th annual EAU congress from 15 to 19 March 2019 has gathered thousands of urologists from all over the world in Barcelona. As always, the large conference was filled with state-of-the-art lectures, lively discussion, novel paradigms and practical sessions.

The huge amount of information produced at the meeting is a challenge to digest, even for those who attended the meeting. For this reason, we have written a congress report, covering a wide variety of topics. This report will guide you to some of the key messages delivered @EAU 2019 in Barcelona.

We hope this congress report issue of Medicom will help you to further increase your knowledge of urology and will help you to scientifically underbuilt your daily clinical practice.

Enjoy the congress report!

Kind Regards,
Frank Van der Aa

Biography

Frank Van der Aa is adjunct head of clinic in the Department of Urology in the University Hospital Leuven and staff member of the National MS Center in Melsbroek, both in Belgium. In addition, he is lecturer of the Faculty of Medicine at the Catholic University of Leuven.
His special clinical interests are in neuro-urology, male and female incontinence and reconstructive urology. His major research interest include animal models of stress urinary incontinence and stem cell applications.
He is faculty member of the European School of Urology (ESU) since 2009, Editorial Board member of Neurourology and Neurodynamics since 2011, and member of the Video Congress Committee of the European Association of Urology (EAU) Scientific Congress Office since 2012. He is board member of the EAU section of Female and Functional Urology since 2012 and president of the working group functional urology of the Belgian Association of Urology (BAU).

Conflict of Interest Statement:
Nothing to disclose

Prostate Cancer

Featured video: Prof. Jelle Barentsz (RadboudUMC, the Netherlands) is questioned by Prof. Jochen Walz (Institut Paoli-Calmettes, France) and Prof. Arnaud Villers (University of Lille Nord de France) about his study on the role of (fast) bi-parametric MRI versus multi-parametric MRI and TRUS-biopsy for detecting clinically significant prostate cancer in biopsy-naïve men with elevated PSA. watch the video

Featured video: This 11-minute interview of GU medical oncologist Prof. Silke Gillessen (St. Gallen, Switzerland) on the updates expected in prostate cancer in 2019, prepared for daily clinical practice of urologists. watch the video

Enzalutamide plus ADT improves outcomes for metastatic hormone-sensitive prostate cancer

Results from the large international phase 3 ARCHES trial show that, in men with metastatic hormone-sensitive prostate cancer (mHSPC), enzalutamide combined with androgen deprivation therapy (ADT) significantly extended radiographic progression-free survival (rPFS) compared with ADT alone.

Enzalutamide has already demonstrated a benefit in men with metastatic and localised castration-resistant prostate cancer (CRPC), but its efficacy when combined with ADT in mHSPC patients has remained unclear. Executed worldwide at sites in the United States, Canada, Europe, South America, and the Asia-Pacific region, the ARCHES trial was a randomised, double-blind, placebo-controlled, international study that enrolled 1,150 mHSPC patients. Patients treated by ADT (with luteinising hormone-releasing hormone agonist or antagonist, or bilateral orchiectomy) were randomised to either receive a daily dose of 160 mg enzalutamide or placebo.

In the ARCHES study, the enzalutamide plus ADT arm corresponded to a 61% reduction in the risk of radiographic progression or death when compared to the placebo plus ADT arm (HR=0.39; P<0.0001).
"The significant benefit in rPFS was seen across all prespecified subgroups, including low- and high-disease volume and with or without prior docataxel therapy," explained Prof. Antonio Alcaraz (Hospital Clinic de Barcelona, Spain), who presented the study at the Breaking News session.

There was also significant improvement in other endpoints, including time to prostate-specific antigen (PSA) progression, reduction in the risk of starting a new antineoplastic therapy, and objective response rate, as compared to ADT alone.

Commenting on the study, Prof. Noel Clarke (University of Manchester, United Kingdom), put the new results into context. "Preliminary safety analysis appears consistent with the safety profile of enzalutamide in previous CRPC trails, and had acceptable toxicity in the medium term." He went on to compare ARCHES data to RCTs studying abiraterone. "This may translate to improved OS, but further follow-up is needed. CHAARTED-defined volume and LATITUDE-defined risk exclusions need to be re-visited in relation to the use of combination ATD studies in hormone-sensitive metastatic prostate cancer." [1]

1. van Soest RJ, de Wit R. BMC Med. 2015 Dec 22;13:304

Prostate cancer active surveillance: Better patient risk stratification and use of imaging

Appears to be safe to expand indication for active surveillance (AS) to Gleason 3+4, but the data on using MRI instead of biopsy in AS are not yet clear.

The 6 Movember Global Action Plan (GAP) consortia are worldwide collaborations between researchers in prostate and testicular cancer tackling questions of unmet needs: biomarkers (GAP1), imaging (GAP2), active surveillance (AS, GAP3), exercise and metabolic health (GAP4), testicular cancer (GAP5), and oligometastatic prostate cancer (GAP6). At EAU19, the Movember GAP3 consortium (Dr Todd Morgan, University of Michigan at Ann Arbor, USA presenting for Hellman et al.) reported on 7,704 men being followed by AS from 14 centres: 6,725 men with Grade Group (GG)1 3+3 disease (87%) and 979 men with GG2 3+4 disease (13%). Discontinuation of AS (40% GG1 vs 50% GG2) was attributable to: switch to active treatment due to progression (19% vs 23%), switch to active treatment without evidence of progression (11% vs 18%), adverse pathology (34% GG1 vs 42% GG2). Future studies will better stratify intermediate risk disease by MRI and genomic profiling (e.g. *BRCA2* or *ATM* gene mutations), which will further elucidate to what extent AS can be expanded to more men with Gleason 3+4 prostate cancer.

Dr Vasilis Stavrinides et al. (University College London, United Kingdom) reported on their AS cohort (n=626) which includes Gleason 3+3 or low-volume 3+4, provided PSA <20 ng/mL and baseline multiparametric MRI scan (mpMRI). The group could conclude that MRI-visible disease was associated with significantly shorter time to AS exit (median follow-up 53 months). A single PCa-related death was reported in their study period. Interestingly, in a subgroup analysis, if a patient was mpMRI-negative upfront, it made little to no difference if their disease was 3+3 or 3+4. These data again indicate expansion of AS to 3+4 prostate cancer.

Yet another study supported this same conclusion. Dr Marco Bandini and colleagues (Università Vita-Salute San Raffaele, Italy) prospectively enrolled 174 patients with D'Amico low-risk prostate cancer (PSA <10 ng/mL, cT ≤2, and biopsy Gleason Score 6). mpMRI of a visible lesion (HR=2.31, P=0.003) upfront was a significant indicator and was more important than any other biopsy pathology parameter.

Another hot topic actively discussed was: can we reduce the number of biopsies by applying mpMRI during follow-up? The data presented at the EAU were somewhat contradictory on this topic (see Table). The first studies in the Table indicate that a stable lesion being followed by active surveillance with MRI has a very small chance of being missed should it grow. However, the fact that you might miss up to 35% cases of prostate cancer if you do not do biopsy in the presence of a normal MRI (Osses et al.), is alarming. In short, there is a discrepancy regarding whether it is safe to rule out biopsy in the active surveillance setting, and we are not yet ready for a full paradigm-shift towards mpMRI for follow-up.

Table: Overview of contradictory results concerning the value of mpMRI vs biopsy at EAU 2019

Study	Methods	Results
Giganti F et al.	150 men with GG1 or GG2 on AS	12-, 24-, and 60-month progression-free survival for PRECISE 1-3, was 98-100% (radiological stability)
Von Beyme Cortes et al.	147 patients with AS with Gleason score of 3+3=6 or 3+4=7a were initially enrolled and received mpMRI (n=55)	NPV was 100%. PPV was 64%. Sensitivity 100% and specificity was 59%
Osses DF et al.	81 men underwent both an MRI ±TBx at baseline and at confirmatory biopsy	Upgrading was detected in stable confirmatory mpMRIs in 35% of men. TBx missed upgrading in 43% detected by TRUS-Bx only
Fishelevitz A et al.	71 men on AS with mpMRI prior to biopsies	Reclassification in 40% of cases

Green text indicates studies supporting mpMRI in follow-up; red text has mixed or negative data.

AS, active surveillance; Bx, biopsy; GG, Grade Group; mpMRI, multiparametric; NPV, negative predictive values; PPV, positive predictive values; TBx, Targeted biopsy; TRUS, transrectal ultrasonography.

The role of pelvic lymph node dissection in prostate cancer: Extended vs standard

One prospective study presented showed no benefit of extended PLND, whereas a large retrospective study did point to decreased mortality after PLND.

Dr Karim Touijer et al. (Sloan Kettering Cancer Center, USA) presented a single-centre prospective RCT including 1,480 men with intermediate- to high-risk disease to assess outcomes of limited vs extended lymph node dissection in patients undergoing open, laparoscopic, and robotic prostatectomy for localised prostate cancer. No differences were observed in biochemical-free survival comparing the limited and extended dissection groups.

The patients were randomised to limited pelvic lymph node dissection (PLND; obturator fossa, n=723) or extended PLND (obturator, hypogastric, and external iliac dissection, n=757) groups, which had similar demographics including age, preoperative PSA, Gleason Grade, the presence of extracapsular extension, nodal disease, and seminal vesical invasion. The primary endpoint was time to biochemical recurrence. Each surgeon was randomised, committing to limited or extended PLND for a 3-month period. The trial reported similar rates of grade 2/3 complications (12 vs 11%) and no grade 4/5 complications.

To summarise findings, no differences were seen in biochemical-free survival comparing the limited and extended template dissection groups. Subgroup analyses or meta-analysis did not render any statistical differences as well. It should be noted that the median number of nodes removed in this study was pretty much the same in both groups, which suggests a surgical bias towards more extensive lymph node dissection in the limited PLND group. Similarly, patients with higher risk of disease were less likely to be enrolled in the study overall.

