Medicom International Conference Series in Urology

EAU21 | VIRTUAL 8-12 July

36th Annual EAU Congress

European Association of Urology

8–12 JULY 2021

PEER-REVIEWED CONFERENCE REPORT

Includes Selected Videos from EAU TV on Prostate, Bladder and Renal Cancer

^{177}Lu-PSMA-617: A New Class of Effective Therapy

^{177}Lu-PSMA-617 added to standard-of-care extended overall survival and radiographic progression-free survival, as was shown in the phase 3 VISION trial.

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IMvigor010: ctDNA as Biomarker for MIBC

Patients with muscle-invasive bladder cancer that have a higher survival benefit from adjuvant immunotherapy could be distinguished by their circulating tumour DNA positivity.

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KEYNOTE-564: Positive Results in Renal Cancer

Results from KEYNOTE-564 support the use of pembrolizumab as a potential new standard of care for patients with RCC in the adjuvant setting.

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Editor Prof. Hendrik Van Poppel, University Hospitals of the KU Leuven, Belgium

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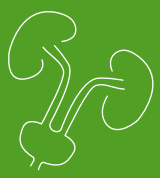

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ISSN	2468-8762 21:14

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Letter from the Editor

Prof. Hendrik Van Poppel

Dear colleagues,

Dear colleagues,

Like last year's congress, EAU21 was again held as a virtual meeting. Some Faculty members, Moderators, and (co)-Chairpersons had the privilege to visit the highly professional studios in Hilversum, close to Amsterdam. This allowed for at least some face-to-face interaction and discussion.

It is my pleasure to highlight some of the topics covered in this report. This report contains presentations selected for the 'Best of EAU' sessions on LUTS and BPH, prostate cancer, testis and penile cancer, bladder cancer, and renal cancer, presented by the different experts, members of the Scientific Congress Office.

Attempts are underway to establish better understandable symptom score systems for patients with LUTS, as well as risk calculators that can predict treatment-induced changes in IPSS scores.

In prostate cancer, ^{177}Lu-PSMA-617 appears promising and is becoming a new class of effective therapy, while in mCSPC the addition of abiraterone to ADT and docetaxel significantly improved the radiographic PFS (PEACE-1).

Management of indeterminate small testis masses is challenging and some important recommendations concerning the preservation of fertility and hormonal function have been described, including the advice to have every case reviewed by a multidisciplinary team.

Patients with muscle-invasive bladder cancer that have a higher survival benefit from adjuvant immunotherapy could be distinguished by their circulating tumour DNA positivity. This was demonstrated in the IMvigor010 trial and will be further investigated in the subsequent IMvigor011 trial.

In renal cancer, KEYNOTE-564 has generated the first positive phase 3 results with adjuvant checkpoint inhibition. These results support the use of pembrolizumab as a potential new standard of care for patients with RCC in the adjuvant setting.

These and more topics from the conference are outlined in this report. Please enjoy the highlights of EAU21 and hopefully next year we will meet again face-to-face, in Amsterdam. We look forward to welcoming you all again.

All the best,

Prof. Dr. Hendrik Van Poppel
Urology, KU Leuven, Belgium
EAU Policy Office Chairman

Biography

Hendrik Van Poppel, MD, graduated in General Surgery and in Urology and received his postgraduate training in London, Barcelona, Copenhagen, Mainz, and Rotterdam. He obtained a PhD in Medical Sciences in 1988. He became Fellow of the European Board of Urology in 1992, full Professor of Urology in 1993, and Chair of the Department of Urology in Leuven in 2002 until 2015 when he became Emeritus Professor.

He was Director of the European School of Urology in 2004, before becoming EAU Adjunct Secretary General, responsible for Education, in 2012 until 2021, when he was voted in as Chairman of the newborn EAU Policy Office.

Prof. Van Poppel attended countless scientific meetings and gave >1,000 lectures at National and International podia. He has published over 220 papers as first author on Uro-Oncology, has co-authored more than 500 and (co-)edited several books on kidney and prostate cancer. He is Reviewer and Editorial Board Member for more than 30 urological and uro-oncological journals.

He received the Distinguished Career Award of the Société Internationale d'Urologie (SIU) in Buenos Aires in 2016 and the Frans Debruyne Life Time Achievement Award of the EAU in 2020, presented to him at the EAU21 Virtual Congress in 2021.

Conflict of Interest Statement:
Nothing to disclose.

LUTS & BPH

Best of EAU: The surgical armamentarium is evolving

New surgical techniques under investigation for the treatment of lower urinary tract symptoms (LUTS) and bladder outlet obstruction caused by benign prostatic hyperplasia (BPH) include the Butterfly, UroLIFT, Rezum, and embolisation. The choice of which technique to use for which patient should be based on the shared goals of patient and physician, such as de-obstruction, symptom relief, quality of life, satisfaction, reduction of (sexual) side effects, and cost-effectiveness.

The surgical armamentarium for the treatment of symptomatic BPH is evolving. Currently available options are resection, vaporisation, and enucleation techniques, which are well established. The vast majority are now recommended in the guidelines, based on level 1 evidence. In the past decade, alternative minimally invasive surgical therapies have been introduced. Prof. Jean-Nicolas Cornu (CHU Charles Nicolle, Rouen, France) presented highlighted abstracts on these new techniques [1].

Butterfly

A prospective, open-label study evaluated the new Butterfly technique in 50 men (Qmax ≤13 mL/sec; international prostate symptom score [IPSS] >12) who were candidates for surgery (NCT03912558) [2]. This device –a removable metallic implant that functions by retracting the lateral lobes of the prostate– was inserted under sedation with no catheter after the intervention. One-year results showed improvements of Qmax by 33%, IPSS reduction by 40%, and sexual quality of life score increase by 38%. No impact on sexual function was reported, with ejaculation preserved in 100% of patients. In 1 patient the device was repositioned; 5 patients chose to remove the device. Seven patients underwent transurethral resection of the prostate (TURP). One patient developed a bulbar urethral stricture.

UroLIFT

The UroLIFT is a trans-prostatic, permanent implant that widens the prostatic urethra. The device was investigated in a large, international, retrospective database, including >2,700 subjects [3]. This study evaluated the predictive factors for likelihood of not undergoing a subsequent intervention for benign prostatic obstruction (BPO), which determines the success of the procedure. Real-world data was compared with the data from the real-world retrospective LIFT trial. "They found that higher IPSS and higher impact on quality of life at baseline may increase the likelihood of subsequent BPH surgery," Prof. Cornu mentioned. "That was the main predictor. Prostate volume did not have a significant predictive value."

Rezum

A European, multicentre study evaluating water vapour therapy with the Rezum device included >600 patients [4]. No significant change was shown in erectile function as measured with the IIEF-5 at follow-up (P=0.80). Antegrade ejaculation was present in 90% of patients, which was predicted for this study. Advantages of the Rezum device are that it is a relatively short procedure, has a quick recovery, is not associated with erectile dysfunction, and has a low risk of dry orgasm (5–10%). A disadvantage is that the patient needs a catheter for 1–2 weeks. Furthermore, in line with other transurethral approaches, the procedure is associated with symptoms such as dysuria and storage problems, failure to remove the catheter, and risk of infections.

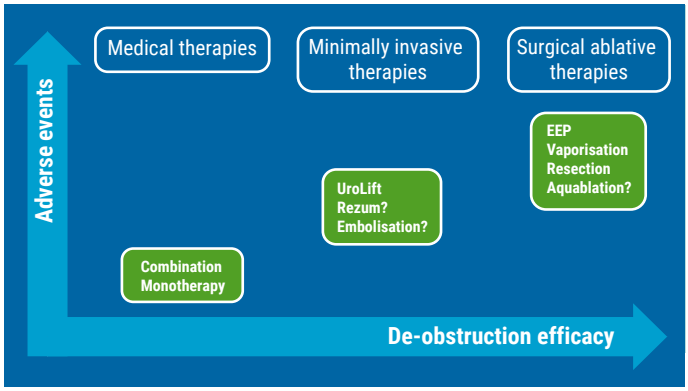
Embolisation

Two-year outcomes of a non-inferiority study comparing prostatic artery embolisation (PAE) with TURP demonstrated that non-inferiority was not met [5]. TURP was also superior to PAE for Qmax, post-void residual volume, PSA, and prostate volume, demonstrating that the effects were evolving in parallel with the anatomical effects of embolisation. However, PAE was associated with fewer complications than TURP. "Hence, patients could be looking for a trade-off – a less effective option with fewer secondary effects," Prof. Cornu suggested [1].

Which technique for which patient?

The main question is which technique do we need for which patient? "The patient's view is lost because there are too many options." Prof. Cornu said. "The surgeon's view shows that there is a trade-off between adverse events and de-obstruction efficacy" (see Figure on the next page).

Figure: Trade-off between adverse events and de-obstruction efficacy [6]



EEP, Endoscopic Enucleation of the Prostate.

The guidelines from the EAU, AUA, and NICE give different advice, mainly based on the acceptance of available evidence. A recent systematic review evaluating patient preferences demonstrated that patients are mainly worried about their sexual function, urinary continence, and pain on urination [7]. They care more about these symptoms than about the obstruction.

Prof. Cornu advised that decisions should be based on shared goals, such as de-obstruction (e.g., Qmax and residual volume), reduction of symptoms (e.g., nocturia, urgency, and voiding) and side effects (mainly sexual), improvement of quality of life and satisfaction, and cost-effectiveness.

