1

SMART GRAFT: Surgeon’s expertise and Machine learning Automated biopsy Reading Towards improving GRaft Assessment For Transplant

European Urology Open Science 2024;567 (Supplement 1): S1

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Introduction & Objectives: Defining reliable criteria for assessment of kidney grafts is an unmet need. Current methods for classifying renal biopsies are cumbersome and highly operator dependent. On the other hand, surgeon's macroscopic assessment of the donor is not standardized, precluding its efficient inclusion in the decision process. We hinted at improving the process of selecting organs for transplant via two contrasting approaches: task 1: developing an automated morphometric process for reading preimplantation biopsies; task 2: constructing a surgical metabolic phenotypic (SMP) score based on the harvesting surgeon's macroscopic assessment.

Materials & Methods: Task 1: all pre-implantation graft biopsies from 1.2020-12.2023 (n=310) were scanned using a whole slide imaging technique. Manual segmentation of the kidney biopsy compartments (vessels, glomeruli, tubules, interstitium) is used to train an automated algorithm to recognize these structures and extract their morphometric features. Its performance is validated against standard human classification. Task 2: all deceased donor surgeries from 1.2023 were prospectively included (n=209 up to 9.2024). A data sheet was created allowing the surgeon to semi-quantitatively categorize the donor's metabolic phenotype (visceral fat, muscle mass, atherosclerosis, and kidney quality – parenchyma aspect, renal artery atherosclerosis, bench graft perfusion). The automated histological evaluation and the SMP score were integrated with the Kidney Donor Profile Index (KDPI) and the standard biopsy score (Remuzzi) and validated through correlation with graft estimated glomerular filtration rate (eGFR).

Results: These are preliminary results. For task 1, we successfully trained an automated algorithm for structural segmentation and morphometric evaluation of biopsies. Preliminary results applied to the vascular compartment (n=133 biopsies) showed good correlation of wall-to-lumen ratio, maximum intimal diameter/vessel diameter and intimal arterial volume fraction- with graft function ($p<0.003$). The variable with the most significant correlation with eGFR was intimal arterial volume fraction ($p=0.0001$). For task 2, we found a significant correlation between SMP score and biopsy score (n=113; $p=0.04$) and the eGFR at 3 (n=149; $p<0.001$) and 12 months (n=49; $p=0.002$). Low visceral fat and atherosclerosis scores were especially predictive of good function in grafts otherwise considered as high risk. Notably, the SMP score showed better correlation with the eGFR during the first year than the Remuzzi score.

Conclusions: Our ongoing study shows promising results regarding a much-needed improvement in the process of graft's selection. This was achieved via two apparently opposing approaches, machine learning and automated digital analysis on one hand, and optimization of the subjective surgeon's assessment of the donor by a novel SMP score on the other.

2

Studies with high-level evidence can unmask false therapeutic myths: Using the example of urolithiasis prophylaxis

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Introduction & Objectives: For over 50 years, thiazides have been the cornerstone of pharmacologic recurrence prevention of kidney stones. However, the NOSTONE trial, the only state-of-the-art trial conducted for pharmacologic recurrence prevention, recently revealed that hydrochlorothiazide is ineffective in preventing kidney stone recurrence. Despite this, nephrologists and urologists continue to grapple with this paradigm shift. Furthermore, thiazides are still being prescribed under the assumption that they improve bone density and promote the spontaneous stone passage (SSP) of kidney stones, although evidence supporting these claims is lacking. Unfortunately, good treatment options remain sparse.

Materials & Methods: A secondary outcome analysis of the randomized, double-blind, 4-arm, placebo controlled NOSTONE Trial was conducted to evaluate the rate of SSP and bone mass density (BMD) in kidney stone patients using CT scans. Additionally, the impact of the SGLT-2 inhibitor empagliflozin on urinary supersaturation profiles was assessed in a randomized, double-blind, placebo-controlled, cross-over study involving non diabetic kidney stone patients with at least one prior kidney stone event and stones composed of either ≥80% calcium or ≥80% uric acid.

Results: After a follow-up period of 2.92 years, a total of 442 stone events were observed in 209 of 383 (55%) patients who had both CT imaging at the beginning and end of the trial. Of these, 217 (49%) were symptomatic SSP, 67 (15%) required surgical removal, and 158 (36%) were asymptomatic SSP. The median size of asymptomatic stones (2.4 mm; IQR, 1.95–3.4) and symptomatic stones (2.15 mm; IQR, 1.68–2.79) that passed spontaneously were not significantly different (P = 0.37). The number of asymptomatic SSP was significantly associated with a higher number of stones detected on CT at randomization (P = 0.001). Mean BMD slightly decreased in all groups; no association was found between placebo and the three different hydrochlorthiazide doses and changes in BMD (p = 0.429). These findings were confirmed in sensitivity analyses for eGFR, body mass index, and in a per-protocol analysis. Our randomized "SWEETSTONE" trial recently concluded. Preliminary data suggest a favorable effect of the SGLT-2 inhibitor on the urinary lithogenic risk profile.