On the other hand, there was retrospective evidence that showed somewhat opposite results, that extended PLND was beneficial to patients at high risk for lymph node invasion. Using the USA National Cancer Database (n=406,409 patients), Dr Akshay Sood et al. (Henry Ford Hospital, USA) showed that patients undergoing extended PLND (HR=1.22) had 8% incrementally lower risk of 10-year mortality as compared to patients undergoing none/limited PLND (HR=1.31). These data were highly significant (P<0.0001), albeit retrospective. The conclusion drawn from these two studies is that there may be a trend for benefit of extended PLND for patients with high-risk prostate cancer.

When to use imaging and imaging-guided therapies

A clinical tool to guide physicians before suggesting ^{68}Ga-PSMA PET/CT.

Which patient with biochemical recurrence after primary treatment for prostate cancer would result in a positive ^{68}Ga-PSMA PET/CT? The 2019 EAU Guideline panel recommends performing ^{68}Ga-PSMA PET/CT if the PSA level is >0.2 ng/mL, providing the results will influence treatment decisions, but it is unclear if this is cost-effective. Dr Lorenzo Bianchi (University of Bologna, Italy) built a prediction model to assess the risk of individual patients to have a positive PET/CT. Prostate cancer patients (n=703) with confirmed biochemical recurrence were stratified according to different clinical settings of recurrence: first PSA relapse (detection rate 40%), biochemical relapse after salvage therapy (detection rate 54%), PSA persistence after primary therapy (detection rate 60%), and disease progression before starting systemic therapies (detection rate 87%). The prediction model thus showed some promise, but will need to learn from this validation process in order to achieve better detection.

Dr Carlo Andrea Bravi et al. (Ospedale San Raffaele, Italy) reported a multicentre study looking at 605 patients treated with salvage lymph node dissection (SLND) for nodal recurrence of prostate cancer at 11 tertiary referral centres between 2002-2018. Outcomes were biochemical recurrence, clinical recurrence-free survival, cancer-specific and other-cause mortality at 8, 10, and 12 years from SLND. The long-term outcomes of these patients are not good; at 10 years post-SLND follow-up, only 15% of patients were free of clinical recurrence; cancer-specific mortality at 10 years was 34%. In a multivariate analysis of these data it became evident that the patients in this study that had a better outcome had been treated with concomitant hormonal/androgen deprivation therapy or a combination of concomitant hormonal therapy plus radiation therapy. This data points to the hypothesis that the combination treatment leads to the best outcomes, not the SLND alone.

Radioguided surgery is the future?

Food for thought: Dr Sophie Knipper et al. (University Hospital Hamburg-Eppendorf, Germany) looked at 47 consecutive patients with pre-operative ^{68}Ga-PSMA-PET/CT positive metastatic lesions that had not been treated with androgen-deprivation therapy and randomised them to a conventional surgical approach (n=27) or to a ^{99m}Tc-PSMA-radioguided surgery (n=20). Short-term PSA-dynamics significantly lean in favour of radioguided surgery (see Table). Further studies are warranted.

Table: Value of radioguided surgery

PSA decline	RGS (n=20)	CSA (n=27)	P-value
Overall	20 (100%)	14 (52%)	0.001
>50%	16 (80%)	8 (30%)	<0.01
>90%	10 (50%)	2 (7%)	<0.01

RGS, radioguided surgery; CSA, conventional surgical approach.

Cytoreductive radical prostatectomy: LoMP trial results

The LoMP trial being run by the University Hospital Ghent, Belgium, reported the outcomes of cytoreductive radical prostatectomy (cRP) vs standard of care.

The hypothesis that cRP will decrease the number of local events in the context of oligometastatic prostate cancer is attractive, but has been not structurally addressed. From 2014-2018, 80 asymptomatic patients were prospectively included in the LoMP trial. cRP was performed in patients with a resectable tumour who were fit to undergo surgery (n=40). Standard of care was administered to patients who were ineligible or unwilling to undergo cRP (n=40), so there was definitely a surgical selection bias in the cohort. The 2-year estimates for overall survival were 92% vs 64% (P=0.003) in favour of cRP; likewise, the 2-year estimate for local event-free survival were 89% vs 58% (P=0.001) in favour of cRP. Although imperfect in study design, these data will be very useful in further exploration of the application of cRP in selected patients.

Prostate cancer: What to expect the next 12 months

On Friday 15 March, the European School of Oncology held their 6th Prostate Cancer Observatory: innovations and care in the next 12 months, as a kick-off session for EAU19. The point of this session is to feature forecasts in prostate cancer management from multidisciplinary viewpoints on what to expect in the coming year.

The room was packed with hundreds of people, and just entering the room took over 20 minutes, reflective of the attractive format this high-level session has adopted to provide the audience with updated and unbiased "sneak peaks" on the near-future expected outcomes for prostate cancer.

Below is the top-12 of what's on the horizon:

1. This last year brought major changes with respect to the implementation of MRI prior to biopsy, and the guidelines have been changed. The coming year will bring incremental and important refinements to the use of MRI (which underestimates tumour volume by 2.7x).

2. In focal therapy, targeting the largest tumour may not be the best strategy. Secondary tumours may be more relevant. More data is expected this year.
3. A Cochrane Review has determined that pharmacological regular use of PDE5 inhibitors does not improve spontaneous erectile function after prostatectomy; this practice will be stopped.
4. Mesenchymal stem cell injection post-prostatectomy is safe, but placebo-controlled trials will be necessary to determine efficacy in averting erectile dysfunction.
5. Low-intensity shock waves for erectile dysfunction after prostatectomy are promising; 2 trials will be reporting this year.
6. Active surveillance may be considered as a new standard of care for all Gleason 6 cases.
7. Results from the phase 3 ENZAMET trial, led by Dr Christopher Sweeney (Dana-Farber Cancer Institute, USA), is likely to be presented soon. ENZAMET is evaluating the addition of enzalutamide to a LHRH analogue as first-line androgen-deprivation therapy.
8. A small but pivotal study "A Study of MRI/US Fusion Imaging and Biopsy in Combination With Nanoparticle Directed Focal Therapy for Ablation of Prostate Tissue" will report in December 2019.
9. The "Robotic surgery after focal ablation therapy (RAFT study)" is also expected to report this coming December.
10. Hypofractionated radiotherapy for organ-confined prostate cancer will become the new standard of care for many patients, reducing treatment to 1-2 weeks, instead of 8-9 weeks.
11. Genomic stratification will be implemented into clinical practice. For example, men that are carriers of *BRCA2* mutations should probably be treated with surgery, and not radiotherapy [1].
12. The STAMPEDE trial in December 2018 [2] instigated a guideline change: Standard treatment for men newly diagnosed with metastatic prostate cancer is currently drug treatment alone. In 2019, there will be a lot of discussion as to whether we should pharmacologically treat non-metastasised patients as well.

1. Castro E, et al. J Clin Oncol. 2019 Feb 20;37(6):490-503.
2. Parker CC et al. Lancet. 2018 Dec 1;392(10162):2353-2366.

Bladder Cancer

Featured video: Watch live surgery "bladder tumour resection" with Prof. Alberto Breda (Fundació Puigvert, Spain) from this year's live surgery host hospital Fundació Puigvert in Barcelona. watch the video

Featured video: Prof. Bedke and Prof. Maria José Ribal (University of Barcelona, Spain) discussed the primary results from the SAUL study with Prof. Merseburger. Watch the featured video. watch the video

Largest safety study of its kind with atezolizumab in metastatic bladder cancer

In the Breaking News session, Prof. Axel Merseburger (University Hospital Schleswig-Holstein, Germany) announced the first results from SAUL, a phase 3b study evaluating the safety of atezolizumab in 997 patients with locally advanced or metastatic urothelial carcinoma (mUC) including several clinically relevant populations reflective of real-world clinical practice. Data from the study showed that both safety and efficacy, a secondary endpoint, were consistent with previous studies in both the overall population and a subgroup of patients corresponding to the patient population of the pivotal phase 3 study IMvigor211 ("IMvigor211-like") [1].

SAUL is the largest prospective safety study of a cancer immunotherapy in mUC and provides information about atezolizumab in a real-world setting. This open label, single-arm, multicentre study was designed to assess the safety of atezolizumab as a second- to fourth-line treatment for people with locally advanced or mUC (95%) or non-urothelial carcinoma (5%) of the urinary tract. What makes this study unique is that it included patients with renal impairment, poor performance status (ECOG PS 2) [2], treated asymptomatic CNS metastases or stable controlled autoimmune disease, which have never been included in a study like this previously. The primary endpoint was safety; secondary endpoints included overall survival (OS), progression-free survival (PFS), overall response rate (ORR) and duration of response (DoR).
The data presented at EAU show that the safety of the atezolizumab monotherapy treatment was consistent with the known safety profile of the medicine, even in this broad and complex patient group (see Table). Grade 3-4 adverse

Table: Adverse events in SAUL

AE, n(%)	All (n=997)[a]	CNS metastases (n=14)	Renal impairment (n=46)	Autoimmune disease (n=35)	Concomitant steroid (n=40)	ECOG PS 2 (n=101)	IMvigor211-like (n=643)[b]
Any grade	880 (88)	12 (86)	37 (80)	32 (91)	38 (95)	77 (76)	577 (90)
Grade 3/4	431 (43)	7 (50)	20 (43)	17 (49)	23 (58)	50 (50)	261 (41)
Grade 5*	37 (4)	0	4 (9)	3 (9)	3 (8)	7 (7)	20 (3)
Treatment-related	530 (53)	6 (43)	18 (39)	24 (69)	22 (55)	35 (35)	355 (55)
Grade ≥3	127 (13)	2 (14)	3 (7)	9 (26)	4 (10)	13 (13)	81 (13)
AE of special interest	305 (31)	5 (36)	7 (15)	16 (46)	14 (35)	20 (20)	201 (31)
Grade ≥3	67 (7)	0	1 (2)	5 (14)	2 (5)	5 (5)	46 (7)
Leading to treatment discontinuation	57 (6)	0	3 (7)	3 (9)	2 (5)	3 (3)	37 (6)

a. Includes but not limited to patients with renal impairment, Eastern Cooperative Oncology Group (ECOG) performance status grade 2, treated asymptomatic central nervous system metastases or stable controlled autoimmune disease
b. All patients corresponding to the patient population in IMvigor211 (locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen)

*Treatment-related grade 5 AEs (n=7, 0.7%): two cases of dyspnoea, one case each of colitis, intestinal perforation, respiratory failure, chronic kidney disease, drug-induced liver injury.

events (AEs) occurred in 43% of the patients, and treatment-related grade ≥3 AEs occurred in 13% of the patients, with most common reported side effects being fatigue, asthenia, colitis, and hypertension (each in 1%). AEs leading to treatment discontinuation occurred in 6% of the patients. Additionally, the efficacy results showed an OS of 10 months (95% CI 8.8-11.9 months) in the IMvigor211-like population. In the overall population, median OS was 8.7 months (95% CI 7.8-9.9). The median duration of follow up was 12.7 months. Prof. Merseburger: "SAUL confirms the tolerability of atezolizumab in a 'real-world' UC and non-UC population. Efficacy in both the IMvigor211-like subgroup and the broader unselected population is consistent with previous anti-PD-L1/PD-1 pivotal UC trials. These results support use of atezolizumab in UC or non-UC, including patients with limited available treatment options.

