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European Association of Urology

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PEER-REVIEWED CONFERENCE REPORT

Clinical Trails based on Immuno Therapy

Results of immuno-therapy in prostate and urethelial cancer were presented.

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New Insights in Prostate Cancer

Novel screening methods and biomarkers are changing the landscape of treatment and aid prognosis.

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Robotic Surgery

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MEDICOM MEDICAL PUBLISHERS

Editor Prof. dr. Frank Van der Aa, University Hospital Leuven, BE

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Letter from the Editor

Prof. dr. Frank Van der Aa

Dear Reader,

Five days filled with urology. The 32nd annual EAU congress was, as ever, a large and lively congress, this year in the vibrant metropole of London. From the joint meetings of EAU with Urology Associations from all over the world on the 24th of March to the congress highlights of the souvenir session on the 28th of March: attendees could choose from a wide array of covered urological themes brought by the experts from Europe and even from around the globe.

Several plenary sessions gave us a nice overview of the current state in that specific domain of urology while others gave us more breaking news. The numerous video sessions were an opportunity for urologists to refresh technical points or to witness new techniques. Poster sessions gave more interactive opportunities between the presenters and the audience.

The wide spectre of the congress is reflected in this congress report issue of Medicom. We have selected several interesting topics, covering the majority of urological subspecialties. We hope the readers can refresh their ideas or get new insights in the covered topics. Attendees can refresh the messages given in the respective sessions, non-attendees can get a taste of EAU@London 2017.

Enjoy the congress report!

Kind regards,
Prof. dr. Frank Van der Aa

Biography

University Hospitals Leuven - UZ Gasthuisberg, Leuven, Belgium
Frank Van der Aa is adjunct head of clinic in the Department of Urology in the University Hospitals Leuven.
His special clinical interests are in neuro-urology, male and female incontinence and reconstructive urology.
He received his MD in 2001 from the Catholic University of Leuven and obtained his PhD in Medical Sciences in 2007 from the same university.
He became Fellow of the European Board of Urology (FEBU) in 2010 and Fellow of the European Board of Sexual Medicine (FECSM) in 2012.

Stone Disease

The latest research suggests that 12-h overnight urine samples are best to assess crystallization risk. Furthermore, upregulated expression of SLC26A6, melamine exposure and SPP1 gene polymorphisms, were found to be a risk factor for stone formation. Also, after initial cysteine stone presentation, being treated straight away lowers the recurrence rate and preserves renal function. Lastly, having urolithiasis may be a risk factor for fractures.

BMI influences stone formation

A retrospective cross-sectional analysis examined the differences in 24-h urine parameters by body mass index (BMI) in a large cohort of high-risk renal stone formers (n=442). Patients with higher BMI had a higher daily excretion of calcium (P=0.026), magnesium (P=0.000), potassium (P=0.000), sodium (P=0.000), oxalate (P=0.000), urate (P=0.000), phosphate (P=0.000), sulfate (P=0.000), chloride (P=0.000) and ammonium (P=0.009) [1].

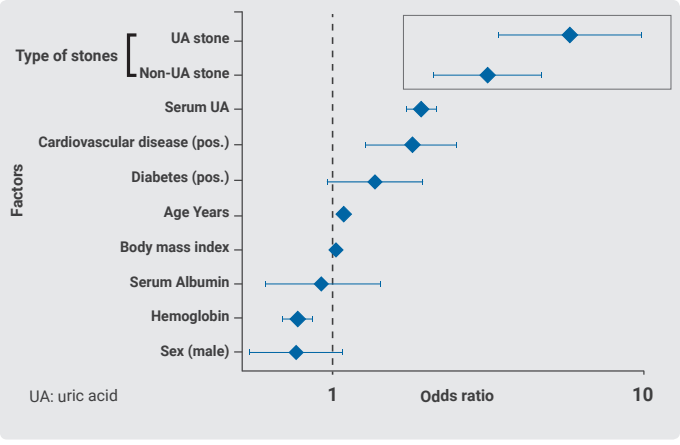
Alternative urine collection

The utility of a simplified alternative to urine collection – the 12-h overnight sample – for the evaluation of the urinary crystallization risk in healthy and stone forming subjects was studied by Casasayas Carles et al. Researchers collected 24-h urine samples from 75 healthy adults and 38 stone formers by using a split collection procedure (12-h daytime and 12-h overnight samples). The results showed that the ion-activity products of calcium oxalate (AP(CaOx)) index [2] was significantly higher in stone formers than in healthy patients in the three sample types. Median values of AP(CaOx) were 0.63 vs 0.74 (P=0.016; 12-h day), 0.60 vs 1.03 (P<0.001; 12-h night) and 0.58 vs 0.91 (P=0.001; 24-h urine). In stone formers, the AP(CaOx) index was higher in the 12-h overnight urine compared to 12-h daytime and compared to 24-h collection. It was concluded that calculation of the AP(CaOx) index, especially in 12-h overnight and the 24-h urine, discriminated the presence of risk between healthy subjects and stone formers. As the highest AP(CaOx) index values were found in 12-h overnight urine samples of stone formers, this suggests that the assessment of crystallisation risk in this type of sample collection might be useful in the clinical practice. However, further research is needed to confirm the usefulness of this simplified collection method in the evaluation of kidney stone disease [3].

Risk factors for chronic kidney disease

Although both hyperuricemia and uric acid stone are potential risk factors for chronic kidney disease (CKD), it is yet unknown which of the two increases the risk of renal function deterioration. However, recent findings by Tanaka et al. indicate that uric acid stone components may strongly influence renal function deterioration, more than hyperuricemia. This was concluded from a study which involved 123 patients with uric acid stones and who were compared with control subjects. Subjects were divided into two groups; hyperuricemia or non-hyperuricemia groups according to the serum UA concentrations (serum UA ≥ 7.0 or < 7.0 mg/mL). Renal function between the uric acid stone and control subjects in each group was compared and was evaluated as estimated glomerular filtration rate (eGFR). The uric acid stone patients had significantly lower eGFR (P<0.01) compared with control subjects, regardless of serum uric acid concentrations. Multivariate logistic regression analysis showed that age, past-history of cardiovascular disease, serum uric acid and stone former were significant factors for stage 3 CKD. UA stone component had a 3-fold chance to develop stage 3 CKD than serum UA concentration (Figure 1). "This means, that the relative odds ratio of uric acid stone was tripled compared to serum UA by a multivariate analysis. Odds ratios of UA stone and serum UA for the chance to develop stage 3 CKD were 5.8 and 1.9, respectively" according to Dr Tanaka [4].

Figure 1 Factors for stage 3 CKD [4]



High expression SLC26A6 as a risk factor for stone formation

Solute carrier family 26 members 6 (SLC26A6) is a multifunctional anion transporter and plays a critical physiological role in the transport of oxalate anions. The role of kidney SLC26A6 in urolithiasis was assessed by Jiang et al. and showed that a high expression level of SLC26A6 may account for the occurrence of kidney stones. Thus, down-regulating SLC26A6 expression in the kidneys may be a potential method to prevent or treat urolithiasis [5].

Urolithiasis an independent risk factor for fractures

Urolithiasis has shown to be an independent risk factor for fractures as was shown by a large Taiwanese study. A total of 27,237 adult subjects diagnosed with upper urinary track stones without a previous diagnosis of fracture, was matched with a cohort of 136,185 age and gender matched healthy controls. The minimal follow-up was 8 years. At the end of follow-up, 19.3% of the study subjects and 16.2% of the control subjects developed fractures. Upper urinary track stones were associated with a significantly increased risk of fracture (hazard ratio (HR) 1.20) when metabolic syndrome was not taken into account. After adjusting for age, gender and metabolic syndrome status, the Cox shared frailty regression analysis still showed that patients with upper urinary track stones were more likely to develop fractures than the patients without urinary stones (HR 1.18). Therefore, a follow-up of bone condition might be considered in patients with upper urinary track stones to decrease the risk of future fractures [6].

Melamine exposure linked to calcium urolithiasis

Melamine is a widely-used chemical found in a variety of everyday products. It is known to increase the precipitation of crystals leading to urolithiasis. However, long-term low-dose environmental exposure to melamine could also possibly induce renal tubular injury, which further increases the risk of urolithiasis. A study in 309 adult patients with calcium urolithiasis showed that urinary melamine levels were significantly positively correlated with the marker N-acetyl b-D-glycosaminidase (NAG) of renal tubular injury in adult patients with calcium urolithiasis. This finding suggests that besides causing the precipitation of crystals, melamine may also increase the risk of calcium urolithiasis by causing renal tubular injury. Further studies are needed to uncover the underlying mechanisms [7].

SPP1 gene polymorphism increases stone risk

Genotyping 9 known single nucleotide polymorphisms (SNPs) in secreted phosphoprotein 1 (SPP1) gene analysing genomic DNA from 1,026 individuals (n=342 patients with first episode calcium oxalate urolithiasis (COU), and n=684 healthy unrelated controls) showed that the SPP1 gene polymorphisms are associated with the COU susceptibility. Subjects with predisposing polymorphisms had decreased serum levels of osteopontin (OPN), furthermore urinary calcium/OPN ratios were higher in subjects with predisposing SNPs of SPP1 gene. Of a total of 28 constructed haplotypes, 6 demonstrated the significant association with COU risk. The results showed no sex difference [8].

Cystine recurrence prevention

A long-term study showed that cystine stone patients, who after their initial presentation receive early medical management, have the lowest recurrence rates and tend to preserve their renal function. Hence, prompt referral for metabolic assessment, early multidisciplinary input and the SaFER (Stone and Fragments Entirely Removed) principle are key to improving long-term function and quality of life (QoL) in this cohort of patients [9].

A small study in 17 cystinuric patients which assessed their adherence to treatment and follow-up and the correlation with clinical outcomes, failed to show any significant clinical benefit with conventional treatments for cystinuria in this cohort of patients. Better management protocols and/or measures of outcome and compliance may be required to optimise the management of this difficult-to-treat population [10].

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Retroperitoneal Surgery

Robotic surgery is making serious advances. Robot-assisted nephroureterectomies, adenomectomies and adrenalectomies were proven to be feasible, safe and effective. Furthermore, robotic adrenalectomy was performed in 13 patients without major complications. Also, (clampless) robotic nephrectomies were reported to be feasible and safe. Robotic surgery could decrease operative time, warm ischemia time and overall costs.

Single-installation robot-assisted nephroureterectomy

A single-installation robot-assisted nephroureterectomy (RAN) technique was assessed by Hugues et al. During nephrectomy, a Maryland Bipolar Forceps is placed on the 1st (cephalic) port, the 30° camera on the 2nd port – the use of a 30° endoscopic camera is essential – monopolar electro-surgical scissors on the 3rd and a ProGrasp forceps on the 4th caudal port. The 10 mm assistant port is used for a suction cannula and Hem-o-Loks positioning. During the pelvic part, a clockwise rotation of the instruments is performed: the ProGrasp Forceps is relocated on the 1st robotic arm, the Bipolar forceps on the 2nd arm, the 30° camera on the 3rd, and Monopolar Scissors on the 4th, without any need of undocking the robot or repositioning the patient. The ureter is then easily dissected until its distal portion, with a bladder cuff, and a water-tight bladder closure is done with 3/0 V-Loc thread. This procedure has shown to be simple, feasible, and it can be easily reproduced thus allowing benefits of robotic surgery [1]*.