1. Cornu JL. Best of EAU21: BPH/LUTS. EAU21 Virtual, 8–12 July 2021
2. Katz R. P0045, EAU21 Virtual, 8–12 July 2021.
3. Kayes O. P0051, EAU21, 8–12 July 2021.
4. Cocci A. P0052, EAU21 Virtual, 8–12 July 2021.
5. Abt D, et al. Eur Urol. 2021;80(1):34–42.
6. Cornu JL. Eur Urol. 2021;80(1):43-5.
7. Malde S, et al. Eur Urol. 2021;79:796–809.

IPSS: Visual alternatives to aid comprehension and new risk prediction models

Many patients find it difficult to complete the international prostate symptom score (IPSS) questionnaire, making its reliability uncertain. To gain insight into the problems with understanding the IPSS, a qualitative study assessed this questionnaire and 2 visual alternatives [1]. Furthermore, a predictive analytics solution was developed to project the change in lower urinary tract symptoms (LUTS) and risk of acute urinary retention or benign prostatic hyperplasia (BPH)-related surgery [2].

Up to 29% of Europeans have a limited health literacy, leading to difficulty with completing the IPSS questionnaire. This led to the development of 2 visual alternatives: the South African Visual Prostate Symptom Score (VPSS) and the French Score Visuel Prostatique en Images (SVPI). In a first qualitative study, the IPSS and the 2 visual alternatives were assessed by Dr Florine Schlatmann (University Medical Centre Groningen, the Netherlands) and colleagues [1]. It was found that visual alternatives are better understood, especially when combined with short textual questions. Based on their findings, the researchers developed a modified questionnaire named the Dutch Reduced Illustrated Prostate Symptom Score (DRIPSS) to reduce problems with understanding.

A second study by Prof. Stavros Gravas (University of Thessaly, Volos, Greece) aimed to predict changes in IPSS score [2]. Over 9,000 patients were included from 3 placebo-controlled trials on dutasteride (i.e. ARIA3001, ARIA3002, and ARIB3003) and 1 trial comparing dutasteride, tamsulosin, and combination (i.e. CombAT). Two independent models were developed to predict responses to active treatments over 4-year of follow-up:

- a Generalised Least Squares model for longitudinal IPSS; and
- a Cox proportional hazards model for time to first acute urinary retention or BPH-related surgery.

The models provided an interactive visualisation to predict outcomes for any combination of predictors which could define a patient's risk profiles.

The models performed heterogeneously across studies. Predictions for active treatments were well calibrated, although some heterogeneity was found. For patients at relatively lower risk of disease progression (i.e. with an IPSS of 12–19, a prostate volume of 30–50 mL, a PSA level of 1.5–4 ng/mL, a Qmax of >11 mL/s, and post-void residual urine of <70 mL), the combination of dutasteride and tamsulosin was predicted to be more effective than tamsulosin in improving LUTS and reducing the risk of acute urinary retention or BPH-related surgery for up to 4 years. These models may be able to predict changes in IPSS and the risk of surgery for LUTS patients at risk of disease progression. Such predictive analytics could aid in the decision-making of the optimal treatment per patient.

1. Schlatmann FWM, et al. First qualitative study into comprehensibility of IPSS and 2 visual alternatives for men with adequate and men with limited health literacy skills, leading to a new, better understood alternative: Dutch Reduced Illustrated Prostate Symptom Score (DRIPSS). P0040, EAU21 Virtual, 8–12 July 2021.
2. Gravas S, et al. A new risk calculator to predict changes in IPSS score and risk of AUR / BPH-related surgery in BPH patients with moderate-severe symptoms at risk of disease progression receiving placebo, dutasteride, tamsulosin, or combination therapy. P0036, EAU21 Virtual, 8–12 July 2021.

Urinary Tract Infections

Prophylactic treatments for recurrent urinary tract infections

Different prophylaxis protocols against recurrent urinary tract infections (RUTI) are available and have proven to be effective. A prospective, multicentre, observational study demonstrated some noteworthy relationships between the clinical profile and the prophylactic treatment chosen [1].

Prof. María Fernanda Lorenzo Gómez (University of Salamanca, Spain) and colleagues evaluated approximately 1,600 adult women who received prophylaxis against RUTI within 1 year. Each doctor could freely assign any prophylactic treatment following the recommendations of the EAU Guidelines on Urinary Tract Infections in shared decision-making with the patient. The objective was to identify the distribution of clinical profiles associated with several prophylaxis protocols against RUTI.

Based on treatment choices, patients were stratified into 3 study groups:

- Group A (n=444) received conventional antibiotic prophylaxis, namely ciprofloxacin, fosfomycin, cotrimoxazole, nitrofurantoin, or amoxicillin.
- Group B (n=732) received prophylaxis with sublingual polyvalent bacterial vaccine.
- Group C (n=438) received adjuvant measures other than antibiotic or polyvalent bacterial vaccine, namely pelvic floor biofeedback, oral D-mannose, endovesical instillation of glycosaminoglycans, or topical vaginal oestrogen.

Groups were compared concerning age, concomitant disease and treatments, and American Society of Anesthesiologists' Physical Status Classification System (ASA) scores.

Mean age was significantly different according to age per group; age was lowest in group B (52.27 years), followed by group A (57.25 years) and group C (60.57 years; P=0.00057). Women using antibiotics as a prophylactic treatment for RUTI more frequently had diabetes mellitus, depression, and insomnia.

Concerning the ASA scores, ASA I was more frequent in group B (63.11%) than in group C (48.63%). ASA II was more frequent in group C (39.73%) than in group A (27.03%) and B (30.33%), and ASA III was more frequent in group C (11.64%) than in group B (6.56%) and A (10.14%).

The use of a polybacterial vaccine to prevent RUTI was associated with less arterial hypertension and lower ASA III. In those who received combined treatments, younger women were more prone to choose pelvic floor biofeedback, whereas older women preferred vaginal oestrogens.

1. Lorenzo Gomez MF, et al. Relationship between the clinical profile of women with recurrent urinary tract infections and the prophylactic treatment chosen. P0154, EAU21 Virtual, 8–12 July 2021.

Failure of conservative management in emphysematous pyelonephritis

As demonstrated in a case series from Tunisia, thrombocytopenia was the main factor associated with risk of failure of conservative management in emphysematous pyelonephritis [1].

Emphysematous pyelonephritis is a serious condition with significant mortality. However, mortality rates have declined with prompt and aggressive medical management and minimally invasive strategies. The management of this condition is either conservative, consisting of antibiotic therapy alone or in combination with urinary tract drainage, or radical based on a salvage nephrectomy.

The current retrospective study from Tunisia aimed to identify factors associated with failure of conservative management. Patients who were diagnosed with emphysematous pyelonephritis between 2010 and 2020 were retrospectively reviewed. All patients were conservatively managed, and a nephrectomy was performed when the conservative policy failed. Included were 52 patients with a mean age of 58.63 years. Diabetes mellitus was present in 38 patients (73%). The mean presentation delay was approximately 6 days. The distribution of the 4 classes of emphysematous pyelonephritis was: class 1, n=23; class 2, n=11; class 3, n=8; and class 4, n=10.

Dr Ahmed Saadi (University of Tunis, Tunesia) and colleagues found 32 cases of severe sepsis (61.5%) and 9 patients (17.3%) developed a septic shock; 6 patients presented with a septic shock refractory to conservative management, requiring nephrectomy with a delay of almost 5 days, and 2 patients died (3.84%).

A univariate analysis demonstrated that only thrombocytopenia was associated with a significantly higher risk of failure of conservative management and emergent nephrectomy (P=0.015). Consequently, nephrectomy should be considered in extensive forms with refractory septic shock or in case of severe thrombocytopenia.

1. Saadi A, et al. Predictive factors of failure of conservative management in patients with emphysematous pyelonephritis. P0158, EAU21 Virtual, 8–12 July 2021.

Antibiotic treatment of healthcare-associated infections

A periodical review of healthcare-associated infections in a urology ward led to changes in the prescriptions of antibiotics, aimed to optimise the management of infections [1]. Healthcare-associated infections included urinary tract infections and surgical wound infections.

Inadequate antibiotic treatment for infections has negative consequences in terms of morbidity and even mortality. On top of that, inadequate antibiotic treatment could lead to the development of multi-drug resistant microorganisms. Regular assessment of the characteristics of infections, including susceptibility patterns, leads to optimisation of antibiotic treatment selection.

A study presented by Dr José Medina-Polo (Hospital Universitario 12 de Octubre, Madrid, Spain) analysed the evolution of antibiotic prescription in patients with healthcare-associated infections who were hospitalised in their urology department from 2012 to 2020. Between 2012 and 2015, the most frequently used antibiotics were third and fourth generation cephalosporins (36.9–48.2%). From 2016 onwards, carbapenems were most frequently prescribed (41.5–51.1%).

Due to the updated protocol for empirical treatment in 2020, the prescription of carbapenems decreased to 28.6% and the prescription of third and fourth generation cephalosporins became 42.9%. From 2012 to 2020, the empirical prescription of quinolones decreased from 6.4% to 1.8%.

During the study period, it was increasingly common to change antibiotics in case an antibiogram (i.e. the antibiotic resistance patterns) was available, aimed to reduce the antibiotic spectrum. Once the antibiogram was available, cephalosporins were more frequently prescribed (55.2%) than carbapenems (12.5%).

These results demonstrated that it is essential to review the antibiogram to select the most appropriate antibiotic and try to reduce the spectrum; thereby minimising the occurrence of multi-drug resistant microorganisms.

1. Medina-Polo J. Evaluation of the evolution of antibiotic prescription in the treatment of Healthcare-Associated Infections (HAIs) in a urology ward after implementing a treatment optimisation programme. P0163, EAU21 Virtual, 8–12 July 2021.