Discussant Prof. Jens Bedke (University Hospital Tübingen, Germany) pointed out that advantages of this trial were its size and involvement of a heterogeneous patient group. He cautioned that while atezolizumab use yielded no increased toxicity, individual data in subgroups was still lacking, and he pointed to the early drops in curves on both arms of the trial. Prof. Bedke also mentioned the costs: €90-95,000 per patient. He concluded that while the data offers some insights, there is a strong need to identify patients that are most likely to benefit from atezolizumab.
Prof. Bedke and Prof. Maria José Ribal (University of Barcelona, Spain) discussed the primary results from the SAUL study with Prof. Merseburger. See the video discussion online [3].

1. Powles T et al. Lancet 2018;391:748-757.
2. Sternberg et at. Eur Urol. 2019 Mar 22. pii: S0302-2838(19)30201-5.
3. https://www.youtube.com/watch?v=dVDOJVtAEeY&t=17s.

Bladder cancer risk and early detection

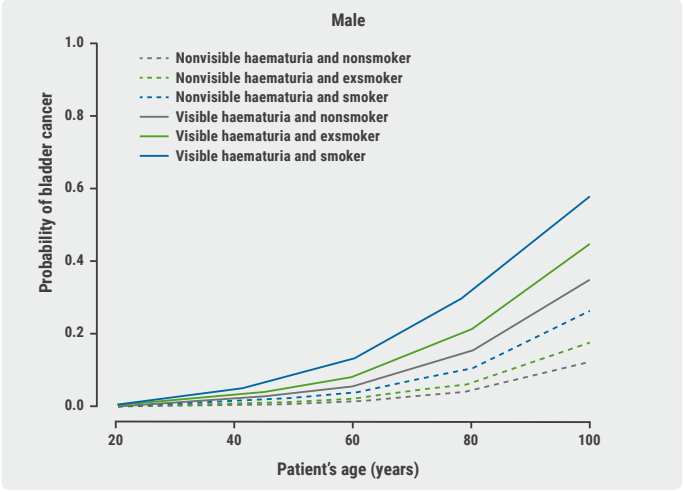
Results of the EDIFICE 6 survey show that tobacco is not recognised as bladder cancer risk factor in the general population. A haematuria cancer risk score was developed and externally validated to identify patients at risk of harbouring bladder cancer. Greatest prognostic value for grade determination is obtained by using both WHO1973 and 2004/16 classification systems.

Knowledge of bladder cancer was tested in the French population through the EDIFICE 6 study which surveyed >12,000 individuals online with no history of cancer. The cohort was demographically validated as a representative cross section of the French population (Dr Thibault De La Motte Rouge, Pitié-Salpêtrière Hospital, France) [1]. Among the top 5 risk factors for bladder cancer queried, tobacco was ranked last by the French population. The results highlight a number of misconceptions and a lack of understanding of bladder cancer, the severity of the disease, and most importantly, tobacco is not recognised as the primary risk factor. The authors' findings highlight the need for tailored education campaigns in the mass media all over Europe.

Dr Wei Shen Tan (University College London, United Kingdom) presented results from the DETECT 1 cohort examining a haematuria cancer risk score (HCRS) developed using 3,539 prospectively recruited bladder cancer patients from 40 UK hospitals and a validation cohort comprised of 656 Swiss patients. A lack of consensus exists regarding type of haematuria and age-specific thresholds used to guide referral for investigation of haematuria. All patients were referred to hospital for the evaluation of macroscopic and microscopic haematuria. Patient age, gender, type of haematuria, and smoking history were used to develop the haematuria cancer risk score, which detected 11.4% (n=8) more cancers which would have been missed by UK National Institute for Health and Clinical Excellence guidelines. The American Urological Association guidelines would have identified all cancers with a specificity of 12.6% compared to the 30.5% achieved by the HCRS. All patients with upper tract cancers would have been identified; these results were just recently published [2].

In short, the HCRS offers good discriminatory accuracy which is superior to existing guidelines. There is no current public health screening protocol for bladder cancer, so this study is potentially high impact. The simplicity of the model would facilitate adoption and improve shared decision-making (see Figure).

Figure: Haematuria cancer risk score in males [2]



Initiated by the EAU Guidelines panel for non-muscle invasive bladder cancer (NMIBC), there was a presentation by Dr Bas van Rhijn (Antoni van Leeuwenhoek Cancer Center, the Netherlands) comparing the prognostic value of the two classification systems for Grade determination of NMIBC. The EAU Guidelines uses both the WHO1973 (G1/G2/G3) & WHO2004/16 (low/high grade), whereas the American Urological Association Guidelines only uses the WHO2004/2016 (see Figure). The panel went back to patient data from 5,049 primary (first diagnosis) Ta/1 NMIBC patients from 17 centres of excellence. Both grading systems were equally capable at predicting progression, disease-specific survival, and overall survival, but not recurrence. The greatest prognostic value was seen to use a combination of WHO1973 and 2004/16. The EAU NMIBC Guideline Panel recommendation is to use both WHO systems, so be sure to ask your pathologist for both readouts.

Figure: NMIBC Grade classification systems

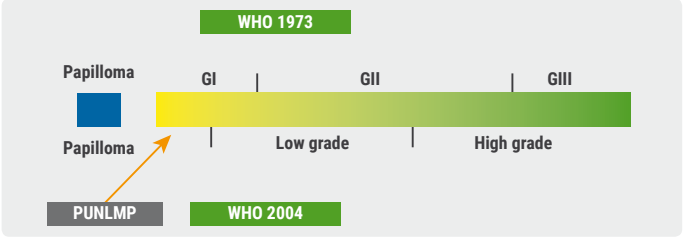


Figure kindly provided by Dr van Rhijn.

Dr Francesco Soria (Azienda Ospedaliera Città della Salute e della Scienza di Torino, Italy) presented an interesting multicentre study (n=291) interrogating the predictive factors for the absence of residual disease at repeated transurethral resection of bladder tumour (TURBT) technique, which involves the laser resection and the wire loop resection.

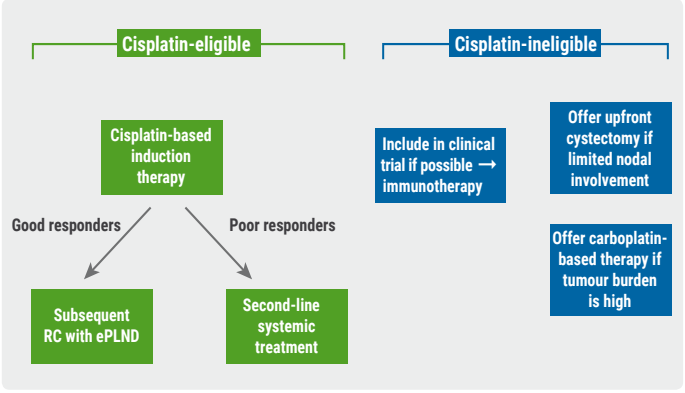
The primary research question was whether it is possible to avoid repeating TURBT in selected patients. All patients included had undergone an exhaustive and complete resection of a pT1 high-grade tumour, with absence of tumour at the time of second-look. Muscle was observed in 70% of pathological examinations at the first TURBT. In a multivariate analysis, the following predictive factors were identified: (1) muscle in the specimen from the beginning (HR 2.14, P=0.01); (2) concomitant carcinoma in situ (HR 0.23, P=0.002); and (3) en-bloc TURBT (HR 9.68, P=0.04). These data are being implemented into a predictive tool to aid the decision of how a patient can best be treated; there is room to challenge the second look as advocated in the guidelines.

1. De La Motte Rouge T et al. J Clin Oncol 2018 36:15_suppl, 1557-1557.
2. Tan WS et al. J Intern Med. 2019 Apr;285(4):436-445.

Consensus treatment pathway for patients with limited pelvic lymph node involvement in otherwise localised bladder cancer

There was a very practical debate between Prof. Jürgen Gschwend (Technical University München, Germany) and Prof. Sergio Bracarda (Ospedale San Donato, Italy) about how to treat patients with limited pelvic lymph node involvement in otherwise localised bladder cancer. The discussion was multidisciplinary, and a consensus treatment pathway was agreed upon (see Figure).

Figure: Consensus treatment pathway



In cisplatin-eligible patients, induction chemotherapy is advocated. Subsequently, patients are then stratified according to their response, choosing additional surgery (radical cystectomy with extended pelvic lymph node dissection) or second-line systemic treatment. In cisplatin-ineligible patients, Prof. Bracarda urged that it is essential to enrol as many of these patients as possible into clinical trials (e.g. immunotherapy) to facilitate the implementation of new approaches for these patients; the current data for carboplatin have been disappointing.