Robotic adrenalectomy

A review of 13 patients who underwent robotic adrenalectomy (RA) with adrenal lesions greater than 4 cm at pre-operative evaluation, showed that RA represents a safe and effective procedure. Mean tumour size in these patients on CT or MRI imaging was 53 mm (median 53 mm; range: 40-78 mm). No intra-operative complications or transfusions were recorded. Mean length of surgery was 146 min and 15.38% post-operative complications were observed, both minor according to Clavien-Dindo scale (CD; 1-2). No major complication (CD ≥3) was observed. Mean timing of drainage removal was on post-operative day 3 and the mean length of hospital stay was 4 days. The pathological specimens mean size was 60 mm. No positive surgical margins were recorded. The rate of malignant lesions was 23.08%. At a mean follow-up of 13 months, no local recurrence of the disease was observed (Table 1) [2]*.

Robotic-assisted laparoscopic adenomectomy

Robotic-assisted laparoscopic adenomectomy for the treatment of aldosterone producing adenomas is feasible and safe, as was demonstrated in a review of 10 robotic assisted laparoscopic adenomectomies on patients with aldosterone producing adenomas. All cases were performed completely robotically. Median operative time was 170 min, median estimated blood loss was 50 ml and the median tumour size measured 1.9 cm. There was no conversion to an open procedure. At a median follow-up of 12.5 months, there were no recurrences and hypertension was improved/resolved in 90% of patients [3]*.

Robotic-assisted thoracoscopic transdiaphragmatic adrenalectomy

Robotic-assisted thoracoscopic transdiaphragmatic adrenalectomy (RATTA) for metastatic clear cell renal cell carcinoma (CCC) was described for the first time in a patient with a history of transabdominal surgeries. The patient underwent concomitant right robotic-assisted thoracoscopic pulmonary wedge resection and left RATTA. The patient's

Table 1 Intra-operative and peri-operative data [2]

Side, n(%) **Left** **Right** **Bilateral**	**38,46% (5)** **53,85% (7)** **7,69 (1)**	**Length of hospital stay, d** **Mean (median)** **Range**	4 (4) (3-7)
Operative time, min Mean (Median) Range	146 (129) (102-265)	Post-op complications, n (%) Minor (CD 1-2) Major (CD ≥3)	15.38% 0% (0)
Estimated blood loss, mL Mean (Median) Range	96 (50) (0-350)	Post-op transfusions, n (%)	7.69% (1)
Intra-op complications, n (%)	0% (0)	Δ Haemoglobin (preop - discharge), g/dL	1.69 (1.60) (0.6 - 3.20)
Intra-op transfusions, n (%)	0% (0)	30-d readmission, n (%)	0% (0)
Surgical conversions, n (%)	0% (0)	Follow-up, months Mean (Median) Range	13 (12) (3-22)
Drainage removal, d Mean (Median) Range	3 (3) (2-7)		

The researchers stressed that standardisation of each surgical step is critical in the achievement of optimal surgical outcomes [2].

operative and post-operative courses were uncomplicated. This novel technique represents a feasible alternative to transperitoneal or retroperitoneoscopic approaches in patients with previous abdominal and retroperitoneal surgeries [4]*.

Robotic partial nephrectomy

A simplified approach of robotic partial nephrectomy (RPN) was presented by Peyronnet et al. A 60-year-old female with a tumour of 42 mm of the lower pole of the right kidney (RENAL SCORE 7a) underwent the procedure which can be summarized in 10 points:

1) no preoperative ureteral stent;
2) no flexion of the table during patient positioning;
3) the choice of a transperitoneal route in every case;
4) no use of the fourth arm of the robot;
5) minimal colonic mobilization;
6) no vessel loops on the renal pedicle;
7) minimal dissection of the perirenal fat;
8) no use of hemostatic agents;
9) early unclamping; and
10) no post-operative drainage.

The operative time was 90 minutes and the warm ischemia was 8 minutes. No intraoperative or postoperative complications occurred and the patient was discharged on postoperative day 2. Pathological exam revealed a renal cell carcinoma PT1B R0. This simplified approach can potentially decrease the costs, the operative time and the warm ischemia time. It could also result in a shorter learning curve for urologists in training [5]*.

Clampless robotic partial nephrectomy

Clampless RPN was performed in 10 of a total of 20 patients who underwent RPN with a median tumour size of 7.5 cm. The results showed that nephron sparing surgery is feasible and safe, also in selected patients with large renal masses. Tumour size alone should not represent an exclusion criterion. A clampless approach should be attempted in every case: intraoperative clamping in the event of major bleeding may ensure a clear view of the operative field [6]*.

Transmesocolic laparoscopic partial nephrectomy

Transmesocolic laparoscopic partial nephrectomy in patients with renal cell carcinoma (RCC) in a horseshoe kidney was performed, although little documentation exists on these particular type of cases. The warm ischemia time was 19 minutes and the operation time was 210 minutes. There were no intraoperative and postoperative complications. The patient was discharged from the hospital after 5 days; no RCC recurrence was observed after 1 year. Thus, a non-standard approach and -usage of armamentarium, enabled surgeons to perform laparoscopic partial nephrectomy, despite aberrant anatomic features of the kidney [7]*.

**This abstract was presented as a video*

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Immuno-Oncology

Promising trial results of several human or humanised antibodies as immunotherapy cancer treatment against prostate cancer, urothelial cancer, renal cell carcinoma and germ cell tumours.

Immunotherapy in prostate cancer

Immunotherapeutic modalities in oncology consist of cellular immunotherapy, therapeutic vaccines and checkpoint inhibitors. A difference with e.g. chemotherapy, is that immunotherapy takes longer to show effects. The only proven efficacy on overall survival (OS) in castration-resistant prostate cancer (CRPC) so far, has been observed with Sipuleucel-T [1]. The IMPACT phase 3 trial showed better OS, compared to controls (4.1-month survival benefit, a reduction in risk of death with 22.5%, HR 0.775, P=0.032) [2]. However, Sipuleucel-T is not yet available in Europe, only in the United States. Checkpoint inhibitors in CRPC are CTLA-4 (ipilimumab) and programmed death (PD)1/ programmed death-ligand (PD-L)1. Two phase 3 trials are conducted with ipilimumab: one pre-docetaxel and one post-docetaxel. The long lasting response has been shown in metastatic (m)CRPC patients, who were progressing post-docetaxel and required opioids for pain management [3]. Another strategy counteracting tumour development and growth, is immune checkpoint blockade; however, the first nivolumab data reported no efficacy, which led to the idea that PD-1/PD-L1 inhibitors in CRPC have limited activity. Recently, pembrolizumab in the KEYNOTE-028 study showed efficacy with a -30% change from baseline in tumour reduction [4]. Turning a cold tumour in a hot one (generating neo-antigens) by targeting both the tumour and the direct microenvironment, to induce a systemic immune response. This could be achieved by increasing the PD-1 inhibition efficacy, by radiation or other local treatments. It might also be achieved by systemic pressure (enzalutamide etc.), a selection of a subgroup, an anti-PD-1/PD-L1 + anti-CTLA4 combination therapy, and perhaps checkpoint inhibition + vaccine. Although vaccine strategy has been a failure so far, a phase 2 study with Prostvac in patients with mCRPC, showed an 8.5 months survival benefit and a reduction in the risk of mortality of 44% (HR 0.56, P=0.0061) [5]. According to Cornford, the current priorities in immuno-oncology for prostate cancer (PCa) are optimising therapies, with more patients who will be able to benefit from these treatments as well as identifying biomarkers [6].

Pembrolizumab in prostate cancer

Pembrolizumab is currently being investigated in the phase 1b/2 KEYNOTE-365 study in mCRPC patients enrolled in 3 cohorts. This trial is designed to evaluate the safety and tolerability of pembrolizumab combined with olaparib, docetaxel + prednisone, or enzalutamide in patients with mCRPC and to estimate the prostate specific antigen (PSA) response rate for each combination cohort. Cohort A consists of mCRPC patients who had prior docetaxel treatment (1 other chemotherapy as well as up to 2 second-generation hormonal manipulations allowed); they will receive pembrolizumab + olaparib. Cohort B consists of mCRPC patients who were treated with abiraterone acetate or enzalutamide in the pre-chemotherapy mCRPC setting; they will receive pembrolizumab + docetaxel + prednisone. Cohort C consists of mCRPC patients which had prior treatment with abiraterone acetate in the pre-chemotherapy mCRPC setting. They will receive pembrolizumab + enzalutamide. Approximately 210 (70 patients per cohort) patients will be enrolled and treatment will continue for a maximum of 35 cycles (approximately 2 years), unless specific discontinuation or withdrawal criteria are met [7].

Pembrolizumab in urothelial cancer

The KEYNOTE-052 (n=370) trial investigated the treatment effects of pembrolizumab in key first-line subgroups of patients with urothelial cancer. This study included adult patients with advanced urothelial cancer of the renal pelvis, ureter, bladder or urethra. Patients were cisplatin ineligible and had received no prior systemic chemotherapy for advanced UC. Pembrolizumab 200 mg was administered every 3 weeks. The primary end point was confirmed by the overall response rate (ORR). A total of 370 patients was included and received ≥1 infusion of pembrolizumab. The ORR was 27% among patients with ≥4 months follow-up (n=307). From the total, 6% of patients achieved a complete response. ORRs were similar among patients, regardless of their reason for cisplatin ineligibility: 26% for Eastern Cooperative Oncology

Group (ECOG) PS 2, 27% for renal dysfunction, 29% for ECOG PS 2 and renal dysfunction. The ORR was 26% in patients ≥65 years of age, 24% for patients with visceral disease and 28% for patients with lower tract disease. Patients which had a combined positive score ≥10% PD-L1 (tumour and immune cell PD-L1 expression) with ≥4 months follow-up had ORR of 44%. Adverse events (AEs) of any grade and grade ≥3 drug-related AEs occurred in 62% and 16% of all patients, respectively. From the total, 5% discontinued treatment due to a drug-related AE and 17% patients experienced an immune-mediated AEs of special interest. Powles noted that biomarker positivity may become a key feature, with regard to eligibility of patients for immunotherapy [8].

Doublet chemotherapy and immuno-therapy for metastatic urothelial cancer

Necchi et al. compared immunotherapy (IT) with doublet chemotherapy (CT) in a meta-analysis, by using the PICO (Population, Intervention, Comparison and Outcome question: which are the outcomes of IT vs single agent CT vs doublet CT as salvage therapy for metastatic urothelial cancer (mUC) strategy. Arms of phase 2 or 3 studies of salvage single-agent anti-PD-1/PD-L1 agents pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, single-agent and doublet CT were included. A total of seven IT trials was analysed (n=1,041); 22 arms received single agent CT (n=1,202) and 24 doublet CT (n=708). The pooled ORR was 21.2% with IT, 14.2% with single-agent CT and 31.9% with doublet CT. Pooled median progression free survival (PFS) was 1.8, 2.69 and 4.05 months, respectively. Pooled median OS was 8.27, 6.98 and 8.50 months. Pooled median ORR and OS of IT for PD-L1+ patients were 30.7% and 11.6 months, respectively. Univariable (UVA) and multivariable (MVA) analyses are shown in Table 2 (only UVA was possible for PD-L1+ patients) [9].