Prostate Cancer

Featured video: EAU TV: Robotic surgery and advanced prostate cancer, hosted by Prof. Maarten Albersen (KU Leuven, Belgium). watch the video

Featured video: EAU TV: The best on prostate cancer and incontinence & andrology, hosted by Prof. Peter Albers (Heinrich-Heine-University Düsseldorf, Germany) and Prof. James N'Dow (University of Aberdeen, UK). watch the video

Best of EAU: Updates on imaging and treatment of prostate cancer

During the Best of EAU21 session, Prof. Alberto Briganti (IRCCS Ospedale San Raffaele, Milan, Italy) highlighted studies about prostate cancer [1]. The topics ranged from bi-parametric and multiparametric MRI and ^{18F}PSMA-1007 PET-CT scanning to salvage radiotherapy and results on apalutamide from TITAN.

The first study Prof. Briganti discussed was STHLM3MRI (NCT03377881), a randomised, population-based, screen-by-intervention diagnostic trial from Sweden. A total of 2,293 men with PSA ≥3 ng/mL or Stockholm3 ≥0.11 were randomly assigned to systematic prostate biopsies or bi-parametric MRI and subsequent targeted plus systematic biopsies. The Stockholm3 test algorithm included clinical variables (i.e. age and previous biopsy status), a single-nucleotide-based genetic score, and measurements of 5 protein levels (i.e. total PSA, free PSA, hK2, MSMB, and MIC-1).

Stockholm3 ≥0.15 provided equal sensitivity to detect significant cancers, 36% fewer MRIs, and 8% fewer biopsy procedures compared with PSA ≥3 ng/ml in the MRI-targeted biopsy study arm. "The combination of the Stockholm3 test and an MRI-targeted biopsy for prostate cancer screening is associated with decreased overdetection," Prof. Briganti concluded, "while maintaining detection of clinically relevant cancer" [2].

Multiparametric MRI

A prospective, single-centre, non-inferiority, randomised trial from Italy compared fast MRI with multiparametric MRI in the detection of clinically relevant prostate cancer in >300 men. There was no significant difference in the detection of prostate cancer in the fast MRI versus multiparametric MRI arms (26% vs 30%, respectively). Fast MRI appeared to have a comparable sensitivity and negative predictive value compared with standard multiparametric MRI but was associated with substantially lower acquisition time and costs [3].

^{18F}PSMA-1007 PET-CT

In a separate study from the Netherlands, lymph node stage was assessed with ^{18F}PSMA-1007 PET-CT in newly diagnosed prostate cancer, using histopathological evaluation as a reference. The interest in this study resides in the use of ^{18F}PSMA-1007 rather than ^{68}Gallium-PSMA PET-CT. "Sensitivity at patient-, template- and side-based level were quite poor, being 50.0%, 13.5%, and 40.0%, respectively," according to Prof. Briganti. Given its low sensitivity, ^{18F}PSMA-1007 PET-CT is unlikely to replace extended pelvic lymph node dissection as a staging procedure in intermediate- and high-risk prostate cancer patients" [4].

Salvage radiotherapy

In a retrospective study from Germany, the role of early salvage radiotherapy was assessed according to EAU biochemical recurrence risk features in ~2,500 patients. Although retrospective, the results appear to recommend this strategy in high-risk patients. Conversely, surveillance might be suitable for low-risk patients [5].

Apalutamide in TITAN

Lastly, the phase 3, randomised, placebo-controlled, double-blind TITAN study (NCT02489318) evaluated the role of apalutamide plus androgen deprivation therapy in 1,052 patients with metastatic castration-sensitive prostate cancer (mCSPC). In the current analysis, patients were stratified according to disease volume. At baseline, 63% of patients had high-volume disease and 37% had low-volume disease.

Apalutamide extended both radiographic progression-free survival and overall survival in mCSPC, regardless of disease volume at baseline. The safety remained consistent in both groups, similar to the overall population [6].

1. Briganti A. Best of EAU21: Prostate Cancer. EAU21 Virtual, 8–12 July 2021.
2. Nordström T, et al. P1014, EAU21 Virtual, 8–12 July 2021.
3. Manfredi M, et al. P0901, EAU21 Virtual, 8–12 July 2021.
4. Hermsen R, et al. P0838, EAU21 Virtual, 8–12 July 2021.
5. Preisser F, et al. P1177, EAU21 Virtual, 8–12 July 2021.
6. Chowdhury S, et al. P0845, EAU21 Virtual, 8–12 July 2021.

Radiographic PFS benefit of adding abiraterone to ADT and docetaxel in mCSPC

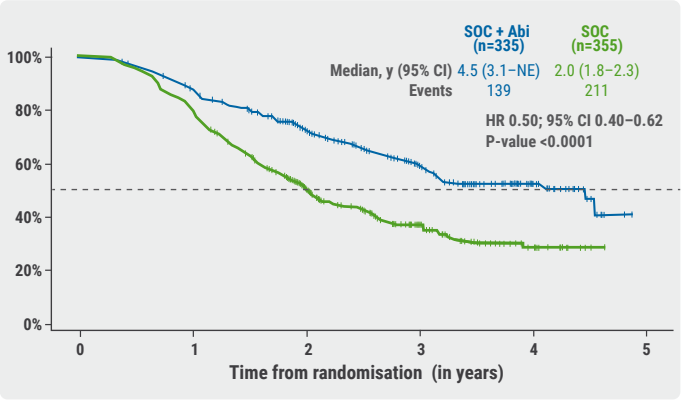
Adding abiraterone to androgen deprivation therapy (ADT) and docetaxel significantly improved radiographic progression-free survival (rPFS) in men with *de novo* metastatic castration-sensitive prostate cancer (mCSPC). This benefit is seen both in high-volume and low-volume metastatic disease. There was no meaningful additional short-term toxicity.

In the last decade, the standard of care (SOC) for men with mCSPC has changed dramatically. Initially, ADT alone was SOC for these patients. In 2015, docetaxel was shown to improve survival. Two years later, the LATITUDE and STAMPEDE trials showed a survival advantage of the addition of abiraterone. In 2019, two additional trials confirmed the advantage of adding 2 other anti-androgen pathway signalling inhibitors, apalutamide or enzalutamide. Radiotherapy to the prostate for oligometastatic (low-volume) disease has also been shown to improve overall survival. The accrual of the phase 3 PEACE-1 trial (NCT01957436) began in 2013. Due to the evolving SOC of these patients, various amendments were implemented during the course of the trial [1].

PEACE-1 included 1,173 men; 57% had a high metastatic burden and 60% received docetaxel. The addition of abiraterone to ADT with or without docetaxel and radiotherapy (i.e. SOC) was associated with a significant improvement in rPFS compared with SOC. Specifically, rPFS improved from a median of 2.0 years to 4.5 years (HR for progression 0.50; P<0.0001; see Figure). "So, we are adding 2.5 years – a big difference," Prof. Karim Fizazi (University of Paris-Saclay, Villejuif, France) said. The benefit of abiraterone was consistent across subgroups analysed.

Overall survival data are not yet mature, so the question remains whether this triplet therapy should be incorporated as a new SOC for patients with *de novo* mCSPC.

Figure: rPFS in the ADT plus docetaxel population [1]



Abi, abiraterone; ADT, androgen deprivation therapy; CI, confidence interval, SOC, standard of care, rPFS, radiographic progression-free survival.

Figure kindly provided by Prof. Fizazi.

1. Fizazi K. Abiraterone acetate plus prednisone added to androgen deprivation therapy and docetaxel in men with de novo metastatic castration-sensitive prostate cancer (mCSPC): detailed analysis of radiographic progression-free survival in the PEACE-1 phase 3 trial. Game changing session 1, EAU21 Virtual, 8–12 July 2021.

^{177}Lu-PSMA-617: A new class of effective therapy

Despite recent therapeutic advances, metastatic castration-resistant prostate cancer (mCRPC) remains invariably fatal. The VISION study showed for men with advanced-stage prostate-specific membrane antigen (PSMA)-positive mCRPC after androgen receptor pathway inhibition and chemotherapy, adding ^{177}Lu-PSMA-617 to standard-of-care treatment extended both overall survival (OS) and radiographic progression-free survival (rPFS). In addition, ^{177}Lu-PSMA-617 was well tolerated.

PSMA is highly expressed in many but not all prostate cancer cells. ^{177}Lu-PSMA-617 is a targeted radioligand therapy that delivers β-particle radiation, which induces DNA damage and double-strand breaks, to PSMA-expressing cells and surrounding microenvironment, destroying cancer cells.

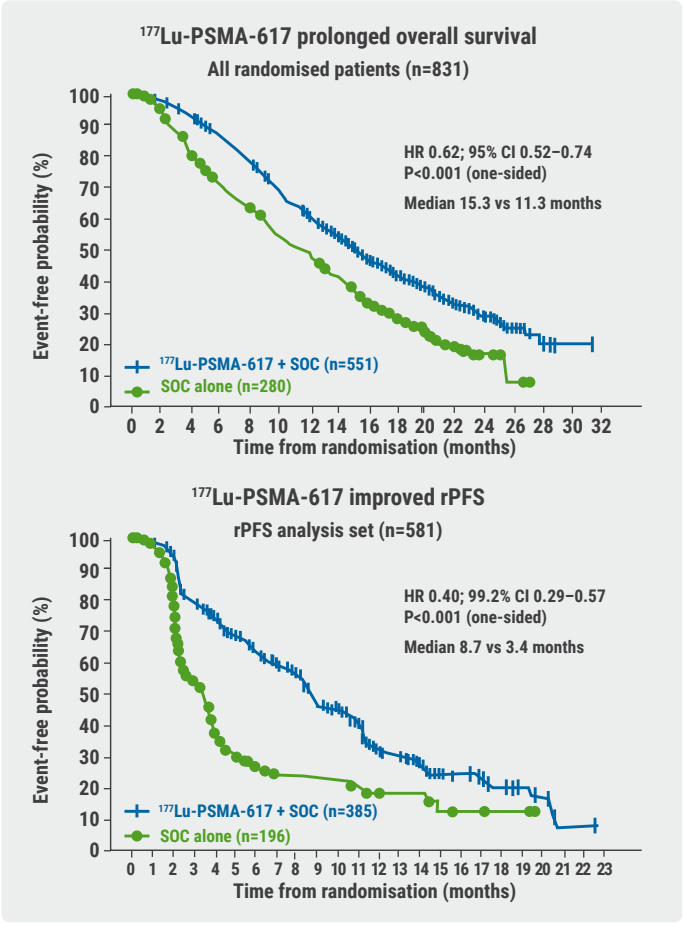
VISION

In the phase 3 VISION trial (NCT03511664), 831 patients were randomised 2:1 to receive ^{177}Lu-PSMA-617 in combination with standard of care (SOC) or SOC alone. SOC was investigator-determined but excluded cytotoxic chemotherapy and radium-223. The 2 treatment arms were well balanced in terms of demographics and baseline characteristics.