Conclusions: While the rate of SSP for symptomatic ureteral stones is well-documented, it is less clear for kidney stones. The NOSTONE trial showed a high rate of asymptomatic SSP, typically involving smaller stones. Furthermore, thiazides not only fail to reduce stone recurrence in patients with recurrent calcium-containing kidney stones, but they also do not confer any benefit in terms of BMD. Non-state-of-the-art trials have perpetuated the false belief that thiazides are effective in preventing stone recurrence. However, SGLT-2 inhibitors may offer a promising new therapeutic option.

3 Obesity and kidney stones

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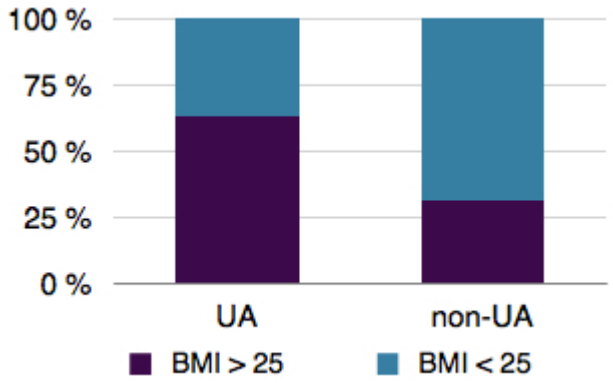
Introduction & Objectives: Obesity doubles the risk of nephrolithiasis. The aim of this study was to explore the association of increasing Body Mass Index (BMI), Metabolic Syndrome and kidney stone disease.

Materials & Methods: Data from a prospective maintained database were retrospectively analysed. In a consecutive cohort of 600 patients with kidney stones, stone analysis (Infrared Spectroscopy) was correlated to BMI, urine pH, presence of diabetes mellitus type 2 (DM2), hypertension, and hypercholesterolaemia. Data was analysed using logistic regression (STATA/IC 18).

Results: Stone analysis revealed the following distribution of kidney stones: 78% Calcium Oxalate; 13% Infection stones; 8% Uric Acid (UA) stones; and 2% other (Cystine, Calcite, Brushite). Female-male ratio was 1/1.7. A BMI>25 was found in 63% of UA stone formers compared to 13% in non-UA stone formers (p<0001) (Figure). Adjusted Odds Ratio (OR) of a UA stone former for having a BMI>25 was 3.7 (p<0.0001). The Odds Ratio of forming UA stones increased by 1.1/unit BMI (p=0.001). Hypercholesterolaemia, DM2 and hypertension were found in 37%, 28%, and 46% of UA stone formers compared to 12%, 4%, and 22%, respectively, in non-UA stone formers. ORs for having hypercholesterolaemia, DM2 and hypertension in UA stone formers were 4.3 (p<0.027); 9.1 (p<0.0001); and 5.3 (p=0.5), respectively. UA-stone formers had significantly lower urinary pH compared to non-UA stone formers (5.3 vs. 5.9 (p=0.0001)).



Conclusions: Data confirmed that increasing BMI is associated to UA-stone formation. The study is the first to demonstrate that OR for UA stone formation progressively increases for every unit increase in BMI. The strong association of UA-stone formation with both a low urinary pH and several components of the Metabolic Syndrome (DM2, abdominal obesity and dyslipidaemia) suggests that the underlying cause is tubular insulin resistance resulting in impaired ammoniagenesis and a low urinary pH that is the main event in uric acid crystallization. UA-stone formation may be considered part of the Metabolic Syndrome, and UA-stone formers should be screened for other components of the Metabolic Syndrome, as appropriate early intervention may prevent serious complications.

4 Percutaneous nephrolithotomy: Impact of intraoperative stone culture

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Introduction & Objectives: Septic complications are the most common clinical problem after endourological stone management. The preoperative evaluation of spot urine does not exclude bacterial colonization of the upper urinary tract and prophylactic antibiotic treatment may be inappropriate for a specific resistance profile. In the case of postoperative sepsis, it would be helpful to have information on such upper tract infections. We have therefore evaluated the clinical benefit of stone culture from intraoperatively removed stone material in a prospective series of percutaneous nephrolithotomy (PCNL).