Table 2 UVA and MVA analyses [9]

	ORR Odds ratio (95%CI); P-value	OS median difference, months (95%CI); P-value
1. IT vs single agent CT		
UVA	1.63 (1.00, 2.66) P=0.049	1.77 (-0.39, 3.92) P=0.109
MVA	1.90 (0.93, 3.86) P=0.075	1.34 (-1.33, 4.01) P=0.327
2. IT vs doublet CT		
UVA	0.58 (0.37, 0.89) P=0.012	0.65 (-2.10, 3.40) P=0.645
MVA	0.88 (0.45, 1.72) P=0.711	0.78 (-1.71, 3.28) P=0.538
3. IT vs single agent CT		
UVA (PD-L1+)	2.67 (1.65, 4.32) P<0.001	4.82 (2.37, 7.28) P<0.001
4. IT vs doublet CT		
UVA (PD-L1+)	0.94 (0.62, 1.44) P=0.790	3.65 (0.61, 6.69) P=0.018

Thus, IT was associated with significantly higher pooled median ORR and OS in PD-L1+ patients compared with single-agent or doublet CT, while significant differences were not observed in unselected patients. These results are hypothesis-generating and suggest the importance of developing companion predictive biomarkers [9].

Atezolizumab in urothelial cancer

In the phase 3, open-label, multicentre, randomised, controlled trial IMvigor01, the efficacy and safety of atezolizumab vs observation in the adjuvant setting in patients with muscle-invasive UC is being assessed. Eligible patients will have histologically confirmed muscle-invasive UC, ECOG PS 0-2 and had radical surgical resection within the previous 14 weeks with no residual disease. No prior adjuvant therapy is allowed. The primary efficacy endpoint is disease-free survival. Secondary efficacy endpoints include OS, disease-specific survival, distant metastasis–free survival and non-urinary tract recurrence-free survival. Patients will be randomised to arm A (atezolizumab 1200 mg IV q3w [16 cycles or 1 year]) or the observation arm with alternating clinic visit/phone call q3w (16 cycles or 1 year). This trial is currently enrolling globally, with a target of approximately 700 patients [10].

Nivolumab in renal cell carcinoma

The CheckMate 025 (n=821) has shown the superiority of nivolumab over everolimus, after 1 or a maximum of 2 regimens of antiangiogenic therapy in OS, overall response, AEs and health-related quality of Life (HRQoL). Based on these results, nivolumab is already implemented in the guidelines for RCC [11-13]. A prospective observational study has now been designed to collect real-world data on the use of nivolumab in stage 3/4 RCC. Patients diagnosed with advanced RCC, with clear-cell and non-clear-cell histology, who start a new systemic therapy with nivolumab only after prior therapy, according to the marketing approval of nivolumab in Germany, are eligible. The treatment consists of nivolumab 3 mg/kg intravenously 2 weeks. Primary endpoint is OS and secondary endpoints are PFS, ORR, OS in subpopulations, safety profile, management of immune-related AEs, treatment patterns and QoL. Presently, 20 patients have been included of the total of 323, which researchers aimed to include [14].

Durvalumab in germ cell tumours

Durvalumab is a monoclonal antibody (mAb) that inhibits the binding of PD-L1, which is frequently used

in immunohistochemistry to make germ cell tumours visible. Tremelimumab – an anti-CTLA4 mAb – is an immunomodulatory therapy. Combination immunotherapy has shown improved activity compared to monotherapy. Necchi et al. are currently investigating the activity of durvalumab alone, or in combination with tremelimumab in chemorefractory germ cell tumours, in an open-label, randomised, 3-stage, phase 2 study. Patients who have failed ≥2 prior CT regimens (including high-dose CT), will be randomised to receive one of the following: 1) durvalumab monotherapy (durvalumab 1.5 g via IV infusion q4w, for up to a total of 12 months (13 doses/cycles), 2) durvalumab 1.5 g via IV infusion q4w + tremelimumab combination therapy, and finally 3) durvalumab 1.5 g via IV infusion q4w. The treatments start on week 16, for up to a total of 8 months (9 doses/cycles) and tremelimumab 75 mg IV q4w, starting on week 0 for up to 4 months (4 doses/cycles). The primary endpoint is the ORR (complete response or partial response with normal markers). The null hypothesis was an ORR rate of ≤10%, whereas alternative hypothesis was an ORR rate of ≥25%, type 1 and 2 error rates at 10% [15].

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Prostate Cancer

The heterogeneity of prostate cancer remains a challenge for stratifying treatment strategies. Developments with identifying appropriate biomarkers and MRI-screening allows determination of correct type of PCa, and could aid individuals at increased risk of harbouring aggressive forms of PCa. Other research indicates that novel combination therapy inhibits resistance in CRCP cells.

EAU guidelines metastatic castration-resistant prostate cancer

CRPC can be defined as a castrate level of serum testosterone <50 ng/mL, as well as biochemical progression (three consecutive rises of PSA, which result in two 50% increases above the nadir value, with PSA > 2 ng/mL) or radiological progression (two or more bone lesions on bone scan or enlargement of a soft tissue lesion based on RECIST criteria). Patients with biochemical CRPC are at high risk for progression; approx. 1/3 develops metastasis within 2 years. However, no evidence for early intervention is available at the moment. The RADAR group consensus statement on these high-risk patients recommends bone and computed tomography scans to be performed when the PSA reaches 2 ng/mL. If the outcome is negative and when the PSA reaches 5 ng/nL as well as after every PSA doubling, the scans should be repeated. Nonmetastatic patients are eligible for 'watchful waiting', and surveillance imaging scheduled as outlined above. The choice of treatment to be initiated depends on patient PS and symptoms. There are several treatment options for asymptomatic or mildly symptomatic

patients: sipuleucel-T immunotherapy (IMPACT), abiraterone + prednisone (COU-AA-302), enzalutamide (Prevail) or docetaxel (TAX 327). For symptomatic patients without visceral metastasis, radium-223 (ALSYMPCA) or docetaxel are suitable treatment options. Docetaxel should also be given to patients with visceral metastasis. The consensus statements by the 2015 Advanced Prostate Cancer Consensus Conference, recommends that patients should be assessed every 2-3 months during which a history and physical examination is performed as well as PSA, complete blood count (CBC) and metabolic tests. With regard to imaging, this should be performed every 6 months and consists of a bone scan and CT chest, abdomen and pelvis. A change of treatment is indicated in case two of these three parameters are met: PSA progression, radiological progression or clinical deterioration. Second-line treatment options include abiraterone (COU-AA-301), enzalutamide (AFFIRM), cabazitaxel (TROPIC), docetaxel or radium-223. It should be noted, that patients who are initiating second-line therapy are at risk of treatment resistance. Asymptomatic patients with poor PS status should be considered to be eligible for watchful waiting. Palliative care should be discussed with the patient and his family in case of a progressive disease. mCRPC patients are likely to experience complications and side effects during their last year of life (Figure 2) [1,2].

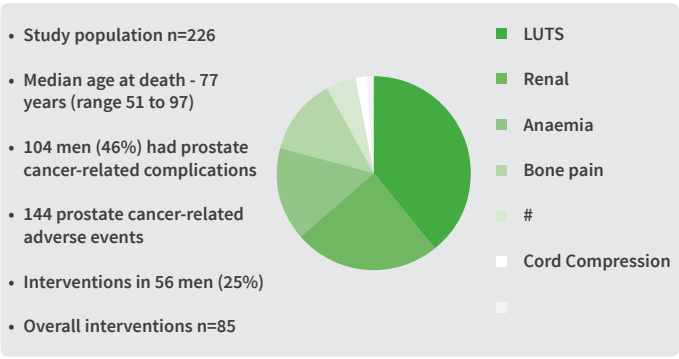
The most common are anemia, lower urinary tract symptoms (LUTS) as well as bone pain and up to one-third of patients will require palliative procedures including ureteral stents, nephrostomy tubes and channel TURP [2].

Biomarkers

Treatment associated small-cell neuroendocrine carcinoma (SCnC) is a poor prognosis CPRC variant; new histological markers of mCRPC – intermediate atypical PCa (IAC) – has been identified. IAC combined with t-SCnC accounts for 43% of all biopsies. IAC and t-SCNC do not appear to be androgen-receptor (AR)-silent and offer an opportunity for co-targeting strategies.

AR-V7 and AKR1C3 two of multiple resistance mechanisms for CRPC, and this can be measured in the blood and are potential predictive biomarkers. New co-targeting approaches can overcome AR-V7 and AKR1C3. ROR-γ is a nuclear receptor that regulates AR expression – it is overexpressed in >50% of CRPC tumours by immunohistochemistry); it directly controls AR gene expression via a novel AR-RORE. ROR-γ drives AR expression and represents a therapeutic target in CRPC; levels of ROR-γ can be detected by sequencing or immunohistochemistry and ROR-γ can be inhibited with new compounds to treat CRPC [3].

Figure 2 The last year of life CRPC [1,2]



Targets for individualised prostate cancer treatment

Stratification is needed as current therapies are not sufficient; emerging biology and genomics indicate stratification. PCa is not one disease, but instead, a highly heterogeneous group of diseases (inter- and intra-patient heterogeneity). Identifying key mutations remains a major challenge, albeit that in the majority of CRPC actionable mutations were found.

There are many genomic aberrations such as AR (mutations, amplification, rearrangements and splice variants), PI3K/AKT (PTEN, PI3K/AKT copy gain/mutation/rearrangements) and DNA repair defects (homologous recombination repair; mismatch repair). Practical recommendations include treatment molecular stratification of PCa, envisioned by immune checkpoint inhibitors for Microsatellite instability-high disease and PARP inhibitors for homologous recombination DNA repair defective disease. Also, analytically validated biomarkers should become widely available to drive stratified clinical trial accrual. Completing key clinical trials will be necessary; AR-SV+ advanced PCa will probably be treated best by taxanes, phosphatase and tensin homolog deleted on chromosome 10 loss patients may benefit from AR+AKT combined blockade and homologous recombination deficiency (HRD) cancers benefitting from platinum-based therapy [4].

Niclosamide against abiraterone and enzalutamide resistance

Gao et al. tested whether niclosamide can overcome resistance and improve therapies by targeting AR variants. Resistant PCa cells to enzalutamide and abiraterone were generated by continuous culturing the cells in media containing increasing doses of either enzalutamide or

abiraterone. Both resistance cells express high levels of AR variants including AR-V7. Drug screening identified niclosamide, currently used as an anthelmintic agent approved by the Food and Drug Administration, for the treatment of tapeworm infections, also as a potent AR-V7 inhibitor in PCa cells. Niclosamide significantly decreased AR-V7 protein expression by protein degradation through a proteasome dependent pathway. Niclosamide also inhibited AR-V7 transcription activity and reduced the recruitment of AR-V7 to the PSA promoter. Niclosamide inhibited resistant PCa cell growth in vitro and tumour growth in vivo. Furthermore, the combination of niclosamide, with either enzalutamide or abiraterone, resulted in significant inhibition of enzalutamide/abiraterone-resistant tumour growth. These results suggest that niclosamide enhances abiraterone/enzalutamide therapy and overcomes resistance to abiraterone/enzalutamide in CRPC cells [5].