The median study follow-up was 20.9 months. The trial met its prespecified endpoint of rPFS. ^{177}Lu-PSMA-617 plus SOC significantly improved rPFS versus SOC alone (median rPFS

8.7 vs 3.4 months; HR 0.40; one-sided P<0.001; see Figure). The alternate primary endpoint of OS was also significantly improved for ^{177}Lu-PSMA-617 plus SOC versus SOC alone (median OS 15.3 vs 11.3 months; HR 0.62; one-sided P<0.001; see Figure). According to Prof. Johann de Bono (The Institute of Cancer Research, London, UK), these findings support the adoption of ^{177}Lu-PSMA-617 as a new treatment modality in patients with mCRPC [1].

Figure: Primary endpoints of OS and rPFS in VISION [1]



CI, confidence interval; rPFS, radiographic progression-free survival; OS, overall survival; PSMA, prostate-specific membrane antigen; SOC, standard-of-care.

Figure kindly provided by Prof. De Bono.

TheraP

The investigator-initiated, phase 2 TheraP trial (NCT03392428) aimed to determine the activity and safety of ^{177}Lu-PSMA-617 in patients with mCRPC who had progressed after docetaxel. Prof. Michael Hofman (Peter MacCallum Cancer Centre, Melbourne, Australia) explained that patient characteristics of TheraP and VISION were comparable. Prior to randomisation, all patients (n=200) underwent ^{68}Gallium-PSMA PET-CT and ^{18}F-FDG PET-CT. The participants were randomised to ^{177}Lu-PSMA-617 or cabazitaxel [2].

The primary endpoint was a PSA response of ≥50% from baseline. PSA responses were significantly higher among men who received ^{177}Lu-PSMA-617 compared with those receiving cabazitaxel (66% vs 37%; P<0.0001). In addition, ^{177}Lu-PSMA-617 delayed progression when measured with PSA or rPFS at 12 months: PFS was 3% in the cabazitaxel arm versus 19% in the ^{177}Lu-PSMA-617 arm (HR 0.63; 95% CI 0.46–0.86; P=0.0028). The observed PFS benefit was similar when measured radiographically (rPFS; HR 0.64; P=0.007) or based on PSA (PSA-PFS; HR 0.60; P=0.002). Among 78 men with measurable disease, objective response rates were significantly greater in the ^{177}Lu-PSMA-617 arm (49%) versus the cabazitaxel arm (24%; RR 2.1; P=0.019). The OS analysis has not yet been performed for TheraP.

With respect to grade 3–4 AEs, the incidence of thrombocytopenia was higher in the ^{177}Lu-PSMA-617 arm (11% vs 0%), whereas more neutropenic events with or without fever occurred in the cabazitaxel arm (13% vs 4%).

Patient-reported outcomes demonstrated improved quality of life in several domains for ^{177}Lu-PSMA-617 versus cabazitaxel, particularly those related to chemotherapy side effects, such as skin rash, palmar/plantar soreness, hair loss, altered taste, dizziness, urinary symptoms, and diarrhoea. Those do not occur with ^{177}Lu-PSMA-617 but can be problematic with cabazitaxel. Overall, quality of life was similar between the 2 arms.

The deterioration-free survival, defined as the time to ≥10-point decrease in QLQ-C30 global health status, progression, death, or treatment discontinuation, favoured the ^{177}Lu-PSMA-617 arm at all time points.

TheraP versus VISION

Next, Prof. Hofman compared the TheraP and VISION trials: "VISION is a phase 3 registration study, providing definitive evidence of an improvement in OS. TheraP perhaps takes this treatment one step earlier by comparing ^{177}Lu-PSMA-617 directly with cabazitaxel instead of initiating after cabazitaxel."

The treatment schedules were very similar, with a median of 5 cycles of ^{177}Lu-PSMA-617 in both studies. There were differences in the percentage of patients excluded from the trial (28% for TheraP vs 12% for VISION) and in the PSA response rate of ≥50% (66% for TheraP vs 46% for VISION).

Prof. Hofman concluded that the combined results of TheraP and VISION showed that ^{177}Lu-PSMA-617 is a new class of effective therapy. "^{177}Lu-PSMA-617 improves outcomes in men with mCRPC following docetaxel and androgen receptor directed therapies. The TheraP study provided some information on activity compared with cabazitaxel, where ^{177}Lu-PSMA-617 appears superior with fewer grade 3–4 AEs and improved quality of life. Optimal patient selection, sequencing, and monitoring of ^{177}Lu-PSMA-617 will continue to evolve."

1. De Bono J. Phase 3 study of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION). Game changing session 5, EAU21 Virtual, 8–12 July 2021.
2. Hofman M. TheraP Phase 2 trial of Lu-PSMA-617 versus cabazitaxel: Results and contrasts to VISION. Game changing session 5, EAU21 Virtual, 8–12 July 2021.

Testis and Penile Cancer

Best of EAU: New advances in testicular and penile cancer

Analysis of microRNA (miRNA) expression allowed to discriminate between viable tumour, teratoma, and necrosis on post-chemotherapy retroperitoneal lymph node dissection (RPLND). A retrospective study underlined that sequential post-chemotherapy residual tumour resection is mandatory. These and other findings were presented in the Best of EAU21 session by Prof. Maarten Albersen (UZ Leuven, Belgium) [1].

Biomarker-guided therapy could reduce overtreatment with post-chemotherapy RPLND in patients with only necrosis in the specimen. Therefore, a German study aimed to identify a combination of miRNAs as potential biomarkers to differentiate between viable tumour, teratoma, and necrosis [2]. miRNA expression was analysed using quantitative real-time PCR (qRT-PCR) in post-chemotherapy RPLND tissues containing necrosis (n=16), teratoma (n=16), and viable tumour (n=16).

When comparing viable tumour versus necrosis, miR-371-3p achieved the highest fold change of 31.1 (P=0.023), whereas miR-375-5p performed best for teratoma versus necrosis with a fold change of 64.2 (P<0.001). Combining the best performing miRNAs for viable tumour and teratoma generated an area under the curve (AUC) of 0.94, with a sensitivity and specificity of almost 94% for both. Positive predictive value was 96.8 and negative predictive value was 83.3.

This study demonstrated that miR-371a-3p and miR-375-5p are potential biomarkers for the discrimination between viable tumour, teratoma, and necrosis in post-chemotherapy RPLND. These results need to be validated in serum.

Residual tumour resection in metastatic germ cell tumour

In patients with metastatic germ cell tumours, post-chemotherapy residual tumour resection is a crucial part of treatment. Surgery should commence at the site with the highest volume of residual disease; concordance has been shown to be up to 90%.

A retrospective study analysed histological concordance between thoracic and retroperitoneal lesions in 54 patients who had undergone retroperitoneal and thoracic residual tumour resection after first-line as well as salvage chemotherapy [3].

Most patients (91%) first underwent retroperitoneal residual tumour resection. The results showed that histology of retroperitoneal and thoracic residual tumour resection matched in 35 patients (65%) and was discordant in the other 19 patients (35%). Of 21 patients with retroperitoneal necrosis, 7 (33%) showed vital cancer or teratoma in the thorax. First-line chemotherapy resulted in a discordance rate of 29%, which increased after salvage chemotherapy to 58% (P=0.087).

This data underlines the need for sequential post-chemotherapy residual tumour resection, since discordance of histology is up to 35%. "They concluded that retroperitoneal necrosis histology did not predict for thoracic necrosis," Prof. Albersen said. "Discordant histology was more prevalent in patients after salvage chemotherapy, which indicates that thoracic resection is needed independent of tumour volume."

Dynamic sentinel lymph node biopsy for penile cancer

Dynamic sentinel lymph node biopsy is routinely offered to patients presenting with >T1G2 cN0 penile cancer, that is, without palpable lymph nodes. Due to concerns about low sensitivity, dynamic sentinel lymph node biopsy is not widely used outside of centralised care systems.

A retrospective analysis of eUROGEN centres evaluated patients with intermediate-high risk cN0 penile cancer [4]. A total of 993 groins in 509 patients were studied. After a median follow-up of 62.5 months, 37 (7.27%) patients had positive histology at dynamic sentinel lymph node biopsy; 34 of them had positive histology at inguinal lymph node dissection. At dynamic sentinel lymph node biopsy, 37 (7.27%) were true positives and 3 were false negatives (0.59%). Sensitivity was 92.5% and specificity was 100%.