FGFR3 gene mutation: Favourable prognostic impact in bladder cancer

The fibroblast growth factor receptor (FGFR) pathway is very important in bladder cancer. Dr Laura Mertens (VU Amsterdam Medical Center, the Netherlands) shared her data analysing activating *FGFR3* mutations vs FGFR3 protein overexpression in bladder tumours and their relation to clinic-pathological parameters and prognosis in a multicentre, multi-laboratory setting. She concluded that *FGFR3* mutation has favourable prognostic impact regardless of FGFR3 protein expression level.

FGFR3 activating mutations are known to be associated with favourable prognosis in bladder cancer [1], yet little is known about whether immunohistochemical detection of overexpression of FGFR3 is a relevant prognostic tool. Because the FGFR3 receptor is an actionable target and there are drugs in the pipeline, Dr Mertens took 1,000 cN0M0 (chemo-naïve) bladder cancer patients who underwent radical cystectomy (in 9 hospitals) and concomitantly screened them for *FGFR3* mutation as well as overexpression. Specimen review by uro-pathologists confirmed that 89% of patients had a tumour ≥pT2.

An *FGFR3* activating mutation (the most common mutation is p.S249C) was found in 11% of the samples; and of those tumours, 73% demonstrated FGFR3 overexpression as stained by immunohistochemistry. In the *FGFR3* wildtype subset of tumours, 22% had overexpression of FGFR3. Notably, p53 overexpression was 69% throughout the cohort (cut-off is 10%), but the relevance of this finding is not yet clear.
Conclusions of this study were: (1) *FGFR3* mutation has favourable prognostic impact regardless of FGFR3 protein expression level; (2) FGFR3 overexpression has no prognostic impact in tumours with wildtype *FGFR3* sequence; and (3) gene sequence of *FGFR3* should be used in the selection for targeted therapy with anti-FGFR3 agents in the future. Developments in this field should be watched carefully because *FGFR3* mutation itself seems to be the key driver, not just amplification of the protein levels.

1. van Rhijn et al. J Clin Oncol. 2003 May 15;21(10):1912-21.

Bladder cancer in young patients

Dr Roland Seiler (Inselspital University Hospital of Bern, Switzerland) showed that bladder cancer morphology appears to be different in younger patients, with urothelial carcinoma being rarely observed in paediatric patients, whereas clear cell adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma are more common. The underlying hypothesis is that there are molecular aspects of bladder cancer that are unique to younger patients.

Dr Seiler explained, "We do tend to see clusters of bladder cancer in some families, but it can be difficult to discern if these are due to shared risk factors, such as environmental exposures or lifestyle choices (i.e. tobacco use), or if these are due to germline mutations within the family."

Importantly, there are currently no guidelines about when to refer younger patients with bladder cancer to genetic counselling. Other malignancies, however, have tackled this unmet need [1], and Dr Seiler pointed out that for the time being we should adopt similar practices. In short, if a patient is <50 years of age, or if they have >3 cases of breast, ovarian, pancreatic, or prostate cancer in close relatives (per definition parents, siblings, or children), it is reasonable to offer genetic counselling.

There is scant data examining germline mutations in bladder cancer to date; one recent study sequenced a selected cancer-related gene panel in 98 bladder cancer patients [2]. Although the authors concluded that germline mutations within this cohort were related to DNA repair, this study was not genome-wide, and was inherently biased because the selected gene panel featured many genes involved in DNA repair.

Analysing the Cancer Genome Atlas Program, a few known somatic differences between older and younger patients with urothelial carcinoma have been identified. For example, inactivating mutations in canonical tumour suppressor genes *RB1* and *TP53* are associated with younger patients, as well as higher neoantigen loads, and higher interferon-gamma signalling and chemokine signalling. Of the known molecular subtypes of urothelial carcinoma, the luminal papillary subtype appears to be more prevalent in younger patients. Interestingly,

this luminal papillary subtype has characteristically low levels of immune infiltrate that make it potentially less likely to show a favourable response to checkpoint inhibition treatment. In exciting complementary data, transcriptome profiling of 368 tumour samples from patients in the IMvigor 210 trials with platinum-refractory or cisplatin-ineligible urothelial carcinoma who were treated with the PD-L1 inhibitor atezolizumab trial revealed that the *TP53* and/or *RB1* mutated samples in neuronal tumours of the Lund subtype classification was associated with the best response [3].

In a video interview, Prof. Morgan Rouprêt (Pierre and Marie Curie University, France) and Prof. Fiona Burkhard (Inselspital University Hospital of Bern, Switzerland) gave insights from the plenary session at EAU19 looking at bladder cancer in the young patient and why is it important to focus on these patients [4].

1. Shuch et al. J Clin Oncol. 2014 Feb 10;32(5):431-7.
2. Na et al. BJU Int 2018 Nov;122(5):808-813.
3. Kim et al. Eur Urol. 2019 Mar 6. pii: S0302-2838(19)30160-5
4. https://www.youtube.com/watch?v=wgGKVB_-7cA&list=PLCVO1Vai8uzXJOGRwfLw5uDBghBvjcfKe&index=8&t=0s

Spanish study directly links surgical volume with mortality in bladder cancer patients undergoing cystectomy

In a retrospective study of 12,154 radical cystectomies performed in 196 Spanish hospitals, the authors uncovered a highly significant relationship between patient volume per hospital and 90-day mortality.

Dr Ana Guijarro Cascales (Hospital Universitario Fundacion Alcorcon, Spain) examined the national registry of Spain from 2011-2015 for the impact of the number of radical cystectomies performed per hospital on 90-day mortality. In the literature, 90-day mortality is variable but generally thought to relate to number of patients treated per year, and reported to be 2.3-7.9% [1]. The majority of hospitals do less than 10 radical cystectomies per year (191/196), with only 5 hospitals performing more than 38 per year. Across all Spanish hospitals, median mortality at 30, 60, and 90 days was respectively 2.9%, 5.2%, and 6.5%.

However, at the five higher volume centres (38+ radical cystectomies per year) the mortality rate at 90 days was just 3.3%. By extrapolation, every additional 10 radical cystectomies performed per year in a given hospital will decrease 90-day mortality by 20% (P<0.001). These data should support the centralisation of radical cystectomy surgery.

1. Marqueen et al. JNCI Cancer Spectr. 2018 Nov;2(4):pky075.

Updated interim results of phase 2 trial of pembrolizumab for high-risk NMIBC unresponsive to BCG

Updated results of KEYNOTE-057 among patients with non-muscle invasive bladder cancer (NMIBC) suggest that systemic immunotherapy with pembrolizumab (200 mg every 3 weeks) has encouraging activity in patients with high-risk, BCG-unresponsive CIS with or without papillary tumours.

Prof. Ashish Kamat (MD Anderson Cancer Center, Houston, USA) shared the interim update on immune checkpoint inhibitors which demonstrated efficacy in metastatic bladder cancer. The PD-1 inhibitor pembrolizumab was studied in BCG-unresponsive patients with CIS (+/- Ta or T1). Out of 103 patients, 31% had an impressive durable complete response, with no individuals progressing to MIBC or developing other metastases. These promising results have already led to the initiation of a phase 3 trial comparing the combination of systemic pembrolizumab plus intravesical BCG to re-introduction of BCG alone, currently open to enrolment (KEYNOTE-676).

The toxicity profiles for immunotherapy necessitate vigilance and timely intervention of any adverse events, since they can potentially be serious, and occasionally fatal if not treated. Radical cystectomy, the current standard of care after BCG failure, however, has a 2-5% post-operative mortality rate [1]. In comparison, finding the best agent or combination of agents to treat these patients is the topic of many research studies.

Prof. Kamat: "The results of these impending trials will almost certainly be practice-changing especially as we are currently are facing a worldwide shortage of BCG" (see Table).

Table: Ongoing clinical immunotherapy trials for bladder cancer

Identifier	Trial
NCT02792192	Phase 1b/2 Safety and Pharmacology study of atezolizumab alone and in combination with BCG in high risk NMIBC
NCT02451423	Phase 2 study of atezolizumab in subjects with non-metastatic TC of the bladder
NCT02844816	Phase 2 study of atezolizumab in recurrent BCG-unresponsive NMIBC
NCT03317158	ADAPT-BLADDER: durvalumab monotherapy (cohort 1) and durvalumab +BCG (cohort 2s and ERBT (cohort 2b) in BCG-unresponsive NMIBC
NCT02901548	Phase 2 durvalumab for BCG-refractory urothelial carcinoma in situ of the bladder
NCT03519256	Checkmate 9UT: Phase 2 nivolumab or nivolumab + BMS986205 +/- in BCG-unresponsive NMIBC
NCT02625961	KEYNOTE-057: Phase 2 study of pembrolizumab in BCG-refractory high-risk NMIBC
NCT03167151	Phase 1/2 Marker Lesion Study assessing safety, tolerability and efficacy if pembrolizumab in intermediate-risk recurrent NMIBC
NCT03711032	KEYNOTE-676: Phase 2 BCG +/- pembrolizumab in high-risk NMIBC that is persistent or recurrent following BCG induction.

1. D'Elia C, et al. Urol Int 2017;98(3):255-261.

Robot-assisted radical cystectomy or open radical cystectomy?

Bladder cancer poses a special challenge to urologists due to unclear data concerning the best approach to radical cystectomy with pelvic lymph node dissection. In a debate with Prof. Jens Bedke (University Tübingen, Germany), Prof. Seth Lerner (Baylor College of Medicine, Houston, USA) argued the case for radical cystectomy over robot-assisted radical cystectomy using data from the recent RAZOR trial. In this trial, 350 patients with bladder cancer were randomly assigned to either open or robot-assisted cystectomy, and the primary endpoint was 2-year progression-free survival [1].