Prostate cancer screening

PCa is a highly heterogeneous disease, ranging from indolent tumours to a rapidly progressing and life-threatening metastatic disease. Although current screening methods such as the PSA blood test can identify prostate cancers, they are not favourable at identifying how dangerous they are, or even whether they should be treated. There is an obvious need for markers that can specifically identify individuals at increased risk of harbouring aggressive forms of PCa. Researchers surveyed the Kallikrein (KLK) region (KLK1-15) for SNPs associated with aggressive PCa (defined as Gleason Score ≥ 8) in 1,858 PCa patients. Discovery cohorts (Swiss arm of the European Randomized Study of Screening for PCa, n=379, and Toronto, Canada, Princess Margaret Cancer Centre, n=540) and a validation cohort (Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial, n=939) were analysed. It was found that several SNPs, in a very strong linkage disequilibrium in the KLK6 region and located within the same haplotype (rs113640578, rs79324425, rs11666929, rs28384475, rs3810287), identified individuals at increased risk of aggressive PCa in both discovery and validation cohorts. The validation cohort revealed another important haplotype with 2 SNPs at the same locus (rs28665094, P=0.006 and rs268890, P=0.005) associated with aggressive PCa. The overall test of haplotype association was highly statistically significant in the discovery cohort, in the PLCO cohort, and in the 3 data sets combined. These germline SNPs predicted relapse independently of standard clinical and molecular factors in the International Cancer Genome Consortium cohort (HR = 3.15, 95%CI = 1.57-6.34 P=0.001). It was concluded that this fine-mapping study has identified novel loci in the KLK6 region strongly associated with aggressive PCa and predicting biochemical relapse. Additional sequencing studies might help identifying rare variants with major effect in this KLK6 region [6].

Magnetic resonance imaging in prostate cancer screening

The European Randomised study of Screening for Prostate Cancer (ERSPC) showed that screening using sextant transrectal ultrasound-guided biopsy (6-TRUS-Bx), reduces mortality but also leads to overdiagnosis. A screening strategy using 12-core TRUS biopsy (12-TRUS-Bx) could increase the high-grade (Gleason score ≥ 3+4) PCa detection, while a magnetic resonance imaging (MRI) +/- target biopsy (MRI ± targeted biopsy (TBx) strategy could reduce overdiagnosis of low-grade (Gleason score 3+3) PCa. A Dutch study compared the 3 biopsy strategies in the 5th screening round of the ERSPC Rotterdam; by giving men in the 5th screening round, with a PSA ≥ 3.0 ng/ml, either 6-TRUS-Bx or the patient chose to be included in the MRI side study, and received a multiparametric MRI. In men in the side study a 12-TRUS-Bx was performed, blinded for MRI results. Additionally, prostate imaging reporting and data system ≥3 lesions were targeted with 2 cores using MRI-TRUS fusion guidance. The PCa detection rates of 3 biopsy strategies were compared: the 6-TRUS-Bx (group 1) vs 12-TRUS-Bx (group 2a) vs MRI ± TBx (group 2b). A total of 177 men with PSA ≥3.0 ng/ml received 6-TRUS-Bx, while 158 men received MRI with 12-TRUS-Bx ± TBx. These men had a mean PSA of 5.1 ng/ml. A total of 55% had a previous negative 6-TRUS-Bx. There were no significant differences in terms of age, PSA and previous biopsy status among men who received 6-TRUS-Bx and men in the MRI side study. From the total 70% of men in the side study had no suspicious lesions on MRI and thus did not receive TBx. The high-grade PCa detection rate of 6-TRUS-Bx (10%), 12-TRUS-Bx (12%) and MRI ± TBx (11%) were comparable. The low-grade PCa detection rate of 12-TRUS-Bx (28%) was significantly higher compared to 6-TRUS-Bx (17%), while the low-grade PCa detection rate of MRI ± TBx (7%) was significantly lower. Thus, the performance of 12-TRUS-Bx, instead of 6-TRUS-Bx, increased only the detection of low-grade PCa. An MRI ± TBx strategy reduces biopsy procedures (70%) and overdiagnosis of low-grade PCa (>50%), while maintaining a similar detection rate of high-grade PCa. The MRI ± TBx strategy is thus preferred, as it tackles the major drawbacks of population-based screening [7].

Active surveillance vs radical prostatectomy or radiotherapy

A Dutch 15-year follow-up study in PCa patients, showed that in appropriately selected patients with active surveillance, no difference in metastasis-free survival is observed when compared to men undergoing radical prostatectomy or radiotherapy. The researchers used the ERSPC Rotterdam (1993-2003) cohort to identify patients diagnosed with PCa during the first and second screening round, and who were considered suitable for active surveillance (n=223). This cohort was compared to patients undergoing radical prostatectomy (n=365) or radiotherapy (n=312). After a 15-year median follow-up, 2% of patients had died from PCa. No difference was seen in PCa specific survival among active surveillance patients (97%), radical prostatectomy (98.5%) or radiotherapy (97.5%; P=0.36). No difference was observed for metastasis-free survival (active surveillance – 96.9%, radical prostatectomy – 97.9%, radiotherapy – 96.6%; P=0.42; Table 3) [8].

It was noted that patients who are considering AS should be appropriately counselled about its specific risks and benefits [8].

PRX302

PRX302 (topsalysin) is a genetically modified pore-forming protein (aerolysin), which is intraprostatically activated only by enzymatically active PSA. Toxicity, side-effects and potential efficacy were assessed in the first proof-of-concept study of MRI-ultrasound fusion-guided intra-prostatic injection of PRX302 to histologically proven, clinically significant, localised low to intermediate risk PCa associated with an MRI lesion. A total of 18 patients with clinically significant localised cancer, defined as either Gleason ≤4+3 with a maximum cancer core length (MCCL) ≤10 mm, or Gleason 3+3 with MCCL ≥ 4 mm, were enrolled. All patients had a single pre-identified lesion, which was injected transperineally using MRI-ultrasound elastic image-fusion software, with up to 5 mL of a standard dosing solution of 20 µg/mL PRX302. Follow-up occurred at 2 days (teleconsult) and at 2, 6, 12, 24 and 26 weeks. A mpMRI-targeted transperineal biopsy of the treated area was carried out at 24 weeks (6 months). Throughout the study, no serious adverse events were reported. Biopsy data at 24 weeks following treatment showed that 11% had complete tumour ablation, with no histological evidence of any cancer at 6 months. From the total 39% had partial ablation, defined as reductions in MCCL or Gleason grade, whereas the remaining 50% had no histological response and in some cases experienced an increase in MCCL or upgrading. The urinary and sexual function was preserved. These findings indicate that a single intraprostatic administration of PRX302 can safely ablate prostate tumour cells. Moreover, optimising the delivery of PRX302 and the dosage based on tumour size, might increase response rates, which were considered lower than expected by the researchers. Further research will test this in a multicentre phase 2 study. It was concluded that PRX302 has the potential to safely ablate clinically significant lesions. In doing so, it could obviate or prolong time to radical therapy in this particular patient population [9].

Table 3 PCa specific survival and incidence of metastatic disease after 15-year follow-up [8]

Outcome measure	Radiotherapy n=312	Radical Prostatectomy n=365	Active Surveillance n=223	P-value
PCa death, n (%)	8 (2.6)	5 (1.4)	5 (2.2)	Log-rank
PCa survival, % (95% CI)				
5 yrs	100	99.4 (98.7 - 100)	99.6 (98.7 - 100)	
10 yrs	98.4 (96.9 - 100)	98.8 (97.7 - 100)	99.1 (97.8 - 100)	
15 yrs	97.5 (95.5 - 99.5)	98.5 (97.2 - 99.8)	97.2 (94.7 - 99.7)	0.36
	9 (2.9)			
M+ disease, n (%)		7 (1.7)	7 (3.1)	
M-free survival, % (95% CI)	100			
5 yrs	97.7 (95.8 - 99.5)	99.2 (98.2 - 100)	99.1 (97.8 - 100)	
10 yrs	96.6 (94.4 - 99.0)	98.9 (97.8 - 100)	98.1 (96.2 - 100)	
15 yrs		97.9 (96.3 - 99.5)	96.9 (94.4 - 99.4)	0.42

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Penile Cancer

Following glansectomy, penile squamous cell carcinoma can recur, potential risk factors were validated using univariate analysis. Furthermore, other research suggests that anti-epidermal growth factor receptor therapy, in combination with surgery, is effective in treating penile cancer.

Local recurrence (LR) after glansectomy predictors

To date, there is little data on predictive factors for LR in patients undergoing glansectomy for penile squamous cell carcinoma (SCC). Albersen et al. aimed to report oncological outcomes and investigate predictive factors for LR, after glansectomy for penile SCC, to develop a risk score for prediction of LR after glansectomy. In a retrospective study, they analysed 172 patients operated on in a supraregional penile cancer centre in the UK, for LR after glansectomy and glans reconstruction. Median follow-up period was 41.4 months. A total of 9.3% of the patients experienced LR. Univariate, but not multivariate logistic regression revealed presence of perineural invasion, carcinoma in situ and high-grade disease to be predictors of LR. A risk model based on these three variables, showed an optimal cut-off point of > 1 risk factors, with an area under the curve of 0.77 (P<0.001, specificity 63%, sensitivity 85%) for prediction of LR. Kaplan Meier analysis reveals a HR of 9.18 (95% CI 3.29 to 25.65) for LR when > 1 risk factor is present. Limitations include the retrospective design, resulting in incomplete data and a low number of events inherent to the rare nature of penile SCC. It was concluded that perineural invasion, carcinoma in situ and presence of high grade SCC predict LR following glansectomy. When > 1 of these factors is present in the specimen, risk of LR increases significantly. Ideally, this risk score and its cut-off need to be validated in larger cohorts, allowing for validation in a multivariate model [1].

Anti-epidermal growth factor receptor effective in metastatic penile squamous cell carcinoma

Evidence has been found by Necchi et al. that anti-epidermal growth factor receptor therapy and surgery is effective in PSCC. Patients with metastatic penile squamous cell carcinoma (PSCC) clinical stage 2-3 and/or M1, loco-regional relapse after previous lymph node dissection, which had neither received CT, nor treatment with any targeted agent, were treated with dacomitinib. This is an oral, irreversible, pan-HER inhibitor, which is in development for advanced non-small cell lung cancer and other solid malignancies. A total of 28 patients were treated, of which 3.6% achieved CR, 28.6% achieved PR, and 32.1% achieved ORR. Frontline therapy can offer a suitable window of opportunity to test new drugs in PSCC [2].