"Dynamic sentinel lymph node biopsy is a good staging examination in penile cancer, with a lower complication rate than inguinal lymph node dissection but a higher false-negative rate," concluded Prof. Albersen. Sensitivity in centralised services was 92.5%. Surprisingly, only 7.27% were true positives, which would have resulted in overtreatment of 92.7% if lymph node dissection had been adopted. Despite having a higher rate of false-negative results (0.59%) compared with inguinal lymph node dissection, dynamic sentinel lymph node biopsy was found to be a well-balanced and accurate staging method for penile cancer.

Triple therapy for advanced penile cancer

Although neo-adjuvant platinum-based chemotherapy combinations have been used for patients with advanced penile squamous cell carcinoma, these treatments have shown poor efficacy rates amounting to 50%. Evidence on combinatorial schedules including targeted agents and checkpoint inhibitors is limited [5].

To this end, a prospective, single-arm, open-label, phase 2 study included 10 patients (median age 55.5 years) with chemotherapy-naïve, advanced penile squamous cell carcinoma (T4 or N3, M0). Patients received toripalimab (anti-PD-1) plus nimotuzumab (anti-EGFR) on day 1 plus chemotherapy intravenously every 3 weeks for 4 courses; 8 patients received >2 courses. Neoadjuvant treatment with subsequent radical surgery was completed by 5 patients, of whom 4 achieved pathologic complete response (pCR). At least 1 treatment-related adverse event of grade 1–2 was experienced by 90% of patients, most commonly numbness of hand and foot (90%), nausea (70%), and decreased appetite (40%). There were no grade 3 or 4 adverse events.

This small cohort demonstrated that triple therapy with anti-PD-1, anti-EGFR, and chemotherapy may be promising for patients with advanced penile cancer. Only 50% of patients proceeded to surgery and pCR was relatively high. Overall response rates were not assessed. This protocol may be promising, although overall response rates are not clear and reasons for discontinuation were not disclosed.

1. Albersen M. Best of EAU: Testis/Penile cancer. EAU21 Virtual, 8–12 July 2021.
2. Nestler T. P0658, EAU21 Virtual, 8–12 July 2021.
3. Buddensieck C. P0665, EAU21 Virtual, 8–12 July 2021.
4. Pozzi E. P0667, EAU21 Virtual, 8–12 July 2021.
5. Shi Y. P0680, EAU21 Virtual, 8–12 July 2021.

Recommendations for the management of indeterminate small testis masses

Currently, the pathway for the management of indeterminate small testis masses is not standardised. The current study assessed the outcomes including imaging surveillance and biopsy of small testis masses to propose a management pathway for small testis masses to avoid unnecessary radical orchidectomy. This study has important implications relating to the preservation of fertility and hormonal function.

In a retrospective analysis of all small testis masses (≤2 cm) from a single centre in the United Kingdom over a 10-year period, each case was discussed by a specialist testis multidisciplinary team [1]. The current analysis included 307 patients (median age 36 years) with a median lesion size of 6 mm (range 1.5–20 mm). Of these, 62 patients (20%) underwent radical orchidectomy, 161 (52%) underwent surveillance with serial ultrasounds up to 12 months, 82 (27%) had an ultrasound-guided testicular biopsy, and 3 (1%) were discharged with reassurance and advice for self-examination.

A total of 115 patients (38%), including 33 patients from the surveillance cohort, underwent a testicular biopsy. Of these patients, 30 (26%) had a histological diagnosis of malignancy. Most malignancies were seminomas, and the remainder were benign lesions including Leydig cell tumours. Tumour markers were not elevated in any of the patients with malignancy.

Orchidectomy for small testis masses has significant implications for fertility and hormonal function. This study

showed that <10% of small testis masses were malignant. The cancer detection rate for patients under surveillance was even lower (4.3% in this analysis). Surveillance can avoid unnecessary biopsy and orchidectomy while ensuring that the lesions that change are biopsied early.

Based on this data, Mr Shafi Wardak (University College London Hospitals, UK) argued that all small testis masses should be reviewed in a testis multidisciplinary team before considering surgical intervention. He recommended ≥3 surveillance scans 3–6 months apart, and to biopsy the lesions that change on serial imaging.

1. Wardak SW. Management of indeterminate Small Testis Masses (STMs): A 10-year single centre experience. P0654, EAU21 Virtual, 8–12 July 2021.

Residual tumour resection in case of elevated markers

In patients with germ cell tumours and elevated serum tumour markers, whether post-chemotherapy residual tumour resection is beneficial is unclear. A retrospective analysis from Germany aimed to better define patients who benefit from surgery in this setting.

By analysing data from their own database, Dr Yue Che (University of Düsseldorf, Germany) and colleagues found 575 post-chemotherapy residual tumour resections, performed in 516 patients, including 153 procedures in patients with elevated serum tumour markers (human chorionic gonadotropin [β-HCG] >2.0 mIU/mL; α-fetoprotein [AFP] >7.0 µg/L). Of these patients, 55 received resection after first-line chemotherapy and 98 after second- or further-line (salvage) chemotherapy [1].

Viable cancer in the resected specimen was more frequently present in the salvage group compared with the first-line group (49% vs 16%; P=0.0002). The presence of viable cancer was a predictor of survival in both groups. In the first-line group, teratoma was the most common type (52.7%), followed by necrosis/fibrosis (30.9%) and viable cancer (16.4%).

Univariate and multivariate regression analysis was performed to determine predictors for residual tumour resection histology and oncological outcome. A preoperative serum level of AFP ≥30 µg/L was a predictor of viable cancer in the first-line group (56%; P=0.016) and in the salvage setting (67%; P=0.0017). The overall relapse-free rate was significantly worse in the salvage group compared with the first-line group (22.7% vs 50%; P=0.00032), as was the survival rate (37.8% vs 65%; P=0.0059). Serum AFP ≥30 µg/L and β-HCG ≥20 mIU/mL were significant factors affecting survival in the first-line group.

Dr Che argued that patients with serum AFP ≥30 µg/L and β-HCG ≥20 mIU/mL after first-line chemotherapy should receive salvage chemotherapy instead of surgery because chances for viable cancer and relapse are high and survival is poor. These patients will probably not benefit from post-chemotherapy residual tumour resection, and salvage chemotherapy should be the preferred treatment. After second- or further-line therapy, the prognosis of patients with elevated markers and surgery is poor, regardless of tumour marker levels. However, 38% of these patients are long-term survivors, which justifies post-chemotherapy residual tumour resection in this setting.

1. Che Y. Post-chemotherapy residual tumor resection in patients with elevated tumor markers. P0662, EAU21 Virtual, 8–12 July 2021.

Bladder Cancer

Featured video: EAU TV: The best on bladder cancer and renal cell carcinoma, hosted by Prof. Arnulf Stenzl (University of Tübingen, Germany).

watch the video

Best of EAU: Highlights on bladder cancer

In the Best of EAU21 session on bladder cancer, Prof. Morgan Rouprêt (Pitié-Salpêtrière Hospital, Paris, France) highlighted 4 noteworthy abstracts [1]. Omitting antimicrobial prophylaxis appears safe in patients undergoing trans-

urethral resection of bladder tumour (TURB); a biomarker test may help to reduce unnecessary cystoscopies in patients with non-muscle invasive bladder cancer (NMIBC); molecular subtyping can improve clinical risk stratification by identification patients at risk of Bacillus Calmette-Guérin (BCG) failure; and nadofaragene firadenovec represents a potential novel treatment option for patients with high-grade BCG-unresponsive NMIBC.

Antimicrobial prophylaxis in TURB

A multicentre, randomised controlled trial assessed whether omitting antimicrobial prophylaxis is safe in patients undergoing TURB. The primary endpoint was post-operative fever.

Of 459 included patients, 202 (44.1%) received antimicrobial prophylaxis and 257 (55.9%) did not. Results indicated that fever occurred in 6 (2.9%) patients with antimicrobial prophylaxis versus 8 (3.1%) without antimicrobial prophylaxis (P=0.44). Furthermore, no differences were found for (clot) retention (P=0.20), tumour size (P=0.20). A multivariable, logistic regression demonstrated no significant harm in omitting antimicrobial prophylaxis when controlled for (clot) retention and tumour size (P=0.85). This data demonstrated that omitting antimicrobial prophylaxis was safe in patients undergoing TURB without an indwelling, pre-operative catheter/nephrostomy/DJ and a negative pre-operative urinary culture [2].

Reducing the frequency of follow-up cystoscopies

To detect recurrence and progression, patients with NMIBC require frequent follow-up cystoscopies. The current multicentre study assessed whether the urinary biomarker test ADXBLADDER could aid in reducing unnecessary follow-up cystoscopies, improving quality of life, and decreasing costs [3].

From all included patients (n=1,416), 126 (8.9%) experienced a recurrence, 41 (2.9%) of whom recurring with a high-grade tumour and/or carcinoma *in situ* (CIS). In a subgroup of 721 patients with non-invasive, low-grade tumour (no CIS) at the previous visit, 85 (11.8%) recurred, 13 (1.8%) had a high-grade tumour and/or CIS. ADXBLADDER was the only significant variable for high-grade tumour and/or CIS in patients that previously had a low-grade tumour without CIS. ADXBLADDER had a sensitivity of 69.2% and a specificity of 75%. A less intensive follow-up surveillance schedule utilising this ADXBLADDER test could lead to a reduction of up to 60% in unnecessary cystoscopies during follow-up.

Transcriptome sequencing of BCG-treated bladder cancer

Patients with T1 high-grade bladder cancer undergo TURB followed by adjuvant intravesical instillations with BCG. Current clinical risk stratification is insufficient to identify patients at risk of BCG failure. To this end, the current study aimed to identify molecular predictors of BCG failure.