Open radical cystectomy (RC) is historically the treatment of choice for patients who present with invasive disease, progressive disease, or disease refractory to intravesical therapy. Although retrospective data has suggested that robot-assisted radical cystectomy (RARC) is safer than RC, prospective data have been lacking. RAZOR indicated that RARC is associated with lower blood loss, lower transfusion rates, and a shorter length of hospital stay which was balanced by operating time (open radical cystectomy was faster); however, the trial did not show a difference in complication rates, which was the original attraction to RARC in the first place (see Table). So: is RARC justified? Some of the discussion was centred around whether the urinary diversions were performed extracorporeally, and whether intracorporeal diversion (less invasive) would demonstrate the benefit of robotic cystectomy. In addition, RARC was performed by surgeons whose operating times (averaging >7 h) were slower than average times for experienced surgeons, suggesting that the data may have been disproportionately affected by a learning curve.

Should RARC be recommended in daily clinical practice on the basis of these results? On the one hand, the RAZOR trial provides level 1 evidence robustly arguing the oncological efficacy of RARC and supporting clinical advantages such as reduced blood loss and reduced hospital stay. On the other hand, RAZOR data indicates that RARC does not lower the rate of perioperative complications. The majority of cystectomies are performed in low-volume centres where robot-expertise is not available. One critical question that was also discussed is whether a cost–benefit analysis will favour one approach over the other. Lastly, high-level prospective data about intracorporeal urinary diversions will help settle this discussion.

Table: Selected findings from the RAZOR trial [1]

	Robotic cystectomy (n=150)	Open cystectomy (n=152)	Difference (95% CI)	P-value
Patients with blood loss data	148 (99%)	149 (98%)	..	..
Blood loss, mL	300 (200-500)	700 (500-1,000)	..	<0.0001
Perioperative transfusion	35/143 (24%)	65/143 (45%)	-21.0 (-31.8 to -10.2)	0.0002
Units of blood transfused	3 (2-5)	4 (2-5)	..	0.46
Intraoperative transfusion	18/139 (13%)	46/136 (34%)	-20.8 (-30.6 to -11.2)	<0.0001
Postoperative transfusion	33/132 (25%)	54/135 (40%)	-15.0 (-26.1 to -3.9)	0.0089
Hospital stay ≤5 days	40/139 (29%)	27/146 (18%)	10.3 (0.5 to 20.1)	0.0407
Length of stay, days	6 (5-10)	7 (6-10)	..	0.0216
Operating time, min	428 (322-509)	361 (281-450)	..	0.0005
Surgical complications within 90 days				
0	49 (33%)	47 (31%)	..	0.80
1	24 (16%)	20 (13%)	..	..
2	44 (29%)	51 (34%)	..	..
3	29 (19%)	28 (18%)	..	..
4	0	2 (1%)	..	..
5	4 (3%)	4 (3%)	..	..
Grades 1-5 vs 0	101 (67%)	105 (69%)	-1.8 (-12.3 to 8.8)	0.75
Grades 3-5 vs 0-2	33 (22%)	34 (22%)	-0.4 (-9.0 to 9.8)	0.94

Prof. James Catto (University of Sheffield, United Kingdom), referring to the UK-based iROC trial responds that he is awaiting iROC to complete accrual, with 219/340 patients registered/randomised at this time, since this prospective randomised controlled trial will either independently validate RAZOR's conclusions, or -if contradictory- raise the discussion to an even more pitched level.

1. Parekh et al. Lancet 2018; 391: 2525-2536

Renal Transplantation and Renal Cell Carcinoma

Featured video: Dr Ignacio Duran (University of Barcelona, Spain) discusses immunotherapy in RCC treatment how combination therapy is probably going to replace monotherapy. watch the video

Featured video: Description of the IGRAPN : Image Guided Robotic-Assisted Partial Nephrectomy. Concomitant use of 3 intra-operative imaging techniques to achieve a zero-ischemia heminephrectomy. watch the video

Renal transplantation

ERUS-RAKT project data supports the use of robotic laparoscopy for living donor transplantations in expert centres and renal transplantation can be considered in complex renal tumours with an imperative indication for organ sparing.

An award-winning poster from Dr Mireia Musquera Felip et al. (Hospital Clinic Barcelona, Spain) reported their experience with robot-assisted kidney transplantation (RAKT) after 3 years, involving 185 RAKTs from 8 European centres (ERUS-RAKT project), most of which were living donor transplantations. The operating times, ischaemia times, and anastomosis times were all reasonable (see Table).

Table: Surgical characteristics of 185 robot-assisted kidney transplantations in ERUS-RAKT project

Variable	Median (SD)
Operative time (min)	258.73 (79)
Console time (min)	155.18 (53)
Warm ischemia time (min) • Cadaveric Cadaveric • Living	 13.55 (11.7) 2.81 (1.35)
Cold ischemia time (min) • Cadaveric • Living	 696.81 (439) 45.61 (46.6)
Rewarming time (min)	50.69 (15)
Anastomosis time (min) Arterial Venous	 19.31 (6.4) 20.8 (7.2)
Estimated blood loss (cm^3)	148 (116)

ERUS-RAKT, EAU Robotic Urology Section – Robot-Assisted Kidney Transplantation

Although some vascular complications were reported in the beginning of the project, the learning curve accelerated and fewer complications were reported later. The authors claim that they provide good surgical and functional results, which are competitive to the open technique. However, it is unclear what the exact benefits to the patient are to justify this approach; for example, ideally less hernia or wound infection would be associated with the same functional outcome.

In another study, Dr Mark Sullivan et al. (Oxford University, United Kingdom) presented a study about renal transplantation for larger kidney tumours (6.2 cm on average). Of the 36 patients included (most presented with solitary kidneys), 34 of the tumours were highly complex. The positive surgical margin rate was 5.6%, Clavien-Dindo III-V complications were reported in 56%, and there was relatively high mortality at 5.6%. With a 60-month follow-up, there was an impressive cancer-free survival of 96%. Furthermore, 79% were recurrence-free, and 83% were dialysis-free. The authors concluded that in selected patients, this approach offers a chance for renal preservation without compromising cancer control; the surgery itself is however complex and potentially hazardous.

Renal cell carcinoma

The benefit of robot-assisted partial nephrectomy over open partial nephrectomy still needs to be proven.

Dr Soo Jung and colleagues (Seoul National University College of Medicine, South Korea) included patients with a renal score of at least 8, comparing robot-assisted partial nephrectomy (RAPN) (n=336) to open partial nephrectomy (OPN) (n=372) in complex renal tumours. Operating times were somewhat faster in the robot-assisted arm, suggesting that they were highly experienced surgeons. The authors saw significant improvements in post-operative pain and median length of hospital stay; however, there was no benefit with regard to the complication rate. Given that a few trials have reported a reduction of complication rates with RAPN [1], the value of RAPN still needs to be determined.

This topic will also be investigated in a study by Prof. Arnulf Stenzl (University of Tübingen Medical School, Germany) and Prof. Marc-Oliver Grimm (Universitätsklinikum Jena, Germany) in a randomised prospective multicentre trial (20 centres, OpeRA study) aiming to compare RAPN vs OPN in patients with a renal score ≥7. A total of 606 patients will be monitored at 30 days and 90 days post-nephrectomy and the patients will receive a number of questionnaires regarding pain, recovery, and quality of life. The primary endpoint is the complication rate, and it is anticipated that this study will conclusively address whether RAPN is associated with fewer complications compared to OPN.

1. Grivas N et al. Minerva Urol Nefrol. 2019 Mar 18.

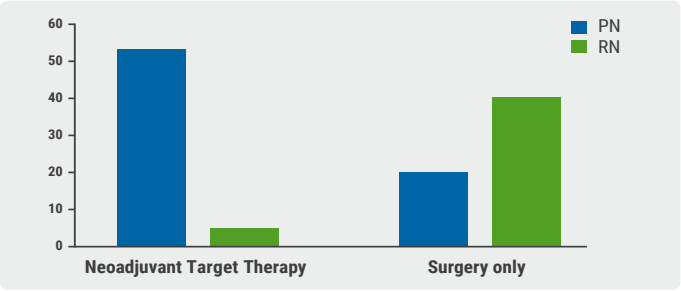
Enhanced recovery after surgery may significantly reduce length of hospital stay without compromising safety

Better known from cystectomies and prostatectomies, Dr John Withington et al. (Royal Free London NHS Trust, UK) analysed enhanced recovery after surgery (ERAS) for nephrectomies following a diagnosis of renal cell carcinoma. The ERAS program starts at referral and ends with discharge. The patients and nurses have checklists, so everything is very well structured and pre-defined. The results from this study indicated that the complication rates were similar, but the length of stay could be halved by this structured approach. The re-admission rate was even reduced in the post-ERAS period and patient satisfaction was maintained. One potential bias the authors investigated was that RAPN was more likely to be performed in the post-ERAS period and in a multivariate analysis, they confirmed that the largest impact on length of stay was indeed ERAS itself and not RAPN. So, this is an opportunity to reduce length of hospital stay.

Neoadjuvant treatment may facilitate partial nephrectomy

In a prospective randomised trial from Dr Oleg Voylenko (Kiev Medical University, Ukraine), 58 patients received 2 cycles of pazopanib prior to scheduled surgery, and 60 patients surgery only. Baseline parameters were balanced between groups, with tumour size averaging 61 mm in the control group, and 63 mm in the neoadjuvant group. In the neoadjuvant group, 86% of the patients manifested some tumour size decrease (average decrease was 12 mm or 20% of the tumour volume); however, there was less shrinkage in high-grade disease. No patient had progressive disease. The surgeons were able to perform a partial nephrectomy in 91% of the cases that had received neoadjuvant pazopanib, compared to only 33% of the patients in the arm that proceeded directly to surgery (see Figure).