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Renal Cell Carcinoma

Combination therapies might be effective treatments for RCC. A carbonic anhydrase IX recognising antibody, with NK cells may be beneficial for metastatic RCC patients. Likewise, a histone deacetylase inhibitor with an antiretroviral drug inhibits the ERK and AMPK/mTOR pathways, leading to ER stress and declining cell growth. In addition, Lim1 is proven to be involved in in vitro and ex vivo RCC, and will soon be tested clinically.

cG250 with natural killer cells in vitro

cG250 is a monoclonal antibody which recognises carbonic anhydrase IX (CAIX), and is highly expressed in clear cell renal cell carcinoma (ccRCC). Clinical studies suggest that cG250 administration can influence the clinical course of the disease, possibly by NK cell-mediated antibody-dependent cellular-cytotoxicity, but the anti-tumour effects need to be improved. To exploit NK cells in cancer therapy, a unique stroma-free, cytokine-based culture system was developed, which was capable of generating clinically applicable NK cell products with high purity and functionality, from umbilical cord blood-derived CD34+ hematopoietic progenitor cells (HPC). The aim of this study was to examine the effects of HPC-NK cells on RCC cells, and to investigate whether addition of cG250 leads to enhanced cell kill through antibody-dependent cellular-cytotoxicity. HPC-NK cells were stained with CFSE and cocultured with RCC target cells in 96-well plates at 3:1; 1:1; 0.3:1 and 0.1:1 E:T ratios, with and without mAb cG250 at concentration of 0.1-1 µg/mL. HPC-NK cells generated from several donors showed high and dose dependent cytolytic activity, for all RCC cell lines tested with >90% cell kill at E:T ratio of 3:1, to approximately 30% cell kill at E:T ratio of 0.3:1, both in monolayer as in spheroids. The addition of mAb cG250 enhanced cytotoxicity in CAIX+ positive cells, whereas not in CAIX-cells, in several donors. In addition, reactivity toward target cells was confirmed by elevated levels of granzyme B (~30%) and IFNγ production by NK cells. Thus, effective CAIX-directed cell kill can be achieved, when HPC-NK are combined with cG250 at very low effector to target ratios. HPC-NK cells combined with mAb cG250 may enhance the clinical benefit suggested in the clinical studies with cG250 alone, in patients with metastatic (m)RCC [1].

Panobinostat + nelfinavir inhibits renal cell carcinoma growth

It was demonstrated by Okubo et al. the combination of the histone deacetylase inhibitor, panobinostat, and the antiretroviral drug nelfinavir, inhibits renal cancer growth by inducing endoplasmic reticulum stress synergistically. Inhibition of the mammalian target of rapamycin (mTOR) and MAPK/Erk pathways, is also an important mechanism of action. This was achieved by treating a panel of renal cancer cells (769-P, 786-O, Caki-2), with clinically achievable concentrations of panobinostat (15-60 nM) and/or nelfinavir (10-20 µM). The combination therapy of panobinostat and nelfinavir, was demonstrated by isobologram analysis, in order to synergistically inhibit cancer cell growth. It also suppressed colony formation significantly ($P<0.05$). The combination therapy also decreased the expression of cyclin D1 and CDK4, leading to the accumulation of the cells in the sub-G1 fraction. Furthermore, it also induced robust apoptosis synergistically: 60 nM panobinostat alone caused slight to moderate increases in the amount of annexin-V positive cells, however, in combination with 20 µM nelfinavir, it drastically increased. The combination therapy also mechanistically enhanced endoplasmic reticulum stress synergistically, this was caused by dephosphorylation of rpS6, which increased the expression of (mTOR) inhibitor AMPK. Thus, proving that the combination therapy also inhibited the mTOR pathway. Finally, they reported that the combination also inhibited the ERK pathway [2].

PD-L1 in Xp11.2 renal cell carcinoma

Although PD-L1 has proven its significant clinical value in many malignancies, the expression of PD-L1 in Xp11.2 translocation renal cell carcinoma (Xp11.2 RCC), and association with clinical outcomes remains unclear. Qu et al. investigated the expression of PD-L1 in Xp11.2 RCC and assessed its prognostic value. Immunohistochemistry was conducted on formalin-fixed paraffin-embedded specimens from 36 adult Xp11.2 RCC patients, who were histologically confirmed by the FISH analysis. Among 36 assessed Xp11.2 RCC patients, 25.0% patients showed high expression of PD-L1 and 75.0% patients showed low PD-L1 expression. High PD-L1 expression was correlated with the presence of advanced tumour stage ($P=0.001$), regional lymph node

metastasis (P<0.001) and distant metastasis (P<0.001). In the multivariate analysis, N stage (HR: 4.316, P=0.032), M stage (HR: 16.561, P=0.009) and high PD-L1 expression (HR: 4.236, P=0.007), were independent prognostic factors of PFS. Moreover, high PD-L1 expression (HR: 6.479, P=0.006), along with distant metastasis (HR: 9.215, P=0.016), were independent prognostic factors after adjusting for covariates. Researchers concluded that high PD-L1 expression is independently associated with tumour progression and predictive of AE prognosis for Xp11.2 RCC patients. These findings may provide a basis for the use of immunotherapy targeting the PD-1/PD-L1 pathway as a potential novel treatment for Xp11.2 RCC patients [3].

Lim1 in advanced clear cell cancer therapy

Hamaidi et al. hypothesized that Lim1 may be implicated in ccRCC metastatic spread as it promotes proliferation and decreases apoptosis both in vitro and in vivo. By testing this ex vivo and in vivo, it was shown that Lim1 was downregulated by more than 95% at every time points and in all cell lines with Lim1 small interfering ribonucleic acid (siRNAs). Motility, migration and invasion, were inhibited in a time-dependent manner by up to 50%. Many proteins were deregulated by Lim1 siRNA included fibronectin, MMP8/9, TIMP1, paxillin, slug, snail, cadherins, and CXCR4. Lim1 was found in all metastatic samples and their corresponding primary tumour. In vivo, as expected, metastases developed mainly in the lung and liver, the classical secondary sites for CCC. These results strongly suggest, that Lim1 is involved in cell movements in CCC. It was shown for the first time that Lim1 is expressed in metastatic tissues. Ongoing in vivo studies will confirm the implication of Lim1 in advanced CCC. In summary, and by combining previous results on tumour growth with the ones obtained here, Lim1 possesses several characteristics that make it a highly promising potential therapeutic target for advanced CCC therapy [4].

Resistance

Due to fast onset of resistance towards standard of care (SoC) drugs, patients with advanced RCC have a poor prognosis. Pronounced intratumoral heterogeneity in RCC could be a potential cause for treatment resistance. A large panel of patient derived xenografts (PDX) from RCC, including a subset of these PDX established by transplanting tumour material from several different regions (for individual renal tumours), was used to evaluate chemosensitivity of these PDX models, in order to improve the understanding of correlations between inter- and intratumoral heterogeneity and SoC treatment response. More than 200 samples from primary and metastatic renal cancers were transplanted, resulting in 34 newly established PDX models. Among these, several models were derived from distinct regions of individual tumours. Altogether, 13 PDX models were obtained from heterogenous tumour regions of 3 patients with advanced disease. All PDX were characterized regarding their sensitivity towards SoC treatment. Those established from distinct regions of individual tumours were further examined. Researchers were able to identify one out of eight regions, from one particularly aggressive RCC, that clearly differentiates from the other regions of the same tumour, with regard to SoC treatment response. Genomic analysis further revealed that this region is different from the other regions in its global gene expression and sequence variation pattern. In addition, to a common MET mutation, this region exhibits a variation in the HRAS oncogene. In total, 34 sequence variations in 20 genes were found, including ATM, MET, TP53 and VHL. It was concluded that distinct regions within one individual tumour exhibit differences in SoC treatment response, as well as genetic profile. These differences and their correlation to their molecular heterogeneity is subject of ongoing investigations to explain and treat resistance [5].

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Bladder Cancer

Non-invasive diagnosis of bladder cancer can be challenging, however detections from urine samples, like e.g. overexpression of mRNA's, high throughput genomic sequencing or TERT mutations, shows promising results. A novel effective treatment therapy includes standard gemcitabine in combination with a checkpoint kinase 1 inhibitor.

Non-invasive diagnosis

The diagnosis of bladder cancer currently requires invasive tests. However, progress is being made in the development of non-invasive – and fast – tests that show good sensitivity, specificity and negative predictive value. For example, a test based on the detection in urine of overexpression of five messenger RNAs. This test proves to have a superior sensitivity and negative predictive value for detecting primary bladder cancer in people with microscopic or symptomatic haematuria, compared to cytology, as was shown in a study including 895 subjects [1]. The same test was also superior to cytology in detecting recurrent bladder cancer [2]. In addition, high throughput genome sequencing on urine sediment has proven to be an objective and sensitive non-invasive tool for the detection of bladder cancer. Using a whole genome abnormality score of 60 as the cut-off value, the sensitivity and specificity of this technique are 82.9% and 83.5%, respectively [3]. Detection of TERT (telomerase reverse transcriptase) promoter mutation in urine samples also shows promising results for the detection of earlier low-grade precursor lesions before they become invasive. TERT remaining positive after initial surgery was associated with residual in situ carcinoma and relapse at 6 months (P=0.0214) [4].

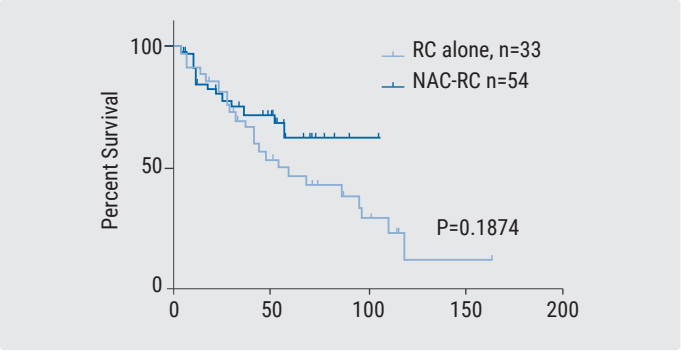
New therapies

The current standard chemotherapy for the first line of metastatic or locally advanced bladder cancer is combination therapy with cisplatin and gemcitabine. However, the 5-year survival rate is still below 50%; therefore additional therapy is needed. Gemcitabine-caused double-strand DNA breaks activate a response that arrests the cell cycle to allow time for DNA repair, which attenuates gemcitabine's antineoplastic activity. Checkpoint kinase 1 inhibitors overcome this arrest and force cells to progress through the cell cycle with unrepaired DNA damage. This concept was successfully tested in vitro on bladder cancer cells. Treatment of the cells with a combination of gemcitabine and the checkpoint kinase 1 inhibitor MK-8776, proved to inhibit bladder cancer cell growth synergistically and cause a 12.1-fold increase of cell accumulation in the sub-G1 fraction [5]. In addition, silencing the expression of LIM-SH3 domain protein 1, a promotor of cancer progression, in bladder cancer cells by using siRNA, augments the anti-cancer effect of cisplatin in bladder cancer [6]. Inducing endoplasmic reticulum stress is a novel strategy used in treating malignancies. An in vitro study showed that this can be achieved in bladder cancer cells by treatment with the pan-deacetylase inhibitor panobinostat plus the proteasome inhibitor ixazomib [7]. In addition, a pre-clinical study showed the trastuzumab-containing antibody-drug conjugate T-DMI to have an anti-metastatic potential for patients with HER2 score 2+/3+ [8].