Gene expression profiling of primary BCG-naïve patients with T1 high-grade bladder cancer identified 3 molecular subtypes that corresponded to clinical outcome after BCG therapy. So, molecular subtyping can improve clinical risk stratification by identification of patients with BCG subtype 3 tumours that are more suitable candidates for early radical cystectomy or novel bladder-sparing treatments given the poor outcome if treated by BCG [4].

Gene therapy for NMIBC

Despite optimal treatment, >50% of patients with NMIBC who have an initial response to BCG will experience recurrence and progression. Because treatment options are limited, there is an unmet need for local, effective, bladder-preserving treatment options.

Nadofaragene firadenovec is a non-replicating recombinant type 5 adenovirus vector-based gene therapy that delivers a copy of the human *IFNA2b* gene. Its safety and efficacy were assessed in a phase 3 trial (NCT02773849) that included 157 patients with high-grade, BCG-unresponsive NMIBC [5].

The results demonstrated no significant differences in response rates at 3 and 15 months between diverse subgroups, including men versus women, age groups, BCG-refractory versus BCG-relapsed, ≤3 versus >3 prior lines of treatment, 0 or ≥1 prior non-BCG regimens, and ≤3 or >3 prior courses of BCG.

These results demonstrated that nadofaragene firadenovec is effective regardless of patient characteristics or prior treatment history. Nadofaragene firadenovec represents a potential novel treatment option for patients with high-grade BCG-unresponsive NMIBC that advance in the current treatment paradigm.

1. Rouprêt M. Best of EAU21: Bladder Cancer. EAU21 Virtual, 8–12 July 2021.
2. Baten E, et al. P0733, EAU21 Virtual, 8–12 July 2021.
3. Sylvester RJ, et al. P0725, EAU21 Virtual, 8–12 July 2021.
4. De Jong FC, et al. P0442, EAU21 Virtual, 8–12 July 2021.
5. Narayan V, et al. P0745, EAU21 Virtual, 8–12 July 2021.

ctDNA can guide adjuvant immunotherapy in muscle-invasive bladder cancer

In the IMvigor010 trial, post-surgical circulating tumour DNA (ctDNA) positivity was associated with a high risk of recurrence and death. ctDNA positivity identified patients with muscle-invasive bladder cancer (MIBC) likely to derive survival benefits from adjuvant atezolizumab. Tumour mutation burden status was also associated with improved outcomes with adjuvant atezolizumab in the ctDNA-positive population [1].

"ctDNA has substantial potential to be used throughout the individual patient journey," Prof. Jürgen Gschwend (Technical University Munich, Germany) explained. It could be useful in many phases, from screening to monitoring for resistance in post-treatment care. For example, ctDNA could be useful to determine the need for treatment intensification, such as the need for perioperative therapy. Post-surgery presence of ctDNA in patients with bladder cancer indicates molecular disease progression that precedes clinical relapse. Prof. Gschwend argued that the use of this marker may shorten drug developmental timelines and may help to avoid treating patients who do not require additional therapy.

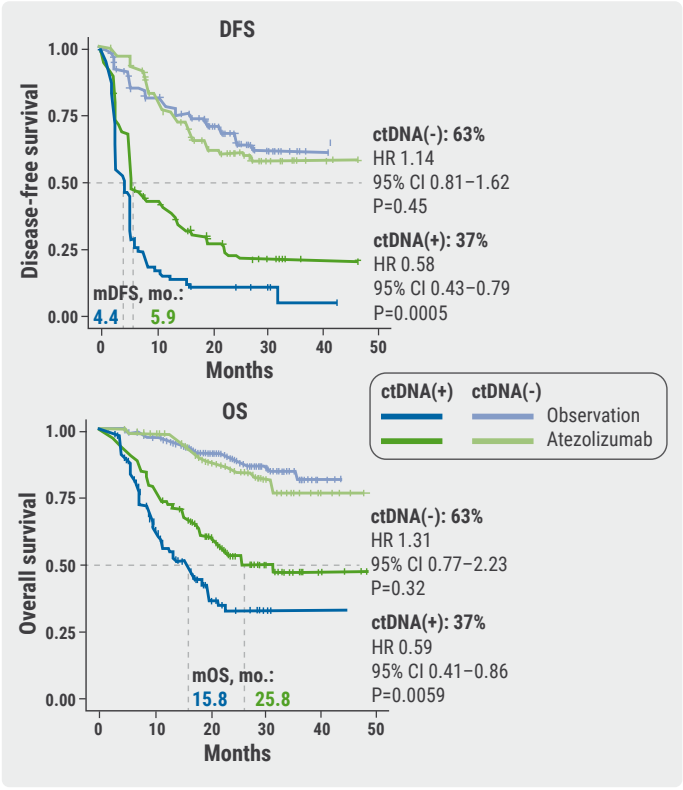
The global, phase 3 IMvigor010 study (NCT02450331) compared adjuvant atezolizumab with observation in patients with MIBC following surgery. Of the 809 patients included, 581 (72%) had biomarker-evaluable tissue.

The primary endpoint of disease-free survival (DFS) was not met: DFS was similar between the intention-to-treat (ITT) and the biomarker-evaluable patient cohort. The same was true for overall survival (OS). "However, an important finding was that ctDNA-positive patients had a significantly improved DFS and OS with atezolizumab compared with observation," added Prof. Gschwend.

Moreover, results from IMvigor010 confirmed the prognostic value of ctDNA status. ctDNA-positive patients had worse DFS and OS rates compared with ctDNA-negative patients. Furthermore, ctDNA-positive patients who received adjuvant atezolizumab performed better than patients who were under observation.

The combination of ctDNA and high tumour mutation burden translated into a more pronounced DFS and OS benefit compared with tumour mutation burden-negative patients. In addition, ctDNA-positive patients treated with atezolizumab were more likely to clear ctDNA (18% vs 3%), and clearance was associated with improved DFS. OS results were similar.

Figure. DFS and OS with atezolizumab compared with observation in ctDNA-positive patients



DFS, disease-free survival; OS, overall survival.
Figure kindly provided by Prof. Jürgen Gschwend.

The IMvigor010 study warrants validation in the currently active IMvigor011 study (NCT04660344). IMvigor011 is recruiting patients with high-risk MIBC who show ctDNA positivity within 20 months after radical cystectomy. ctDNA-positive patients will receive either atezolizumab or placebo for 1 year. If confirmed, the results may change our understanding of post-surgical care.

1. Gschwend JE, et al. ctDNA guiding adjuvant immunotherapy in urothelial carcinoma. Game changing session 3, EAU21 Virtual, 8–12 July 2021.

Durvalumab ± tremelimumab by cisplatin eligibility in metastatic urothelial carcinoma

The randomised, phase 3 DANUBE trial did not achieve its co-primary endpoints. Therefore, data presented at EAU21 were exploratory. Durvalumab showed activity in the cisplatin-ineligible, PD-L1^{high} population, which is in line with results for other immune checkpoint inhibitors in this population. Tremelimumab appeared to improve the activity of durvalumab when given in combination [1].

Based on single-arm trials, atezolizumab and pembrolizumab are currently licensed in cisplatin-ineligible, PD-L1-positive patients in the first-line setting. Randomised phase 3 trials have not yet shown overall survival (OS) benefit for these immune checkpoint inhibitors over chemotherapy. There is little prospective data on the comparative efficacy of cisplatin and carboplatin in patients with a good performance status, but carboplatin is considered inferior to cisplatin.

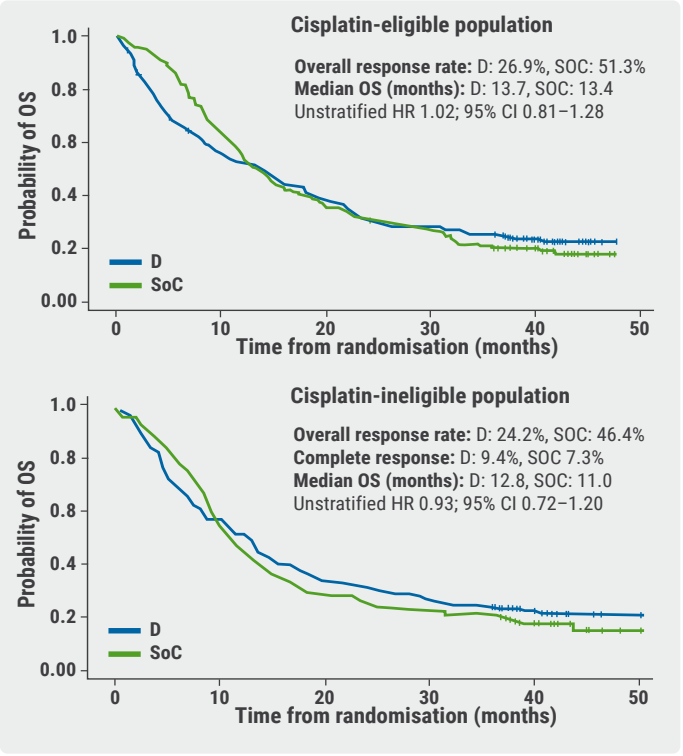
The DANUBE trial (NCT02516241) evaluated treatment with durvalumab ± tremelimumab in patients with metastatic urothelial carcinoma. Previously published results demonstrated that DANUBE did not meet its primary endpoint [2]. There was no significant benefit of durvalumab ± tremelimumab in median OS compared with standard-of-care (SOC) chemotherapy (gemcitabine/cisplatin or gemcitabine/carboplatin, at the discretion of the treating physician). Concerning progression-free survival, no significant difference was observed between the different regimens in the control arm (median PFS 5.7 months for carboplatin vs 7.0 months for cisplatin; P=0.31). Median OS trended towards improvement with cisplatin (14.2 months) versus carboplatin (10.6 months; P=0.09). This suggests that carboplatin-treated patients do better than historical controls with good performance status.