Figure: Type of surgery for neoadjuvant targeted therapy vs surgery only for localised RCC



In the group of patients receiving 2 rounds of neoadjuvant targeted therapy (TT; n=58), 91% were able to undergo partial nephrectomy (PN). In the surgery-only group, 66% of the patients had to undergo radical nephrectomy (RN). RCC, renal cell carcinoma.

Positive surgical margin is an independent predictor of recurrence-free survival

Dr Aaron Bradshaw (University of California San Diego, USA) and colleagues studied the impact of positive surgical margins (PSM) in a retrospective multi-centre analysis (n=2,737) undergoing partial nephrectomy (cT1a 1842 and cT1b 774). With a median follow-up time of 44 months, there was a PSM in 4.3% of patients (n=113). Using multivariate and univariate analyses, the authors demonstrated that PSM was an independent predictor of recurrence-free survival (HR 2.8, P<0.01). The authors also concluded that patients with *cT1B* tumours are at increased risk of recurrence and mortality and require a closer follow-up or even a secondary nephrectomy.

No apparent benefit of partial nephrectomy over radical nephrectomy in young (<50 years) and healthy patients

Dr Hung-Jui Tan (University of North Carolina at Chapel Hill, USA) et al. considered the outcome after partial nephrectomy vs radical nephrectomy in the young (<50 years) healthy patient in the US National Cancer Database. Median age of this cohort was 44 years, and included 2,454 radical nephrectomies and 555 partial nephrectomies (18.4%) with a long median follow-up of 109 months. No differences in long-term overall survival between the two groups was observed (weighted HR 0.83, P=0.196). The authors conclude that, assuming familial tumour syndromes have been excluded, there is no need to take an oncological risk in the young and healthy patient with highly complex tumours. The patients have enough functional reserve; the advantage of partial nephrectomy in these patients has to be carefully questioned.

Pancreatectomy is an option in selected patients with oligometastatic disease

Dr Steven Rodgers et al. (Sylvester Comprehensive Cancer Center, USA) performed a systematic review of 31 non-

randomised studies, totalling 566 patients to examine the role of pancreatic metastasectomy for advanced renal cell carcinoma. The median age at pancreatic resection was 63.9 years. Most patients were metachronous (87.6%, vs 12.4% synchronous) after a median disease-free interval following primary resection between 40-160 months. Recurrence in the pancreas is usually late. The median overall survival in the various studies was between 15-148 months. The median disease-free survival was notably long at 34 months; these data support the notion that pancreatectomy might offer a good opportunity to manage disease for long-term remission. The overall operative morbidity, however, was high (13-57%), with 4.5% perioperative mortality. The conclusion of this systematic review is that there may be benefits for selected renal cell carcinoma patients with pancreatic metastases but there is a substantial perioperative risk.

New strategies/more research needed to optimise follow-up in curative surgery for RCC

Dr Saeed Dabestani (Lund University, Sweden) examined image-based follow-up after surgery, using results from a multicentre database (RECUR). Imaging intensity was studied with regard to outcome after disease detection in 1,612 patients with 17,333 imaging procedures analysed. A total of 336 recurrences were observed. Overall survival did not improve for patients for whom more than twice the number of imaging procedures were performed than recommended by the EAU guidelines. Interestingly, patients who received fewer procedures than recommended by the EAU guidelines had nearly identical OS curves as well (see Figure). It is of note that per patient treated for recurrence and remaining tumour-free after treatment, 542 imaging procedures were required (in high-risk patients, 697). In short, there was no survival benefit associated with additional imaging procedures.

Figure: RCC overall survival after recurrence detection, stratified by imaging ratio

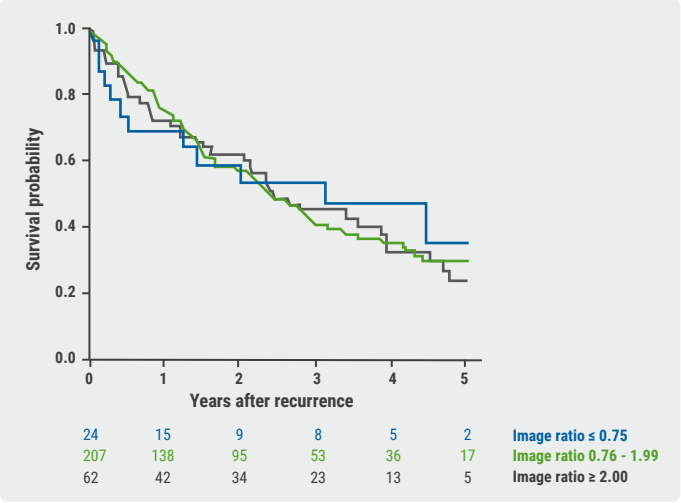


Image ratios defined as total number of imaging divided by estimated number of imaging for the given follow-up period according to the 2017 EAU guidelines follow-up imaging recommendations. No statistically significant difference between the groups was demonstrated. RCC, renal cell carcinoma.

Figure kindly provided by Dr Dabestani.

Andrology

Featured video: Microsurgical retrieval of sperm from the testicle is a possible treatment for male infertility defined by azoospermia, which can be caused by minimal sperm production or obstruction. watch the video

Featured video: Live Penile Implant Surgery (Dr Sean Park). watch the video

HPV and penile cancer

Some notable advances presented at the EAU strongly suggest that HPV probably does not affect fertility and that targeted therapies for penile cancer are on the near horizon.

Human papilloma virus (HPV) is a major public health problem not only in malignant disease (see Table) but also in benign disease. The group of Dr Andrea Salonia (University of Milan, Italy) presented their recently published research that the presence of HPV in sperm affects motility [1]. Furthermore, the group of Prof. Stéphane Droupy (University of Nîmes, France) performed a prospective study in a cohort of 350 couples undergoing assisted reproductive techniques with the aim to study the association between the presence of at least on HPV subtype and the outcome of pregnancies. They showed that at least one HPV subtype was present in 26.9% of women and 14.4% of men. Exposed couples gave birth in 23.3% of the cases to live children and non-exposed couples gave birth in 30% of the cases, which was not statistically significant (P=0.2). This study probably disposes the hypothesis that the HPV has an impact on fertility because they applied a really hard endpoint. Further research is understandably needed, and we will hear more about this association in the coming years.

Table: Number of all cancer cases annually attributable to HPV by region, cancer site, and gender. Modified from de Martel et al. Int J Cancer 2017

Region	Europe	World
Cervix uteri	58,000	530,000
Vulva	5,100	20,000
Penile	2,700	13,000
Anus male	2,700	17,000
Anus female	4,200	18,000
Head and neck male	11,000	30,000
Head and neck femal	2,800	7,500
All HPV related cancer	87,000	630,000

HPV, human papilloma virus

In penile cancer there is clear evidence for a pathophysiological relationship with HPV infection and the development of penile cancer [2]. In a very well attended and interesting thematic session about penile cancer, we heard that vaccination coverage rates are insufficient in most countries in Europe. Female/girl vaccination is reasonably well implemented with fairly good coverage, but boys are lagging behind and there is data that are really convincing to start vaccinating boys in those countries that have not implemented this yet. Dr Philippe Spiess (Moffitt Cancer Center, USA) gave an exceptional overview of targeted therapies being developed for penile cancer: "Advances in our understanding of the molecular pathways and driving mutations implicated in penile squamous cell carcinoma will with all likelihood result in additional personalised therapeutic options being integrated in our treatment armamentarium." For example, he pointed to a recent phase 2 clinical trial [3], where a combination of immune checkpoint blockade using nivolumab and a tumour-specific vaccine for patients with incurable HPV16-related cancer was explored. Although most of these tumours were oropharyngeal tumours, the results were very impressive with overall response rates of 33%, including complete responses seen in 8%, and several patients exhibiting durable responses up to 5 years. What made the results all the more exciting is that this combination approach has been trialled in a high-risk study population with patients often failing prior platinum-based chemotherapy or multiple lines of systemic therapy.

1. Boeri L et al. Hum Reprod. 2019 Feb 1;34(2):209-217.
2. Olesen TB et al. Lancet Oncol. 2019 Jan;20(1):145-158.
3. Massarelli E et al. JAMA Oncol. 2019 Jan 1;5(1):67-73.

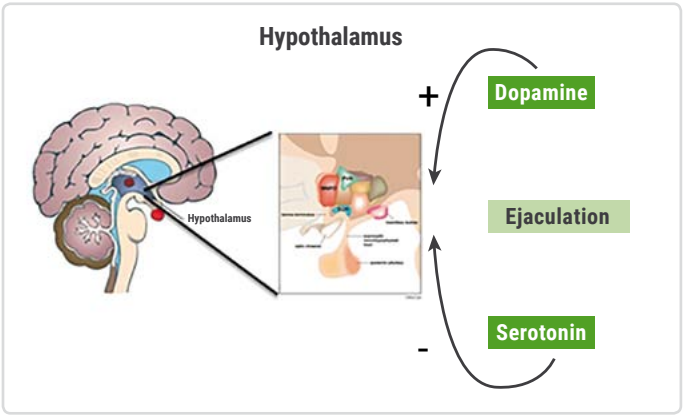
Male infertility/Premature ejaculation

Novel approaches for assisted reproduction and pharmacological treatment of premature ejaculation.

On the topic of male infertility, Dr Jonathan Ramsay (London, United Kingdom) presented that sperm harvested directly from the testes of 63 men with evident infertility has the same DNA integrity/quality as ejaculated sperm of 76 healthy donor men. This is important to know because sperm from infertile men is often burdened by excessive DNA damage and this can cause troubles with the success rates of Intracytoplasmic sperm injection and other forms of assisted reproduction techniques. In a comment from Prof. Maarten Albersen (Catholic University Leuven, Belgium) about this

study, he warns: "However, we have to interpret these results with caution; certainly because they are now available in the lay press, association of course is not causation, and an adequate interventional design is needed to assess whether selection of certain patients with DNA damage with TESE [eds, Testicular/Epididymal Sperm Extraction] rather than using ejaculated sperm facilitates the success rates of assisted reproduction."