Neo-adjuvant therapy

Radical cystectomy has been the gold standard for the treatment of locally advanced bladder cancer. However, 50-60% of the patients develop recurrent or metastatic disease after cystectomy. The SWOG-8710 trial (n=317) showed neo-adjuvant chemotherapy to improve the 5-year overall survival rate. Now, Hanna et al, confirmed the results of SWOG-8710 in a cohort of 8,732 patients with non-metastatic muscle-invasive urothelial carcinoma of the bladder, who underwent radical cystectomy between 2004 and 2012 of whom, 1,619 (19%) received neo-adjuvant chemotherapy. Following propensity score adjustment, receipt of neo-adjuvant chemotherapy was associated with an overall survival benefit (HR: 0.88, P=0.017) [9]. In addition, a retrospective analysis of data from 88 elderly patients treated for muscle-invasive bladder cancer, showed no statistically significant survival benefit of neo-adjuvant chemotherapy (Figure 3) [10].

Figure 3 Overall survival of neo-adjuvant chemotherapy



MicroRNA: a prognostic biomarker for survival

Micro-RNA (miRNA) expression is altered in urologic malignancies, including bladder cancer. Individual miRNAs have been shown to modulate multiple signalling pathways that contribute to bladder cancer. Using a panel of 9-miRNAs, Inamoto et al were able to design a miRNA signature that has prognostic value for survival. Of these 9 miRNAs, 6 were associated with high risk and 3 were shown to be protective. Patients with the high-risk miRNA signature exhibited poorer overall survival than patients expressing the low-risk miRNA profile (HR = 7.05, P<0.001) [11].

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Infections in Urology

Urinary tract infections can be treated with antibiotics, yet there is an increasing amount of multi-drug resistance due to antibiotic overuse, importantly it will soon be possible to screen for resistances in the clinical setting. Likewise, it is possible to effectively treat urinary tract infections with bacterial vaccines.

Urosepsis

The recently proposed sequential organ failure assessment (SOFA) score based sepsis definitions have been analysed in urosepsis cases within urology wards. Based on the 2002 definition and the 2016 definition, 30-day mortality rates and 30-day morbidity rates were compared. Tandoğdu et al. concluded that patients stratified as not septic are at risk of organ failure and deterioration, and that the new definitions can be useful for mortality stratification, where previous classifications were falling short. However, the benefit of the new definition in urinary tract infections (UTIs) is still unclear; SIRS patients are at high risk to progress to sepsis and/or develop organ failure [1].

Older patients, especially with worse performance status (PS) and lower serum albumin, should be more intensively treated in the earlier stage of urosepsis, as these patients are at increased risk of mortality. This was investigated by Fukunaga et al. by evaluating 80 patients with urosepsis. Patients were divided into 2 groups, the first consisted of deceased patients (including patients who died within 30 days of hospitalisation, n=5), and the other group of patients that were alive (n=75). The deceased group was significantly older than the alive group. No significant differences in mortality with regard to sex or underlying disease were observed. In 69% of patients, PS was 2 or greater. PS and age were significantly higher in the deceased patients than in the alive group. In the blood test, low albumin, large amounts of white blood cells (WBC), high aspartate transaminase (AST) and lactic acid dehydrogenase (LDH) were significantly related to mortality. Multivariate analysis demonstrated that the risk factor for mortality was age (P=0.007). In the subgroup analysis of older patients (≥75 years), poor PS and lower serum albumin were significantly related to mortality (P=0.003, P=0.045, respectively) (Table 4) [2].

Table 4 Subgroup analysis in older patients [2]

		Univariate
Factors		P-value
Characteristics	Performance status	0.003
Clinical feature	Pseudomonas aeruginosa	0.089
	Temp (<35, >38°C)	0.319
	WBC (<4 or 12< 10^3/μl)	1
	AST (>37 IU/L)	0.337
	ALb (<3.0 g/dL)	0.046
	Hb (<9 g/dl)	0.131
	LDH (>250 IU/L)	0.069

Currently, Tandoğdu et al. are identifying the impact of urological and medical baseline risk factors on the time to recover from urosepsis. This is being done by a prospective, multinational, observational study. To date, 247 patients of a total of 600 planned patients have been recruited. The interim results show that in patients with simple sepsis (59%), the median recovery time is 136 hours, whereas this is 152 hours for those with severe sepsis (41%). Complete recovery until day 30 is achieved in 88% of all patients (89% for simple sepsis and 87% for severe sepsis). The time to recovery in patients with catheters is longer, as is the recovery in patients with severe sepsis, who were previously hospitalised. Assessment scores were not useful to risk-stratify patients for the time to recovery in urosepsis [3].

Antibiotic use/urinary tract infections

Pooya et al. investigated any probable differences between common uropathogens and their multi-drug resistant (MDR) and extended-spectrum beta-lactamase (ESBL) patterns, in 2 different (general and poisoning (the ward where they treat conditions like overdose)) intensive care unit (ICU) wards. This was a 6-year study in which 557 isolates from 526 patients of the poisoning ICU ward, and 147 isolates from 115 patients hospitalised in the general ICU ward were recovered. Escherichia coli (*E. coli*) was the main uropathogen in both ICUs (42% poisoning vs 29% general), followed by *Klebsiella pneumonia*. In total, the resistance pattern was significantly more predominant in the general ICU. Both *E. coli* and *K. pneumonia* showed the MDR pattern 2.38 times more in the general ICU. The highest rate of MDR was observed in the *Acinetobacter* isolates (73% in the poisoning and 92% in the general ICU). This was also observed for the gram-negative bacteria according to their ESBL patterns. So, although it might seem that common uropathogens cause UTIs in different ICU wards, their antibiotic resistance pattern seems to be more complicated in the general ICU, which should be mentioned prior to antibiotic treatment [4].
Urinary tract infections (UTIs) are among the most common bacterial infections with *E. coli* being the most frequently encountered pathogens in most settings. Antimicrobial resistance is driven by overuse of broad-spectrum antibiotics. Although empirical antibiotic treatment with broad-spectrum antibiotics is often not necessary, it has become a common practice due to the delayed results of susceptibility testing by urine culture. The aim of the study by Fritzenwanker et al. was to determine the resistome of the urine *E. coli* from the local university's urology department and to find predictors of antibiotic resistance and susceptibility as well as devising a point of care testing (POCT) panel for *E. coli* resistance in urine samples. This POCT can thus be used to aid clinicians in the treatment of complicated UTI, in order to distinguish those patients who would require broad-spectrum antibiotics from those who can be treated with narrow spectrum antibiotics. All *Enterobacteriaceae* were collected from urine samples of outpatient and hospitalised patients from urology wards of the Giessen University Hospital in Germany, regardless of phenotypic resistance. A customised gene screening panel using LAMP (loop-mediated isothermal amplification) technology was used, based on the local resistome. It emerged that a significant portion of isolates are sensitive to β-lactamantibiotics and/or trimethoprim/sulfamethoxazole and resistance against β-lactams is conferred mostly through blaTEM1B and blaCTX-M-15. Resistance against trimethoprim/sulfamethoxazole is sul1, sul2 and dfrA17 mediated. It was concluded that direct and rapid detection and resistance testing of urine samples is possible; however, further development is required as is implementation into the clinical setting. Screening- and resistance panels for other uropathogens are necessary, particularly for *Klebsiella*, *Proteus* and *Enterobacter* [5].

Drug resistance patterns and risk factors for ciprofloxacin resistance of *E. faecalis* strains isolated from 2,015 chronic bacterial prostatitis (CBP) patients, were assessed using culture specimens. A total of 144 *E. faecalis* isolates were found. The isolates revealed ciprofloxacin sensitivity in 88.88%, 2.08% in intermediate, and 9.02% in resistant groups. From various clinical characteristics, only previous fluoroquinolones prescriptions within 6 months, may predict the ciprofloxacin resistance in *E. faecalis* isolates (odds ratio (OR) 12,086, 95% confidence interval (CI) 3,417-42,755, P=0.001). So, although fluoroquinolones have been the preferred antibiotics for treating CBP, and are still suitable therapeutic agents for *E. faecalis* strains for CBP, careful attention should be paid to fluoroquinolone prescription in patients with a recent history of the same categorical drugs [6].
Risk factors related to healthcare-associated infections are comorbidities, such as, prior urinary infection or urinary catheter before admission, according to a prospective observational study (Table 5) [7].

Table 5 Risk factors multivariate analysis [7]

	P-value	OR	95% CI
Immunosupression	0.010	1.735	(1.138 - 2.646)
ASA III-IV	0.004	1.217	(1.063 - 1.392)
Prior Urinary Infection	0.021	2.648	(1.161 - 6.041)
Indweling uninary catheter prior admission	<0.001	1.838	(1.427 - 2.366)

Although *E. coli* was the most frequently isolated microorganism (25.6%), pathogens such as *Enterococcus spp.* (18.2%), *Klebsiella spp.* (13.8%), and *Pseudomonas aeruginosa* (11.7%) were likewise commonly found. ESBL-producing *Enterobacteriaceae* occurred in 26.9% and 42.4% of cultures where *E. coli* and *Klebsiella spp.* were isolated, respectively [7].

A prophylactic regimen consisting of a single-dose ciprofloxacin infusion during induction of surgery, showed a higher efficacy as a preoperative antibacterial preparation and in protection against postoperative infectious complications in patients undergoing percutaneous nephrolithotomy (PCNL), compared to cefotaxime, [8].

Prevention catheter-associated urinary tract infection

Catheters which are able to reduce catheter-associated urinary tract infection can potentially improve the care for millions of disabled and elderly patients, as well as reduce the enormous costs of managing complications associated with an indwelling Foley catheter. In the first trial, to test the efficacy of the Sharklet micropattern on the urinary catheter surface in a clinical setting (n=50), promising results were observed. The outer surface of the Sharklet micropattern catheter had significantly less biofilm formation in all parts of the catheter, when compared to the standard silicone catheter. These findings open up new possibilities for novel mechanical modifications on the catheter surface, which may be both cost-effective and clinically beneficial [9].

Adherence to guidelines

Transurethral resection of the prostate (TURP) is one of the most commonly performed urological procedures worldwide. With the increasing rate of perioperative multi-resistant infections and urosepsis, it is mandatory for urologic surgeons to follow the recommendations of the Guidelines on Urological Infections in order to reduce infectious complications. Köves et al. evaluated guideline adherence regarding TURP procedures, by using a side questionnaire to the Global Prevalence Study of Infections in Urology between 2006 and 2009. A total of 853 patients from 56 participating centres worldwide were included (Table 6) [10].

Table 6 Patient characteristics [10]

Characteristics	Patients (n=853)
Age - years (mean ± SD)	69.0 ± 8.6
Catheter on admission - nr (%)	314 (36.8)
Days on catheters - (mean ± SD)	44.67 ± 68.4
Catheter changed in 1 week - nr (%)	120 (38.33)
Antibiotics before surgery - nr (%)	413 (48.47)
Duration - days, mean ± SD	5.43 ± 6.52
Urine culture taken - nr (%)	488 (57.54)
Reported HAUTI - nr (%)	109 (12)

In 48.47% of the patients, antibiotics were given prior to surgery. The mean duration of perioperative antibiotic prophylaxis was 5.43 days. Only 21.73% of non-catheterised patients received a single day prophylaxis. Preoperative antibiotics were administered with the lowest and highest rates in Asia (45.74%) and South America (70.45%), respectively, according to hospital types in district hospitals (41.58%) and other hospitals (80.0%). Preoperative urine culture was taken in 57.54% of the cases with ranges from 55.16% to 72.73% in Europe and South America, respectively, and from to district hospitals (55.72%) and other hospitals (83.33%). In 36.8% of patients with a catheter on admission, a mean duration of 44.67 days hospital admission was observed. The catheter was replaced 1 week prior to the surgery only in 38,33% of all the catheterised patients, with the lowest rates in South America and the highest rates in Africa (50.0%). According to hospital type, the lowest rate was reported in other hospitals (12.8%), while the highest rate was reported in teaching hospitals (43.16%). It was concluded that guideline adherence related to TURP is moderate, despite the recommendations of the Guidelines on Urological Infections. Antibiotic prophylaxis was administered and urine cultures were performed prior to surgery only in 48.47% and 57.54% of cases, respectively. Better guideline adherence is necessary in order to decrease the rate of perioperative infectious complications in endourological practices [10].