Prof. Thomas Powles (Barts Cancer Centre, London, UK) shared results of an exploratory post-hoc analysis of durvalumab ± tremelimumab by cisplatin eligibility and in the first-line carboplatin-treated population [1]. In the intention-to-treat (ITT) population, no significant difference was observed between durvalumab and SOC in OS rates, regardless of cisplatin eligibility (see Figure). Even in the PD-L1^{high} cohort, there was no difference between durvalumab (HR 0.91; 95% CI 0.67–1.22) and SOC (HR 0.87; 95% CI 0.62–1.21). Nonetheless, in the cisplatin-ineligible, PD-L1^{high} cohort, response rates were similar to other immune checkpoint inhibitors. Adding tremelimumab to durvalumab appeared to improve activity of durvalumab in the PD-L1^{high} population.

Biomarker analyses based on tumour mutational burden (TMB) demonstrated that OS favoured durvalumab plus tremelimumab over SOC at prespecified blood TMB cut-off ≥24 mut/Mb and tissue TMB cut-off ≥10 mut/Mb. These biomarker analyses suggest that components of immune and tumour expression may be relevant in determining outcomes.

The combination of durvalumab plus tremelimumab will be further explored in the randomised, phase 3 NILE and VOLGA trials.

Figure. OS by cisplatin eligibility in the ITT population for durvalumab versus SOC [1]



D, durvalumab; HR, hazard ratio; OS, overall survival; SOC, standard of care.
Figure kindly provided by Prof. Powles.

1. Powles T, et al. DANUBE post-hoc analysis: Outcomes for durvalumab with or without tremelimumab by cisplatin eligibility and PD-L1 biomarker status in metastatic urothelial carcinoma. Game changing session 3, EAU21 Virtual, 8–12 July 2021.
2. Powles T, et al. Lancet Oncol. 2020;21(12):1574–88.

Circulating tumour cells could aid in the decision to give neoadjuvant chemotherapy

The benefit of neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer and no circulating tumour cells detectable may be limited. Although the CirGuidance study did not meet its primary endpoint, counting the number of circulating tumour cells at the moment of diagnosis could still aid in the decision to give neoadjuvant chemotherapy for patients with muscle-invasive bladder cancer [1].

Although international guidelines for the treatment of non-metastatic muscle-invasive bladder cancer recommend neoadjuvant chemotherapy, this treatment modality is under-

utilised in the clinic. In the Netherlands, only 20% of patients receive neoadjuvant chemotherapy. "Hence, there is a need for biomarkers to guide treatment decision-making on neo-adjuvant chemotherapy," explained Dr Nick Beije (Erasmus Medical Center, Rotterdam, the Netherlands). Circulating tumour cells (CTCs) are a strong prognostic marker in muscle-invasive bladder cancer for overall survival (OS), progression-free survival (PFS), and cancer-specific survival in these patients. Hypothesised was that the absence of CTCs might identify patients with such a good prognosis that neoadjuvant chemotherapy is not justified.

The observational, multicentre CirGuidance study (NTR4120) included adults with clinical stage T2-T4a N0-N1 M0 muscle-invasive urothelial carcinoma of the bladder who were fit to undergo radical cystectomy. Patients with no detectable CTCs underwent radical surgery without neoadjuvant chemotherapy, whereas patients with ≥1 detectable CTC were advised to receive neoadjuvant chemotherapy followed by radical surgery; neoadjuvant chemotherapy could be refused.

Of 315 patients screened for eligibility, 273 patients (median age 69 years) were enrolled in the study. A total of 203 patients were CTC-negative and 70 were CTC-positive. The study did not meet the primary endpoint of OS >75%. In CTC-negative patients, OS was 69.5% versus 58.2% in CTC-positive patients. However, CTC-positive patients had better OS when they received neoadjuvant chemotherapy. In CTC-positive patients, cancer-related mortality (HR 1.61; 95% CI 1.05–2.45; P=0.03) and the incidence of relapse (HR 1.87; 95% CI 1.28–2.73; P=0.001) were higher than in CTC-negative patients. Dr Beije concluded that CTCs may still be a valuable biomarker as an addition to other already available markers.

1. Beije N. Circulating tumour cell-driven use of neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer: final results of the CirGuidance study. Game changing session 3, EAU21 Virtual, 8–12 July 2021.

Renal Cancer

Featured video: EAU TV: The best on bladder cancer and renal cell carcinoma, hosted by Prof. Arnulf Stenzl (University of Tübingen, Germany).

watch the video

Best of EAU: Immune cell populations have prognostic value in RCC

During the Best of EAU21 abstracts session, Dr Alberto Breda (Autonomous University of Barcelona, Spain) highlighted 6 representative abstracts on renal cancer, including 4 from Italy, his country of origin [1]. Assessment of immune cell populations on nephrectomy specimens was shown to have prognostic value in renal cell carcinoma (RCC). Another study externally validated the guidelines for Von-Hippel Lindau disease (VHL) genetic testing. Furthermore, a study on the oncological outcomes of neoadjuvant target therapy and 3 studies on robot-assisted partial nephrectomy were presented.

As opposed to other tumour types, higher levels of tumour-infiltrating lymphocytes have been associated with worse outcomes on systemic treatment in metastatic RCC. Investigators from Leuven, Belgium, included 143 patients of whom 103 (72.0%) experienced disease recurrence and 67 (46.9%) died of RCC [2]. The aim was to explore the impact of immune and stromal cell populations on disease-free survival (DFS) and cancer-specific survival (CSS).

The results demonstrated that Leibovich score and CD8+ T-cell infiltration were both independently associated with poorer DFS (HR 1.27; P<0.001 and HR 2.36; P<0.001) and CSS (HR 1.36; P<0.001 and HR 2.00; P=0.009).

Transcriptome-based estimation of tumour-infiltrating CD8+ T cells on nephrectomy specimens was associated with worse DFS and CSS in clear cell (cc)RCC patients, independent of the established Leibovich risk score. This data demonstrated that assessment of tumour-infiltrating CD8+ T cells on nephrectomy specimens could be easily implemented to refine prognostic information and guide subsequent disease management.

External validation of the VHL Alliance guidelines

In absence of guidelines for VHL genetic testing, the 2020

VHL Alliance recommendations support selective testing of patients with an aggressive phenotype. A study from Italy externally validated these recommendations in a ccRCC cohort [3].

The results demonstrated that among 2,410 ccRCC patients, 11% had a high risk of VHL. However, only 5% exhibited a positive genetic test (VHL genetic mutation). A VHL clinical phenotype was shown in 9% of ccRCC patients, among those the proportion of genetic counsellor referral was 59%.

In this special population, approximately 1 in 10 ccRCC patients harboured a high risk of VHL. However, genetic counsellor referral was observed in little over half of the patients. The remarkably low proportion of genetic counsellor referral in case of high-risk phenotype urges clinicians to pay special consideration for VHL risk profile after ccRCC diagnosis.

Oncological outcomes of neoadjuvant targeted therapy in patients with localised RCC

The role of neoadjuvant target therapy for localised RCC is not clear. It can be used to reduce tumour volume, simplify surgery, and treat micrometastasis. A prospective study from Ukraine was set up to determine whether pre-surgical target therapy with pazopanib facilitates nephron-sparing surgery and improve oncological outcomes for patients with localised RCC (n=167) [4].

In this prospective, randomised trial, pazopanib (800 mg) was administered for 2 cycles of 8 weeks. Neoadjuvant target therapy led to tumour size decrease up to 11.5 mm on average (from median 61.3 mm to 49.8 mm). Tumour downsizing was observed in the vast majority of cases (n=74, 89.2%), with an average decrease of 20.4%. Tumour downsizing after target therapy led to nephron-sparing surgery in 75 (90.3%) patients compared with 41 (48.8%) in the control group (P=0.01). Five-year overall survival rates were comparable in both groups: 91% in the target therapy group versus 80% in the control group (log-rank P=0.18).

This study demonstrated that the use of neoadjuvant target therapy in patients with localised RCC resulted in a tumour size reduction of ~20% but without impact on overall survival.

IGNITE

Currently, pre-operative 3D reconstruction needs to be manually oriented during laparoscopic surgery. An Italian group investigated a new dedicated software called 'IGNITE', which is able to automatically anchor preoperative reconstruction with the endoscopic vision of the real organ [5].

Ten cases were enrolled in this pilot experience. Automatic 3D model overlapping led to a correct identification of the tumour, even in endophytic and posterior cases, without risk of complications or positive surgical margins. These findings suggest that the new evolution of the evaluated augmented reality platform based on computer vision algorithm allows for its application in robot-assisted partial nephrectomy.

Renal function deterioration after robotic partial nephrectomy

Totally endophytic "deep" renal tumours represent one of the most challenging scenarios for the urologist. In a retrospective series of Italian patients with cT1-2 renal tumours who underwent robotic partial nephrectomy, severe renal function deterioration rates were analysed and compared with a selectively collected group of patients with deep renal masses, treated with the same intervention in the same institutions [6].

Based on these findings, deep renal masses must be considered as a separate category of tumours due to their technical complexity. This complexity was regardless of renal score, showing a higher rate of severe renal function deterioration over time. These challenging cases are inevitably exposed to a 2-fold increased risk of developing severe chronic kidney disease (CKD) over time.

Robot-assisted radical nephrectomy plus thrombectomy

Radical nephrectomy with inferior vena cava tumour thrombectomy for RCC represents one of the most challenging urologic surgical procedures. A single tertiary-care centre from Italy reported perioperative and oncologic outcomes of 30 consecutive cases of completely intracorporeal robot-assisted radical nephrectomy with inferior vena cava tumour thrombectomy [7]. Thrombectomy levels were level I in 20%, level II in 30%, and level III in 50%.