Figure: Schematic overview of pathways controlling ejaculation



Dr Cath Mercer et al. (University College London, United Kingdom) presented recent data supporting that serotonin is important in ejaculatory control in men [1]. We have long known from preclinical models that stimulation of serotonin 1A receptor 5-HT1A precipitates ejaculation [2]. However, despite data gathered from patients taking selective serotonin reuptake inhibitors (SSRIs) demonstrating modest effects on ejaculation latency time [3], interventional studies in humans have been lagging. At this conference, there was a new double-blind, placebo controlled phase 1 study presented with a new antagonist to this receptor (7 mg GSK958108 treatment group) that showed that intravaginal ejaculation latency time was shown to be 77% longer (95% CI 28%-144%). The main common adverse effect was headache, reported by 20%. Collectively, we can conclude that developments in premature ejaculation are finally translating to the clinic and we might see new drugs available in the near future.

1. Choi JB et al. J Urol. 2019 Jan;201(1):147-152.
2. Arnone M et al. Behav Pharmacol. 1995 Apr;6(3):276-282.
3. Sun Y et al. World J Urol. 2017 Dec;35(12):1817-1831.

Testosterone replacement therapy: Safe and maybe even protective

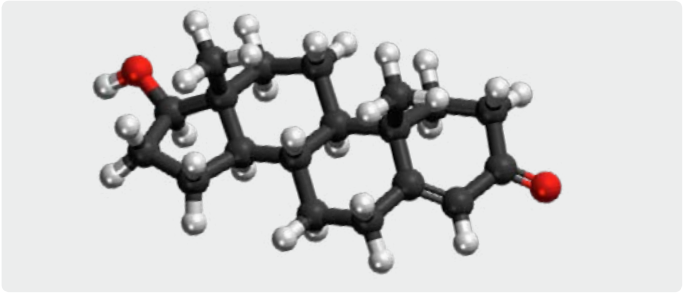
There was an exciting plenary debate on the safety of testosterone therapy after curative treatment of prostate cancer between Dr John Mulhall (Memorial Sloan Kettering Cancer Center, USA) and Prof. Bertrand Tombal (Catholic University Leuven, Belgium). The final conclusion from both speakers was that testosterone therapy is probably safe to give to certain patients with confirmed signs and symptoms of hypogonadism, even if they have been treated for prostate cancer with curative intent.

In the largest such study so far undertaken, Prof. Thomas Ahlering (University of California at Irvine, USA) presented a study where patients were selected for testosterone replacement after primary treatment of prostate cancer with robotic radical prostatectomy, in hopes of improving recovery of sexual function. You can watch Prof. Ahlering perform this surgery, streamed live on 29 January 2019 online [1]. Patients (n=834) undergoing radical prostatectomy were included; a subset of 152 low-risk patients with no evidence of disease were treated with testosterone replacement therapy. After a median of 3.1 years following surgery, they tested the patients for biochemical recurrence of the cancer, as indicated by measurement of the Prostate Specific Antigen levels. They found that the cancer had recurred in only approximately 5% of treated patients, whereas the cancer had recurred in 15% of the patients who did not receive testosterone. Overall, after accounting for differences between the groups, they found nearly a 3-fold reduction by 3 years. Dr Maxwell Towe (University of California at Irvine, USA) followed up with his data that in hypogonadal men, treatment with testosterone was associated with longer time to recurrence and delayed disease progression compared with standard management.

Prof. Ahlering commented, "This is not what we set out to prove, so it was a big surprise: not only did testosterone replacement not increase recurrence, but it actually lowered recurrence rates. While the testosterone is not curing the cancer per se, it is slowing the growth of the cancer, giving an average of an extra 1.5 years before traces of cancer can be found. We already know that testosterone can help with physiological markers such as muscle mass, better cholesterol and triglyceride levels, and increased sexual activity, so this seems to be a win-win".

The abstract from Ribeiro Morgado et al. (Centro Hospitalar de São João, Portugal) examined the cost-effectiveness of screening for testosterone deficiency which is now done step-wise. Their analysis conclusively showed that omitting this step-wise approach and performing a full-screening of the hormonal axis at the very beginning when you have a symptomatic patient is more cost-effective; this study is expected to lead to a change in the EAU Guidelines recommendations.

Figure: Ball and stick model of the testosterone molecule



1. https://www.broadcastmed.com/urology/8834/videos/robot-assisted-radical-prostatectomy-rarp

Focus on treatment of erectile dysfunction and Peyronie's disease

In Peyronie's disease (PD) two abstracts, one from Italy and one from the US (Gocci et al., and El-Khatib et al., respectively), reported substantial efficacy of intralesional collagenase injection in atypical or hourglass PD curvatures and ventral deformities.

While the initial studies were performed in typical PD with dorsal curvature [1], the Italian study demonstrated improvement of >20 degrees in 57% of their cohort; whereas in the US study 90% patients had an improvement of >20 degrees. Both studies convincingly showed that, for atypical PD patients, injection of this therapy seems to confer benefit and it can be used to avoid surgery in these cases. In more news about PD, we saw some exciting basic research from Dr Uros Milenkovic and colleagues (Catholic University Leuven, Belgium) who performed state-of-the-art RNA sequencing of the fibrotic plaques from PD. To their surprise, despite the fact that all plaques were taken from patients in the chronic phase of this disease where inflammation has presumably subsided, the data indicated that even though there is still a high turn-over of the extracellular matrix, it seems that this process is not necessarily maintained by myofibroblasts. Instead, a persistent immunological signature was apparent mainly involving macrophages. The novel hypothesis the authors proposed states that in PD fibrotic lesions, NF-KB-signalling can activate and maintain the presence of macrophages, which in turn activate the adaptive immune system involving T cells. The molecular understanding of PD pathophysiology might lead to the discovery of new targetables for pharmacological treatment, perhaps allowing an alternative to morbid surgery.

In terms of erectile dysfunction (ED), several treatment options are being explored. Shockwave therapy is an up and coming treatment for ED; treatment consists of non-invasive low-intensity sound waves that pass through erectile tissue, restoring natural erectile function by clearing plaques out of blood vessels and stimulating the growth of new blood vessels. Dr Antonio Ruffo and colleagues (Hospital Santa Maria delle Grazie, Italy) combined shockwave therapy with platelet-rich plasma (which is also being explored in this setting [1]) in a randomised control trial (n=60). They found that while shockwave therapy had a modest improvement in IIEF scores, the addition of platelet-rich plasma to shockwave therapy made these scores go up by about 8 points, allowing these men to have improved unassisted spontaneous erections. Percutaneous angioplasty for ED was tested in a small case series of only 6 patients by Marcer et al. (University Hospital Verona, Italy). This cohort was not responsive to pharmacological treatment before the experimental angioplasty. At 8 months after angioplasty, three men were fully responsive to PDE5 inhibitors, two men became responsive to intracavernosal injection therapy, and one patient did not respond at all but had to resort to a penile implant.

Dr Amr Abdel Raheem (Cairo University Hospitals, Egypt and University College London Hospital, United Kingdom) presented interim results (n=70, total will be 160) of his phase 2 randomised control trial that explored the efficacy and safety of botulinum toxin injection in the corpus cavernosum. He concluded that the botox-treated patients had a median improvement of 4 points in their IIEF5 scores over the placebo-treated group, indicating that this may be a promising treatment we may see emerge in the next few years.

1. Epifanova MV et al. Sex Med Rev. 2019 Mar 19. pii: S2050-0521(19)30008-3.

Penile prosthesis implantation

Measuring glucose and HbA1c in diabetic patients prior to surgery is not necessary; new antibiotic prophylaxis regimen for diabetic patients; report on ongoing studies on patient satisfaction after penile implantation.

Urologists may be reluctant to implant an inflatable penile prosthesis (IPP) in diabetic patients because of higher risk for infections [1]. Common practice is to screen patients for glycated haemoglobin A1c and blood glucose prior to surgery. Dr Mahmoud Osman et al. (Assiut University, Egypt) demonstrated that this precaution is not necessary and that comorbidity scores are a better predictor for infections and other complications. In support, the work of Dr Mohamad Habous et al. (Jedda, Saudi Arabia) similarly affirmed that the Charlson Comorbidity Index is a stronger predictor of outcome in 716 diabetic patients undergoing IPP in 15 US institutes and in a retrospective series (n=218) by high-volume surgeons in Jedda.

The current American Urology Association guidelines for antibiotic prophylaxis in the prevention of infections in diabetic patients that have undergone a penile prosthesis recommend gentamicin and vancomycin. A study by Prof. Thomas Ahlering and colleagues (University of California at Irvine, USA) showed that when you use this protocol there is a very high 7.7% infection rate, but when you add fluoroquinolone to the combination it drops to 1%. This abstract might be practice-changing and guideline-changing in the near future.

Which patient will benefit the most from IPP implantation?

Dr Frederico Dehò et al. (Università Vita-Salute San Raffaele, Italy) presented an abstract of the Italian registry of penile implants, currently at 265 patients operated on by 45 surgeons [2]. This study showed that patients with post-pelvic surgery or radiotherapy are more satisfied with their surgery and are reported higher quality of life measures when operated at high-volume centres. This prospective registry is now being expanded to the European setting within the PHOENIX study registry. There was a call to all urologists who perform implants to please get involved with PHOENIX for the best opportunities to improve best practice. Endpoints of PHOENIX will be patient satisfaction score at 12 weeks and 1 year after implantation, and then subsequently every 2 years of follow-up for 9 years.

1. Lipsky MJ et al. Sex Med. 2019 Mar;7(1):35-40.
2. Pescatori E et al. Arch Ital Urol Androl. 2016 Jul 4;88(2):122-7.

Functional Urology

Featured video: EAU animated video about how to treat OAB that can be shared with your patients. watch the video

Decision aids are too difficult for patients

An elegant study by Dr Florine Schlatmann and Dr Michael van Balken (Rijnstate Hospital Arnhem, the Netherlands) studied all available Dutch shared decision-making tools for urological patients and analysed them for complexity. Their conclusion was that almost none of the patients understood the decision aids given to them.