Materials & Methods: Patients undergoing PCNL were included from October 2023 to May 2024. All patients received perioperative prophylaxis or specific antibiotic treatment if an infection was detected in spot urine. Stone fragments were retrieved for culture. PCNL was performed as previously described (BJU Int 2007). Relevant pre- and postoperative parameters were documented.

Results: A total of 80 patients were evaluated. The mean stone size was 2.8 cm. 26% of the patients had positive urine culture preoperatively, while bacteria were detected in 54% of stone cultures. Bacteria were different in urine and stone cultures in 9%, while in 5.2% only spot urine was positive. The most common germs were E. coli and Proteus mirabilis. No patient had postoperative sepsis; fever occurred in 10% of the patients. In three patients with fever, we could detect bacteria only in stone culture.

Conclusions: Positive stone cultures are common, even in patients with preoperative negative spot urine analysis. Though we did not have septic patients where information on stone cultures had an immediate clinical impact, such a situation may occur. As the stone material for culture is easy to obtain, we recommend implementing stone culture into clinical routine.

5

The impact of haemostatic agent used during robot assisted radical prostatectomy on post-op infection and anastomotic leak

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Introduction & Objectives: Despite the widespread use of Robotic assisted radical prostatectomy (RARP), considerable variation exists in practice with regards to post-operative cystograms prior to trial without catheter (TWOC). Our practice was to undertake a cystogram at 7-14 days post-op and proceed with TWOC if the leak was small or absent. In this study we evaluate the risk factors for anastamotic leak and post-op urinary tract infection (UTI), while assessing the impact of using powdered haemostat Arista AH to rationalise the use of cystograms.

Materials & Methods: The study was carried out in 2 phases, the first a retrospective review of 154 patients undergoing RARP between January-October 2022, where Oxitamp was used for haemostasis. The second phase was prospective, involving 62 patients between November-June 2023, in whom Arista AH was used. Data was collated from a prospectively collected database (REDCap) and electronic patient records. RARP was performed by two surgeons using similar techniques. Analysis was carried out on R-studios, using Fishers Exact Test for categorical variables and unpaired student t-test for continuous variables.

Results: Post-op UTI occurred in 24 (16%) patients in cohort 1 and leaks were associated with 20 (83%). In comparison 7 (11%) patients in cohort 2 suffered from post-op UTI, and only 1 (14%) was associated with leak. There was an overall reduction in leaks on post-op cystograms from 44 (29%) in cohort 1 to only 9 (15%) in cohort 2 (p=0.036). 100% of the leaks in cohort 2 were small, compared to 9 (20%) in cohort 1 (p=0.0002).

Conclusions: A selective approach can be implemented with regards to post-op cystograms. We propose that when using Arista AH cystograms should be carried out in patients in need of bladder neck reconstruction. We will also continue to undertake routine cystograms in those with a history of TURP or in salvage prostatectomy cases.

6

Survival results of PSMA/PET-based salvage radiotherapy for recurrent prostate cancer

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Introduction & Objectives: Aim of our study was to analyze prognostic factors of biochemical recurrence (BCR)-free survival and disease specific survival (DSS) after early salvage whole-pelvic radiation therapy (sRT) in men who had pN1 prostate cancer (PCa) and no distant metastases in PSMA/PET scan.

Materials & Methods: sRT was offered to 212 pN1 patients who had BCR after robot-assisted radical prostatectomy. All patients received intensity-modulated and image-guided sRT to the prostatic fossa/pelvic nodal areas and 3-years of androgen deprivation treatment (ADT). Patients were excluded if distant metastases were detected on PSMA-PET scan. Univariable and multivariable Cox regression analysis were used to evaluate clinical and pathological prognostic factors of DSS and BCR-free survival after sRT.

Results: 5-year DSS and BCR-free survival were 95.8% and 86.9%, respectively. On multivariable analysis, prognostic factors of worse DSS were: ISUP≥4 vs 1-2 (hazard ratio [HR], 0.39, 95% CI, 0.12-0.98, p=0.038), positive margin status (HR, 0.22, 95% CI, 0.057-0.92, p=0.03), pT stage (≥pT3b vs pT2: HR, 0.03, 95% CI, 0.0-22.9, p = 0.028) and number of positive nodes (>2 vs 1-2: HR, 0.63, 95% CI, 0.75-1.07, p = 0.037). The AUC of our model was 0.741. On multivariable Cox analysis, prognostic factor of worse BCR-free survival was only ISUP≥4 vs 1-2 (HR, 0.68, 95% CI, 0.45-0.88, p=0.034).