Bacterial vaccine against recurrent urinary tract infections

The first experience in the United Kingdom with a bacterial vaccine against recurrent UTI in women was described by Yang et al. A total of 41 women with a mean age of 58 years (range: 21 - 86) who suffered from recurrent UTIs (as defined by a minimum of one proven infection every 3 months), despite lifestyle corrections and medical treatment, received 3 months of an inactivated whole bacteria vaccine, which contained an equal mixture of inactive *E. coli*, *Klebsiella pneumoniae*, *Proteus vulgaris* and *Enterococcus Faecalis*, delivered as a sublingual spray. The majority of women (98%) completed the whole course of treatment, and 84% of those reported no subsequent UTIs (8 women with UTI recurrence were post-menopausal). One woman discontinued this vaccine due to lifestyle and personal reasons. With regard to side

effects, these were classified as very mild and did not lead to discontinuation of therapy. It was suggested that this vaccine is both effective and safe in women with recurrent UTIs. The vaccine may offer a potential alternative to long-term antibiotic prophylaxis. Further studies are required in a larger group of patients with longer follow-up periods, to evaluate the efficacy of this vaccine. A large international multi-centre randomised control trial is currently underway [11].

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LUTS

One-third of males of 65+ reported moderate/severe LUTS problems, the progression of which is low, but presumably caused by benign prostate hyperplasia (BPH) or treatment-related side effects. LUTS severity may be correlated to cholesterol levels, age and storage symptoms. Furthermore, for patients with ED and BPH-LUTS, PDE1 inhibits may marginally improve their QOL. Metabolic syndrome and smoking doubled the risk of moderate or severe nocturia in men with LUTS/BPE.

Prevalence and progression LUTS

Venderbos et al. examined the prevalence of LUTS in the 1st ERSPC Rotterdam screening round, assessed the rate of progression on the International Prostate Symptom Score (IPSS) score 4 years later and predicted progression using questionnaire-based baseline characteristics. A descriptive analysis including 36,486 screening and control arm participants (age 55-75 years), for whom an IPSS score (0-7 points = mild, 8-19 points = moderate, 20-35 = severe) was used. Upon entry into the ERSPC study, 70.6% of men reported mild, 23.6% moderate, and 6% reported severe LUTS. The prevalence of moderate symptoms increased with age. Of 9,458 men aged 55-69 years, with mild complaints at baseline, an IPSS score was available at repeat screening 4 years later. From the total, 8.9% of men progressed from mild to moderate symptoms, while 0.5% progressed from mild to severe. The earlier enlarged prostate is significant when predicting mild to moderate progression, while having heart disease and cancer (not PCa) are significant predictors for mild to severe progression. The latter may be treatment related since a large part of these men suffer from colon or bladder cancer. The areas under the curve for the mild to moderate and mild to severe models are 0.556 (95% CI 0.534-0.577, P<0.001) and 0.525 (95% CI 0.504-0.546, P=0.018), respectively. The results of the multinomial regression analyses are shown in Table 7 [1].

Table 7 Multinomial regression to assess predictive capability of baseline characteristics [1]

No progression = reference			
Progression → mild to moderate	**Exp(B)**	**95% CI**	**P-value**
Age	1.003	0.986-1.020	0.728
Comorbidities			
• Heart disease	1.196	0.972-1.471	0.091
• Diabetes	0.816	0.563-1.181	0.281
• High blood pressure	1.055	0.864-1.289	0.598
• Cancer	0.842	0.523-1.357	0.481
• Other comorbidities	1.120	0.924-1.358	0.249
Earlier enlarged prostate	2.421	1.914-3.061	<0.001
Earlier prostatitis	1.146	0.777-1.691	0.491

Progression → mild to severe	**Exp(B)**	**95% CI**	**P-value**
Age	0.947	0.882-1.017	0.136
Comorbidities			
- Heart disease	2.058	1.005-4.215	0.048
- Diabetes	0.420	0.057-3.070	0.393
- High blood pressure	1.827	0.918-3.638	0.086
- Cancer	3.803	1.339-10.802	0.012
- Other comorbidities	1.377	0.659-2.873	0.395
Earlier enlarged prostate	1.544	0.526-4.533	0.429
Earlier prostatitis	2.392	0.705-8.111	0.162

In summary, it was shown in a large sample of the general male population, that 30-35% of men above the age of 65 report moderate/severe LUTS problems. The 4-year rate of progression is low, mainly driven by benign prostate hyperplasia (BPH) or treatment-related side effects and difficult to predict on the basis of questionnaire-based characteristics alone [1].

Cardiovascular risk factors

It has been hypothesised that endothelial dysfunction and pelvic atherosclerosis may contribute to LUTS. The relationship between cardiovascular risk factors and LUTS severity in male patients, presented to urology clinic, was assessed in a cross-sectional study including 966 patients. Cardiovascular risk factors including; components of Framingham Coronary Heart Disease Risk Score, BMI, uroflowmetry, IPSS, fasting blood glucose and serum PSA, were assessed. Patients who had been diagnosed with urinary tract malignancy, urethral stricture or bladder stone were excluded, as well as those with a history of urinary tract surgery or ketamine abuse. Multinomial logistic regression analysis showed that severe LUTS significantly associated with Framingham score (P=0.016) and its components of total cholesterol (OR = 1.290; P=0.018) and age (OR = 1.034; P=0.002) compare with mild symptoms. Linear regression also showed that total cholesterol (CC = 0.271; P=0.034) and age (CC = 0.084; P<0.0001) increased with storage symptoms. It was concluded that the severity of LUTS and storage symptom significantly increases with total cholesterol level and age [2].

Phosphodiesterase inhibitors for BPH-LUTS

A literature review examined the available literature till date, with regard to efficacy and safety of calmodulin-stimulated cyclic nucleotide phosphodiesterases inhibitors (PDE1i) (tadalafil) in the treatment of BPH-LUTS, compared to placebo. Included were randomised controlled trials of men with BPH-LUTS, with or without ED, comparing PDEI to placebo. Primary outcomes were treatment effect on IPSS total, Benign Prostatic Hyperplasia Impact Index and treatment emergent adverse events. The findings showed a higher symptom relief with PDEI in BPH-LUTS compared to placebo. However, the quality of evidence is moderate, as per the GRADEpro criteria and the magnitude of the effect is modest for a therapeutic agent, considering the extent of improvement obtained even by placebo. There is a marginal improvement in both the QOL indices in BPH-LUTS patients with ED, but none without ED. AEs are significantly higher in short term usage of 12 weeks whereas long-term safety is unknown at present. Therefore, the clinical relevance of the consistent statistical significance across randomised controlled trials and meta-analyses for efficacy parameters like IPSS-total merits scrutiny. As of now, incremental benefit by PDEI must be weighed against the long-term AEs of the drug as well as the cost of therapy [3].

Nocturia and LUTS-benign prostatic enlargement

De Nunzio et al. evaluated the relationship between smoking, metabolic syndrome and nocturia in patients with LUTS and benign prostatic enlargement (BPE). A total of 492 patients with LUTS-BPE were enrolled (excluding patients on medical treatment for LUTS). Evaluated parameters were IPSS, prostate volume (PV) assessed by transrectal ultrasound, BMI, waist circumference and blood pressure, PSA, fasting glucose, triglyceride and high density lipoprotein. Metabolic syndrome was defined according to Adult Treatment Panel III. Moderate or severe nocturia was defined as more than two nocturia episodes. Moderate or severe nocturia was reported in 43.1% of patients; for metabolic syndrome, this was 29.9%. A total of 60.5% presented moderate or severe nocturia (P=0.001) and 21.3% had a smoking addiction. It was concluded that metabolic syndrome and smoking doubled the risk of moderate or severe nocturia in men with LUTS/BPE (Table 8) [4].

Table 8 Multivariate analysis for predicting moderate/severe nocturia [4]

	Moderate/severe nocturia	P-value
Age	1.067 (1.036-1.098)	0.001
Prostate volume	1.011 (1.003-1.019)	0.006
Metabolic syndrome	2.509 (1.571-4.007)	0.001
Smoking status	1.861 (1.088-3.185)	0.023

Assessment of patients smoking and metabolic status is suggested in patients with LUTS/BPE, and possible implications for treatment should be considered [4].

Nocturia and high salt intake

Patients with nocturia and high salt intake might be advised to reduce their salt intake together with appropriate lifestyle guidance. Salt intake reduction might also be beneficial for patients who respond poorly to medications for nocturia and have a high salt intake. These were the findings of a Japanese study with subjects including those with one or more episodes of nocturia during sleep and with high

salt intake (≥8 g/day for men and ≥7 g/day for women). Participants were given written guidance on salt intake reduction. A frequency volume chart was used to assess voided volume, urinary frequency, etc., before and 12 weeks after initiation of decreased salt intake. Changes in LUTS before and after the study were compared using the Core Lower Urinary Tract Symptom Score. Those with organic or functional abnormalities including neurogenic bladder, were excluded from the study. Medications for LUTS were not changed during the study period. The daily salt intake was estimated by examining the sodium and creatinine concentrations of spot urine samples, using a formula that was adjusted for body height, body weight and age. A total of 321 subjects with a mean age of 64.3 years were evaluated. Of these, 69.5% successfully reduced daily salt intake during the observation period (Success group), while 30.5% did not (Failure group). Mean estimated daily salt intake in the Success group decreased from 10.7 g to 8.0 g (P<0.001). Nighttime Frequency improved from 2.3 times to 1.4 times (P<0.001). Nocturnal Polyuria index (NPi) improved from 30.2 to 27.7 (P<0.001). Mean estimated daily salt intake by the Failure group increased from 9.6 g to 11.0 g (P<0.001), and nighttime frequency increased from 2.3 times to 2.7 times (P<0.001). The NPi in the Failure group before and after the study was 30.8% and 30.5%, respectively, showing no change (P=0.583). In the Core Lower Urinary Tract Symptom Score for the Success group, Q1 (diurnal frequency) improved from 0.8 to 0.4 (P<0.001), Q2 (nocturia) improved from 1.9 to 1.3 (P<0.001), and Q3 (urgency) changed from 1.0 to 0.9 (P=0.001). Moreover, the QOL parameter improved significantly, from 3.6 points to 2.7 points (P<0.001). In conclusion, in this clinical study the subjects which had nocturia and high salt intake, both nighttime frequency and NPi decreased significantly, improving the quality of life, in the group that succeeded in decreasing salt intake (the Success group) [5].