Asking the challenging question, "How do we involve our patients and do they understand what we are saying?", the researchers took all Dutch decision aids that are available for urological patients and looked at the quality of their clearness in informing patients. There were 13 decision aids in total, of which 4 had an Easy Read quality mark supposedly ensuring patient-friendly language. The texts were analysed, validated with software, and then scored for complexity; level 1 being the easiest (travel blog level) to level 4 being the hardest (scholarly article level). The difficulty of most of these aids landed between level 2 and 3. Their data showed that university-educated people could understand about 80% of aids that scored a 1; whereas people with a lower level of education only understood about 50%. In a decision aid scoring a 4, fewer than 10% of the text was comprehensible to people with an average education. The overwhelming conclusion was that most decision aids in the Netherlands are too difficult to understand for most of our patients, and extrapolating, this may even be a bigger problem in other countries.

Over-active bladder

An improved 10-site injection protocol of onabotulinumtoxin A reduces clean intermittent catheterisation use; BMI and UDI are independent predictors of sling surgery outcomes; urgency and nocturia are not being adequately addressed by muscarinic antagonists and possibly the greater family of ß-3 agonists.

Dr Kurt McCammon (Eastern Virginia Medical School, USA) compared data from 10-sites of injection of onabotulinumtoxinA vs the standard 20-site approach (both arms administered the same total amount of botox) in females with over-active bladder (OAB). He concluded that 10 injection sites (avoiding the bladder dome) preserved retention, improved quality of life, and was associated with lower clean intermittent catheterisation use. This study tested the outcomes of patients treated with the same number of onabotulinumtoxinA units, but in only 10 injection sites, 2 being placed in the trigone, and none in the bladder dome. The investigators observed that the efficacy of urinary incontinence episodes in the onabotulinumtoxinA 10-site group was better

than the placebo group (to be expected), but also that the patients that were completely dry at week 2, 6, and 12 were significantly higher in the onabotulinumtoxinA 10-site group. In total, 5% in this alternative group had no retention, which is similar to the rates reported to 20-site onabotulinumtoxinA injection. The authors concluded that the improvements in urinary incontinence as well as quality of life standards was similar with the alternative injection paradigm to those achieved with the standard 20-site regimen. However, the alternative 10-site injection paradigm cohort required no (0%) clean intermittent catheterisation use vs 5.2 % with standard paradigm. Adverse event safety was consistent with previous studies associated with low clean intermittent catheterisation use. These data strongly suggest that we do not have to use 20 injection sites, but that the same effect with can be achieved with 10 sites and that we should stay away from the dome to preserve contractility.

Dr Philip Toosz-Hobson (Birmingham Women's Hospital, United Kingdom), a uro-gynaecologist, interrogated whether patient characteristics influence the outcomes of sling surgery for stress incontinence. Delving into the 19,000 cases in the British Society of Urogynaecology database, they investigated body mass index (BMI, nearly all patients could be analysed) and urodynamic investigation (UDI) prior to surgery (n=9,737). Patients with a low BMI receiving slings had the fewest OAB symptoms post-surgery; those with high BMIs had linearly more symptoms, and the data clearly indicated that BMI stratification alone can predict outcome. To their surprise, when they stratified the smaller subset of patients with UDI results, UDI was also a strong predictor of the outcome of sling surgery; patients with a straightforward urodynamic-based diagnosis of stress incontinence had clearly better outcomes than those patients for whom unusual activity observed by UDI.

Prof. Martin Michel (University of Mainz, Germany) held a presentation about unmet needs in OAB patients. In particular, he focused on how many patients actually become symptom-free after treatment with propiverine. Using real-world evidence, he concluded that whereas marked improvement was reported in incontinence and frequency symptoms as a result of propiverine treatment, neither urgency nor nocturia were generally improved. This conclusion may be applicable to all muscarinic antagonists as well as possibly the greater family of ß-3 agonists. These data underscore a gap in medical treatment; the greatest medical needs in OAB efficacy are urgency and nocturia, since both have major adverse impact on quality of life, yet these are precisely the two symptoms that are not being improved by medical treatment.

There are two possible explanations for this conundrum: (1) that the pathophysiology at the time of diagnosis and start of treatment is at a stage where nocturia/urgency is fully reversible, and (2) that an unidentified "master switch" can improve all outcomes for individual patients. For the latter, there is an urgent need to identify subsets of OAB patients with specific pathophysiology associated with easily assayed biomarkers. The major conclusion drawn by Prof. Michel was that significant efficacy gains may not come from new drug classes if the overall OAB population is targeted, because the important quality of life parameters are not being adequately addressed. Stratification of patients by symptoms and pathophysiology will determine future success of symptom relief in OAB.
For an EAU animated video about how to treat OAB that can be shared with your patients, watch the featured video.

Office urology

The new European General Data Protection Regulation (GDPR), implemented on 25 May 2018, has practical implications in daily urological practice.

Dr Stefan Heansel (Franciscus Hospital Rotterdam, the Netherlands) explained how GDPR may influence clinical practice because we cannot spontaneously gather data anymore without asking the patient for consent in a specific and structured manner. The main purpose of GDPR is: (1) to establish the right of control and access to personal data, (2) to protect the rights of patients and confidentiality of personal data, and (3) to ensure that all health organisations are able to prove that they meet GDPR standards. GDPR applies to public data (name, address, birthdate), genetic data ("inherited or acquired genetic characteristics of a person which give unique information about the physiology or health of that natural person"), and health data ("data related to the physical or mental health of a person, including the provision of health care services, which reveal information about his or her health status"). Important take-home messages were that sharing data is allowed between institutions and does not require separate consent, meaning that an office practice can always consult with colleagues at the hospital without approaching the patient specifically for that purpose. The conditions are that the exchange must be appropriate, limited to what is necessary for the patient's immediate health, and that the other institution is also bound by professional secrecy. Examples of approved transfers of data are referrals, transmural video conferences, or additional information from earlier consultations. The main message is that transfer of patient data should not be discouraged by GDPR, but that organising your network properly will facilitate optimal treatment of your patients within the constraints of this law.

Lower Urinary Tract Symptoms

The Urodynamics for Prostate Surgery Trial

Insights from the UPSTREAM study, the best time for intervention, clinical efficacy for BPH, and invalidating fake news were covered during "What is the optimal treatment for patients with male LUTS?".

The Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods (UPSTREAM) compared two assessment pathways for men who are seeking further treatment for difficulty passing urine, including the possibility of surgery. In his presentation, Prof. Marcus Drake (North Bristol Hospital, United Kingdom) shared that symptom outcomes are non-inferior when urodynamics (UDS) is included in the assessment of male lower urinary tract symptoms (LUTS). However, in a patient preference analysis, most patients supported the inclusion of UDS to facilitate understanding of their condition.

One problem that must be addressed, according to Prof. Drake, is that presenting symptoms are often categorised as storage LUTS, directly affecting patient quality of life. However, therapy is often focussed on treating these patients for voiding LUTS by healthcare professionals. Obviously, this approach is misinformed and negligent to the patients' actual symptoms. Prof. Drake underscored that key symptoms are best identified by the International Consultation on Incontinence Questionnaire – Male Lower Urinary Tract Symptoms (ICIQ-MLUTS) [1] due to inclusion of urgency urinary incontinence, post micturition dribble, and individual symptom bother.

Discussant Prof. Stavros Gravas (University of Thessaly, Greece) asserted that the UPSTREAM trial reinforces that UDS use is best applied for selected patients only, and is not for general implementation. He also pointed out that UPSTREAM independently confirmed the EAU diagnostic pathway as a realistic and practical approach for the evaluation of men with LUTS.
Critically, UPSTREAM provides additional information on the values and preferences of patients, and how to counsel them. Data was also gathered on how centres perform UDS, how their standard operating procedures are adhered to, and how urologists interpret diagnostic results.

Timing of surgery was also considered: "To determine the best time for surgery, clinical progression (i.e. complications and refractory symptoms) and deterioration of the progressive bladder function should be taken into account," stated Prof. Ferdinando Fusco (University of Naples, Italy). One concern he raised was that accurate evaluation of bladder function in male patients with BPO currently requires invasive methods. New non-invasive methods such as near infrared spectroscopy may prove effective in the near future. He also stressed that more consideration should be given to objective common measures of BPO progression so that surgery can be performed before irreversible bladder damage occurs and affects surgical outcomes. "We can choose the best therapeutic window for our surgical activity, not only after medical treatment has been exhausted, but even before some irreversible damage in the bladder has been established," concluded Prof. Fusco.

1. http://iciq.net/iciq-mluts

Minimally invasive surgical techniques must compete against pharmacotherapy in benign prostate hyperplasia (BPH)

In his Société Internationale d'Urologie (SIU) lecture "What are we aiming at? Balancing costs or optimal clinical efficacy for intervention in BPH", Prof. Damien Bolton (University of Melbourne, Australia) said, "While TURP has and probably will remain the benchmark in terms of metrics, voiding flow, and International Prostate Symptom Score (IPSS) result, it does not tell the whole story."

Treating BPH with drugs vs surgery has demonstrated substantial reduced costs, can be associated with less patient morbidity, and can delay definitive treatment if necessary or desired. Prof. Bolton stated that even though symptomatic improvement might be suboptimal, it is acceptable to most patients as they prioritise quality of life over their flow rate.
Prof. Bolton postulated that minimally invasive surgical techniques must compete against pharmacotherapy to demonstrate advantages and to become the established standard of care. Until robust prospective data are obtained, pharmacotherapeutic therapies need to be weighed against surgery on aspects such as time in hospital, reduced time off work, side-effect profiles, and deferred cost of definitive treatment.