Conclusions: Long-term DSS and BCR-free survival can be achieved with whole pelvic sRT in selected men with pN1 PCa. A negative PSMA-PET scan can be used as a selection tool for these patients. Adverse pathology at radical prostatectomy specimen is the most important prognostic factor of reduced DSS and BCR-free survival.

7

Can we take a MEASURED (MRI-Enabled Active Surveillance Using Risk adaptEd decisions) approach to active surveillance for prostate cancer?

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Introduction & Objectives: Traditional risk stratification in localised prostate cancer uses PSA, clinical stage and Gleason score to identify those suitable for active surveillance. Follow up in traditional active surveillance uses repeat PSA, DRE and biopsy to re-assess risk over time. We have developed an MRI led AS programme using PSA and multiparametric MRI routinely, with biopsy used where PSA or MRI suggest an increase in risk. We report outcomes of a cohort of 1047 patients, and assess risk of progression to treatment according to baseline characteristics.

Materials & Methods: Patients were included in the analysis if they had a paired MRI and biopsy at the start of active surveillance. We stratified patients according to baseline Gleason score, MRI visibility (Likert ≥4), PSA density and maximum cancer core length. Outcomes were upgrade to Gleason > 4+ 3, active treatment, progression to watchful waiting or death. We also report the biopsy frequency across the cohort.

Results: 1047 men with localised prostate cancer, and a matched MRI and biopsy with follow up imaging were included. 635 (61%) had Gleason 3 + 3 disease, with 412 (39%) having Gleason 3 + 4 disease, and 396 (38%) having MRI visible disease. For the cohort overall, event free survival was 86% at 3 years, 73% at 5 years, and 49% at 10 years. 444/1047 (42%) of the cohort had a further biopsy on AS. Histological upgrade to > Gleason 4 + 3 was rare, and seen in 63/1047 (6%) patients. 1 in 4 of the cohort had treatment at a median of 5 years. Only 29 patients (3%) chose treatment when clinical parameters were stable.

Risk factor	Cox model
	Hazard ratio (confidence interval)
Gleason grade & MRI visibility	
GS 3+3 NV	Ref
GS 3+3 V	2.30(1.65 -3.20)
GS 3+4NV	2.17(1.53 – 3.09)
GS 3+4V	4.04(2.84-5.74)
PSA density	
PSAD (<0.10)	Ref
PSAD (0.10-0.15)	1.35(0.97 -1.89)
PSAD (PSAD >0.15)	1.76(1.27-2.43)
Maximum cancer core length	
MCCL < 4	Ref
MCCL 4-<7	1.61(1.22-2.14)
MCCL 7 -<10	1.97(1.29-3.00)
MCCL > 10	2.73(1.50-4.94)

Gleason score, MRI visibility, maximum cancer core length and PSA density (at baseline) were identified as predictive factors for likelihood of upgrade and progression to active treatment. Those with non-MRI visible Gleason 3 + 3 disease had 3, 5 and 10 year treatment free rates of 96%, 90% and 68%. Those with MRI-visible Gleason 3 + 4 disease had 3, 5 and 10 year treatment free rates of 67%, 46% and 24%. The addition of PSA density and maximum cancer core length added value to risk stratification by Gleason score and MRI visibility alone.

Conclusions:

MRI-led risk adapted surveillance allows those at lowest risk to safely avoid time-based biopsy, whilst detecting higher risk disease as it develops. We recommend considering this approach in men suitable for surveillance.

8 Novel enhancement of multimodality treatment of prostate cancer, combining radiotherapy, vascular-targeted photodynamic therapy, and immunotherapy

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Introduction & Objectives: The prostate cancer (PCa) tumour immune microenvironment (TIME) is characterised by immunosuppression. There is an unmet clinical need to overcome this immunosuppression to generate effective anti-tumour immune responses. We have previously demonstrated that multimodality therapy with sequential delivery of fractionated radiotherapy (FRT) and vascular-targeted photodynamic therapy (VTP) improves PCa tumour control in a pre-clinical model, compared to FRT or VTP monotherapy. Here, we investigated TIME changes induced by combined FRT and VTP, and identify a key mediator of immunosuppression that can be targeted following sequential delivery of FRT and VTP to enhance tumour control effects of multimodality treatment.