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Andrology / Male Sexuality and Dysfunction

Non-hormonal contraceptive methods are most promising for males. For ED, regenerative stem cells therapy following prostatectomy seems both safe and viable. For Peyronie's disease curvature correction and grafting might be a possible long-term treatment.

Fertility

Although contraception has been focused mainly on women, there has been a growing interest in male contraceptive methods over the past decades. Current methods of male contraception are withdrawal (pulling out), condom use and vasectomy. Although currently widely used, male contraception accounts only for 14% of all contraception used worldwide. Even though it has important disadvantages, such as a high failure rate for withdrawal (first-year failure 19%) and condoms (17% per year), which make them far from ideal. Ideal male contraception would consist of a combination of characteristics outlined in Table 9 [1,2].

New methods include male hormonal contraception, which can be divided into androgen monotherapy (testosterone enanthate, testosterone undecanoate, and alternative testosterone formulations), a combination of androgens with gonadotropin-releasing hormone (GnRH) analogues and androgen-progestin combinations. The percentage of non-responders varies between 5-20% in various clinical trials, but the main issue is safety, with reports of depression and suicidal tendencies in users. Non-hormonal contraceptive methods currently comprise the most promising field of research for male contraception; they target more specific biological processes and could possibly have fewer side effects [2].

Infertility

Infertility in men is estimated to affect approx. 7.5% of men in Europe (which accounts for 18.6 million individuals) of which 10-15% are azoospermic. However, men should not be

considered infertile until they have a micro testicular sperm extraction (TESE). MicroTESE should be the gold standard for the survival sperm retrieval technique for patients with irreversible non-obstructive azoospermia. MicroTESE, when compared to conventional TESE, almost doubles the chance of successful survival sperm retrieval [3].

Erectile dysfunction

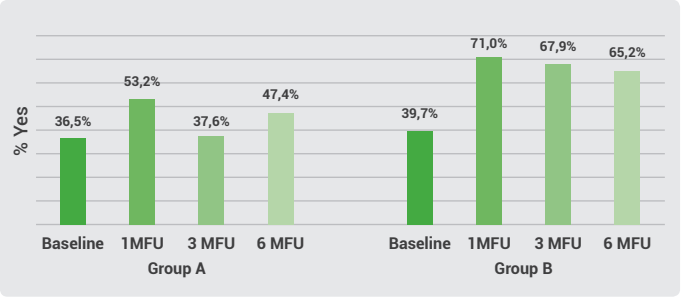
Regenerative stem cells have shown to statistically significantly improve erectile function in a small study of 21 continent men, who had been treated with full pharmacological intervention, without sufficient effect prior to inclusion. In contrast, incontinent men did not regain erectile function. No serious AEs were recorded after injection or during follow-up. The researchers suggest that regenerative stem cells represent a safe and promising novel interventional therapy for erectile dysfunction (ED) following prostatectomy [4]. The safety and feasibility of VL#FIA3-30, a topical cream containing a combination of Moxisylyte, isosorbide dinitrate (vasoactive substances) and which possesses a tunica-penetrable delivery system in patients with ED, was evaluated in 32 men using a mean International Index of Erectile Function (IIEF). Three patients experienced a drop of >20 mmHg without clinical effects and were excluded. No significant concentrations of isosorbide dinitrate or Moxisylyte were detected in all tested samples, as well as their active metabolites (ISMN-2, ISMN-5 and DAM plasma concentrations were 12.7, 15.0, 10.2 ng/ml, respectively). One-third of patients reported significant penile engorgement, and 6 and 2 patients were able to complete intercourse with and without the use of medication, respectively. It was concluded that VL#FIA3-30 in men with ED is promising, the safety profile has prompted an in-depth evaluation of its clinical efficacy [5].

Low-intensity shock wave treatment (LiSWt) with Aries, has shown to be effective in 66.7% of patients, achieving minimal clinically important difference. Two groups of men were treated with LiSWT: group A (n=21) received one session/ week and Group B (n=21) received 2 sessions/week, for 6 weeks in total. It was found that LiSWT improved erectile function in both groups, but there was a trend towards improved efficacy in the high-dose group (12 sessions in 6 weeks; Figure 4) [6].

Table 9 Characteristics of ideal male contraception [1,2]

• Be at least as effective as the corresponding female methods
• Be acceptable by both partners
• Have quick results
• No significant adverse effects, especially in relation to virility, libido and erectile function
• Not affecting offspring
• Reversible as concerns fertility
• Readily available and affordable

Figure 4 Sexual Encounter Profile diary (questionnaire 3): did your erection last long enough for you to have successful intercourse? [6]



Younger patients with greater loss in erectile function upon phosphodiesterase type 5 inhibitor (PDE5i) washout, were likely to benefit more from LiSWT. Treatment sessions may be applied either once or twice/week without intervals. LiSWT has been shown to be safe, using any of the proposed treatment protocols [6].

Boeri et al. assessed the relative impact of low total testosterone (TT) and low calculated free testosterone (cFT) on androgen-related sexual symptoms, in 485 men with ED as a primary compliant. It was found that low cFT, even with normal TT, was associated with a worse clinical profile and impaired sexual and depressive parameters, compared to normal TT/normal cFT in a cohort of ED patients. Of clinical relevance, normal cFT, irrespective of low TT, was not associated with signs and symptoms suggestive of testosterone deficiency [7].

Peyronie's disease

The surgical and functional outcomes in two groups of patients which underwent inflatable penile prosthesis implantation and plaque incision with grafting for residual curvature using 2 different grafts –small intestinal submucosa (Group A) and Tachosil (Group B) – was assessed in 60 patients. The average follow-up time was 35 months. The average operative time was 155 minutes for group A and 120 minutes for group B. No major intraoperative complications were reported. The average hospital stay was 3 days for the group A and 3.5 days for group B. Postoperative haematomas were more frequently observed in group B compared to group A. Only 3 patients developed a major postoperative complication requiring a second surgical intervention: 1 patient in group

A for a mechanic failure, and 1 patient for each group for inflatable penile prosthesis infection. No recurrent bending of the penile shaft was observed. The IIEF score improved from 36 to 62 in the group A and from 38.5 to 63.5 in the group B. The multivariate statistical analysis (performed by SPSS), did not show any significant difference for all the variables analysed between the two groups, with the exception of the operative time, which resulted significantly in favour of Tachosil [8].

A study involving 32 patients with severe and/or complex penile curvature, showed that plaque incision and four-layered porcine small intestinal submucosal grafting, achieves long-term curvature correction in a follow-up time of 43.41 months. It has an acceptable possibility of complications and high patient-reported overall satisfaction. ED according to IIEF-5 was normal in 43.8%, mild in 37.5%, mild-to-moderate in 6.3%, moderate in 3.1% and severe in 9.4% of patients as per patient-reported outcomes. However, ED is often manageable with pharmacotherapy (88.9% of 18 patients were treated with ED treatment) [9].

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Urogenital Reconstruction

The state of the art penis reconstruction technique includes a microsurgical technique capable of nerve coaptation and transfer of tissue. Furthermore, treatment of one-stage buccal mucosal graft urethroplasty at a high-volume centre, is associated with excellent QoL and erectile function parameters.

Penile reconstruction

The surgeon's ideal goals in performing phalloplasty range from phalloplasty as a one-stage surgical procedure, whilst giving the patient an aesthetic penis with erogenous and tactile sensation, allowing the patient to urinate while standing and have sexual intercourse.
The indications for penile reconstruction are outlined in Table 10 [1].

Table 10 Indications for penile reconstruction [1]

Congenital conditions (disorders of sexual development)	• Aphallia or penile agenesis • Idiopathic micropenis • 46,XY disorder of sexual development • Extrophy • Cloacal extrophy
Genital trauma	• Injuries / penile amputation • Surgery
Female-to-male gender dysphoria	

The first penile reconstructions reported, were complex and multistage procedures, using a single abdominal tube skin flap. Later, local pedicled flaps were used in penile reconstruction, either a fasciocutaneous flap (extended groin flap, superficial inferior epigastric skin flap or pedicled island ALT flap) or a pedicled myocutaneous flaps (rectus abdominis myocutaneous flap or tensor fascia lata myocuteneus flap). The current state-of-the-art in penile reconstruction, is the use of microsurgical technique which allows free tissue transfer and nerve coaptation. In patient evaluation, the anatomical requirements, as well as the functional requirements are of utmost importance, however also the aesthetic requirements of shaping an aesthetically pleasing phallus and scrotum, need to be taken into account. For optimal penile reconstructive surgery, a multidisciplinary approach is required, which involves not only the urologist and reconstructive plastic surgeon, but also a psychologist. The surgeon's capability and experience play an important role, as does an individual patient's approach, according to the reconstructive, functional and aesthetic requirements, the patient's preferences and the donor site/s morbidity. As there are so many techniques for penile reconstruction available, none can be considered preferable [1].

Buccal mucosal graft urethroplasty

To date, evidence of functional outcomes after buccal mucosal graft urethroplasty (BMGU) is scarce and mainly based on small sample sizes. Vetterlein et al. evaluated postoperative erectile function and QoL parameters in a contemporary homogeneous cohort of patients treated at a high-volume centre. The secondary aim of the study was to compare outcomes between patients undergoing onlay vs inlay BMGU. A total of 719 men undergoing one-stage BMGU were retrospectively assessed by chart review; patients with > 1 transplant sites were excluded from final analyses, which yielded a final sample of 644 men. From the total, 82% and 18% men underwent onlay and inlay BMGU, respectively. Patients with onlay BMGU were slightly slimmer (mean BMI 27 vs 28; P=0.033), had undergone fewer previous urethroplasties (19% vs 28%; P<0.001), had more bulbar stenoses (74% vs 3%; P<0.001), and had smaller median graft length (4.5 cm vs 5 cm; P<0.001), compared to those undergoing inlay BMGU. In total, > 90% of patients did not report any problems regarding their mobility (to walk about), self-care and usual activities (e.g. housework or leisure activities) postoperatively. From the total, 73% did not report any pain or discomfort and 85% were anxiety-free showed no symptoms of depression. Finally, 81% of all patients were satisfied with the outcome of their urethroplasty. There was no statistical difference in any of the EuroQol 5 dimensions questionnaire between the two treatment groups (both P>0.07). Sufficient rigidity at erection and adequate glandular tumescence, was reported by 65% and 92%, respectively. While in 71% ejaculation volume was adequate, 18% reported a reduced volume. More than 90% were painless at ejaculation and did not report any scrotal or penile numbness. Furthermore, 91% and 88% did not suffer from penile deviation or decrease in penile length at erection, respectively. Among patients undergoing inlay BMGU, the penile deviation was more common, than in those undergoing an onlay technique (16% vs 8%; P=0.014). Regarding the other erectile function parameters, there was no statistically significant difference between the treatment groups. Thus, when it is performed in a high-volume setting, one-stage male BMGU is associated with excellent QoL and erectile function parameters: the surgical technique does not seem to affect the functional outcomes significantly. However, it was observed that more patients reported penile deviation postoperatively in those undergoing an inlay technique, which may be related to the different anatomical premises. Further evaluation of differences in pre- vs postoperative outcomes is necessary [2].

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