There was no need for conversion to open surgery. Perioperative complications Clavien III-V were present in 13% of patients. At a median follow-up of 26.5 months, overall survival was 50%, CSS 43%, locoregional recurrence-free survival (LRFS) 93.3%, and metastasis-free survival (MFS) 43.3%. The current small cohort with limited follow-up and the

heterogeneous population including a high rate of adjuvant medical treatment (46.7%) preclude definitive conclusions about the oncologic safety of this procedure.

This data suggests that radical nephrectomy with inferior vena cava tumour thrombectomy appears a feasible and safe procedure for RCC in tertiary referral centres, even in the most advanced indications.

1. Breda A. Best of EAU21: Renal Cancer. EAU21 Virtual, 8–12 July 2021
2. Roussel E. P0549, EAU21 Virtual, 8–12 July 2021.
3. Larcher A. P0636, EAU21 Virtual, 8–12 July 2021.
4. Semko S. P0568, EAU21 Virtual, 8–12 July 2021.
5. Amparore D. V23, EAU21 Virtual, 8–12 July 2021.
6. Tuderti G. P0577, EAU21 Virtual, 8–12 July 2021.
7. Anceschi U. P0625, EAU21 Virtual, 8–12 July 2021.

KEYNOTE-564: First positive phase 3 results with adjuvant checkpoint inhibition in RCC

KEYNOTE-564 is the first positive phase 3 study with adjuvant immunotherapy in patients with renal cell carcinoma (RCC). These results support the use of pembrolizumab as a potential new standard of care for patients with RCC in the adjuvant setting.

Nephrectomy is the standard of care for the treatment of locoregional RCC. Nearly half of patients eventually experience disease recurrence after surgery. Patients with M1 stage and no evidence of disease (NED) after resection of oligometastatic sites are also at high risk of relapse. Relapse after surgery for high-risk clear-cell RCC (ccRCC) is associated with shortened survival. To reduce the relapse risk, effective perioperative treatments are needed, and adjuvant immune therapy might offer an attractive potential strategy for these patients.

The phase 3, double-blind, multicentre KEYNOTE-564 trial (NCT03142334) investigates pembrolizumab versus placebo in patients with ccRCC [1]. Patients with histologically confirmed ccRCC (n=994) were randomised 1:1 to pembrolizumab 200 mg or placebo every 3 weeks for ~1 year. Patients were in one of the following risk groups:

- pT2, grade 4 or sarcomatoid, N0, M0;
- pT3 or pT4 any grade, N0, M0;
- pT4 any grade, N0, M0;
- pT any stage, any grade, N+, M0; or
- M1 with NED after surgery of primary tumour and resection of oligometastatic lesions.

Prof. Thomas Powles (Barts Cancer Centre, London, UK) shared the results of the study.

After a median follow-up of 24.1 months, the primary endpoint of disease-free survival (DFS) was met. Median DFS was not reached for both arms. The estimated DFS rate at 24 months was 77.3% with pembrolizumab versus 68.1% with placebo (HR 0.68; 95% CI 0.53–0.87; P=0.0010; see Figure). Overall, DFS benefit was consistent across risk subgroups.

Figure: DFS by investigator in the intention-to-treat population [1]

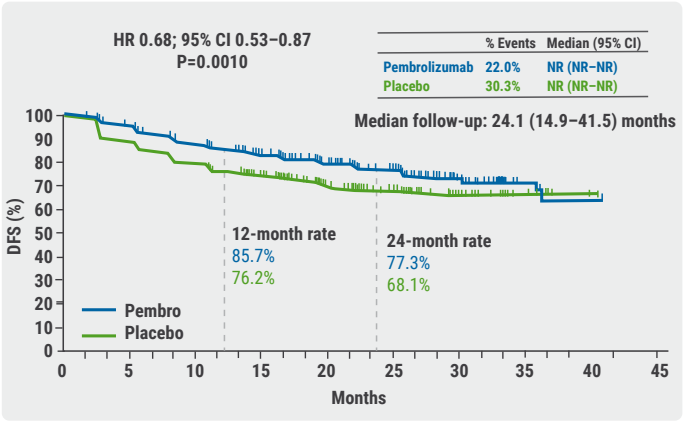


Figure kindly provided by Prof. Powles.

The key secondary endpoint was overall survival (OS). Interim results demonstrated an estimated OS rate at 24 months of 96.6% with pembrolizumab versus 93.5% with placebo. Median OS was not reached for both arms (HR 0.54; 95% CI 0.30–0.96; P=0.0164). Due to a prespecified p-value boundary, these results were not significant.

Safety results were in line with expectations; no new safety signals were observed. Grade 3–5 all-cause adverse events occurred in 32.4% with pembrolizumab and in 17.7% with placebo. No treatment-related deaths occurred with pembrolizumab.

Adjuvant pembrolizumab after nephrectomy demonstrated a statistically significant and clinically meaningful improvement in DFS compared with placebo in patients with intermediate-high, high-risk, or M1 NED ccRCC. The benefit was consistent across subgroups, including the M1 NED population, potentially extending the use of pembrolizumab to these patients. Although the number of participants who had partial nephrectomy was small, DFS benefit was consistent in this population. Additional follow-up is planned for the key secondary endpoint of OS.

1. Powles T. Pembrolizumab (pembro) vs. placebo as post nephrectomy adjuvant therapy for patients (pts) with renal cell carcinoma (RCC): randomized, double-blind, phase 3 KEYNOTE-564 study. Game changing session 4. EAU21 Virtual, 8–12 July 2021.

Worse renal function after radical versus partial nephrectomy

Both radical and partial nephrectomy harbour a non-negligible risk of post-operative chronic kidney disease (CKD) events, even in patients with normal renal function at 5 years post-surgery. However, radical nephrectomy patients tend to compensate the acute loss of renal function derived from the absence of the contralateral kidney with an increase of estimated glomerular filtration rate (eGFR), whereas eGFR in partial nephrectomy patients tends to remain stable over time.

CKD represents a major post-operative long-term complication in renal surgery for renal cell cancer (RCC). This is the case both for radical and partial nephrectomy and despite major advances in surgical techniques. Whether the renal hyperfiltration mechanism after an acute loss of nephron mass could promote a compensatory process over time in oncological patients is still under debate. Therefore, a retrospective study by Prof. Francesco Trevisani (IRCCS Ospedale San Raffaele, Milan, Italy) and colleagues compared the eGFR decay at different time points in patients who underwent radical (n=153) or partial nephrectomy (n=118) [1]. eGFR was evaluated prior to surgery, at hospital dismissal, and at 6, 12, 24, 36, 48, and 60 months of follow-up. Included patients had normal renal function at baseline.

Median basal eGFR was 92.3 mL/min/1.73m^2 for radical nephrectomy and 95.4 mL/min/1.73m^2 for partial nephrectomy (P=0.01). Most patients were men, with a men-women ratio of 3.2 for radical nephrectomy and 1.8 for partial nephrectomy (P=0.04). CKD class differed between radical nephrectomy (class I in 64% and class II in 36%) and partial nephrectomy (class I in 76% and class II in 24%; P=0.03). The results demonstrated that eGFR decreased significantly more in the radical nephrectomy group versus the partial nephrectomy group (P<0.001 for all timepoints), but that the radical nephrectomy patients tend to improve their eGFR over time.

A prospective comparison multicentre study with living kidney donors is ongoing.

1. Trevisani F. Renal functional outcomes at 5 years from radical and partial nephrectomies in normal renal function patients: An untold story of failed hyperfiltrations. P0623, EAU21 Virtual, 8–12 July 2021.

PSMA PET-CT more accurate than standard-of-care imaging in RCC

In the largest series considering the role of prostate-specific membrane antigen (PSMA) PET-CT in renal cancer, PSMA improved diagnostic accuracy compared with standard-of-care (SOC) imaging and can lead to informed treatment modification, as was found in 39% of patients.

Accurate staging of renal tumours with imaging prior to treatment is a challenging aspect of urological practice. Given the novel implications of PSMA in non-prostatic malignancies, Dr Arsalan Tariq (Royal Brisbane and Women's Hospital, Australia) and colleagues sought to further define the role of PSMA-based imaging in renal cancer [1]. They performed a multicentre, retrospective cohort study of all PSMA PET/CT scans for primary or recurrent staging of renal cell carcinoma (RCC) and incidental renal lesions between 2015 and 2020.

Assessed were 118 PSMA PET/CT scans of mostly men (75%) with a median age of 65 years. Histopathology was performed on 55 primary lesions, of which 50 were PSMA avid (90.9%). Clear cell RCC (ccRCC) represented 42 of these primary lesions, of which 94% were PSMA avid.

PSMA PET/CT identified a greater number of nodal or metastatic lesions than SOC imaging for 36% of patients and disproved SOC imaging findings for another 10% of patients. Additionally, in lymph node staging, PSMA had a positive predictive value of 91% compared with 53% for SOC imaging, and a negative predictive value of 76% versus 29% for SOC imaging. Overall, 39% of patients had their treatment modified as a result of PSMA PET-CT imaging.

Dr Tariq argued that these results suggest that PSMA avidity may indicate a malignant primary tumour. Most primary tumours were PSMA avid and PSMA PET-CT led to improved diagnostic accuracy compared with SOC imaging and treatment modification. Further assessment in prospective studies is warranted.

1. Tariq A. Prostate Specific Membrane Antigen (PSMA) PET/CT compared to standard of care imaging in the assessment of renal cancers: A multi-institutional series. P0624, EAU21 Virtual, 8–12 July 2021.