Materials & Methods: TRAMP-C1 PCa flank tumour allografts in syngeneic immunocompetent C57BL/6 mice were treated at 100 mm^3 tumour volume with combined sequential FRT (3 x 5 Gy) and VTP, and compared against monotherapy-treated tumours (FRT or VTP alone), and untreated control tumours. 12-days post-treatment, and at 400 mm^3 tumour recurrence endpoint, tumours were harvested for nanoString immune cell gene analysis. This identified Nt5e (CD73) as being significantly upregulated in combined FRT and VTP-treated tumours versus FRT-alone. Further experiments investigated the tumour growth delay effects of combined sequential FRT, VTP and anti-CD73, versus FRT and VTP as control.

Results: At 12-days post-treatment, combined FRT and VTP-treated tumours demonstrated increased expression of mRNA transcripts associated with immune cells within the TIME, including Dendritic Cells and cytotoxic T-Cells. However, at the 400 mm^3 tumour recurrence endpoint, combined FRT and VTP-treated tumours demonstrated decreased expression of mRNA transcripts associated with immune cell function, suggesting the presence of an ‘immune desert phenotype' within the TIME at recurrence following combined FRT and VTP. Differential gene expression analysis at the 400 mm^3 tumour recurrence endpoint identified the immunosuppressor Nt5e (CD73) as being the most significantly differentially expressed gene between combined FRT and VTP-treated tumours and FRT-treated tumours. Administration of anti-CD73 following combined FRT and VTP treatment of flank PCa tumour allografts led to a significant tumour growth delay compared to combined FRT and VTP tumours without immunomodulation.

Conclusions: These results suggest that whilst combined sequential FRT and VTP can enhance tumour control compared against monotherapy, an immunosuppressive ‘tumour immune desert' arises within recurrent tumours, driven in part by CD73. Combining anti-CD73 with FRT and VTP multimodality therapy can significantly enhance the tumour control induced by sequential FRT and VTP. This approach to enhance anti-tumour immune-mediated PCa therapy warrants investigation in first-in-man studies.

9

Office-based MRI fusion cryoablation: Impact on PCa treated natural history

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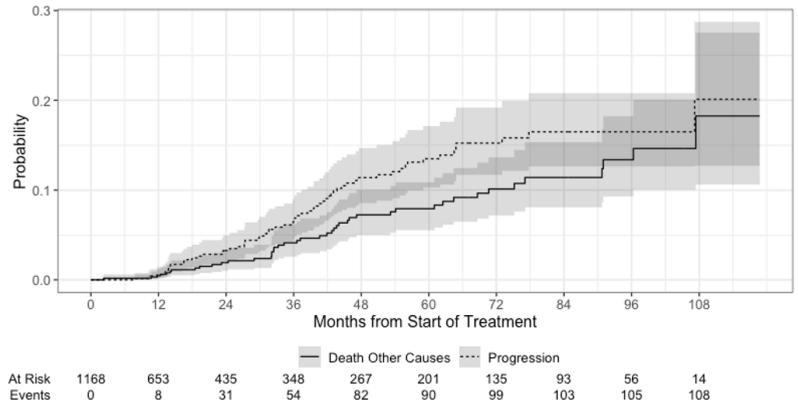
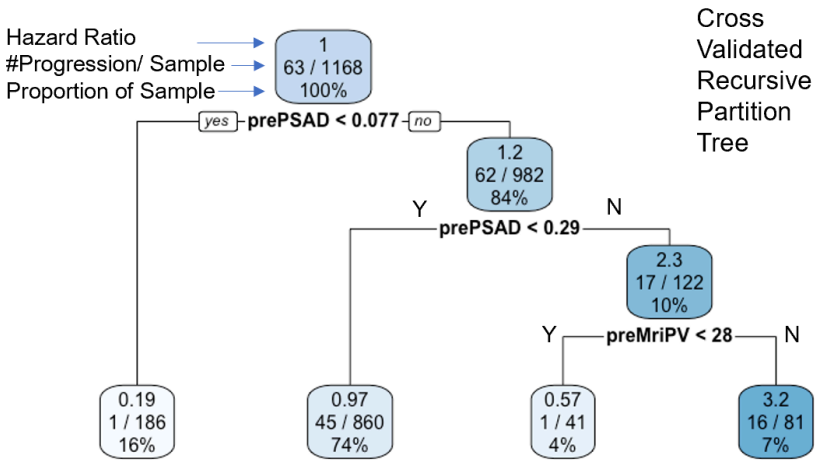
Introduction & Objectives: Randomized trials that compare radical treatments with Active Surveillance (AS) for prostate cancer have demonstrated negligible or minimal survival advantages, underscoring the necessity for alternative, safe, and personalized strategies. MR Fusion Target Cryoablation (MRTFC) offers the potential to reduce instances of overtreatment while enhancing the quality of life by minimizing side effects. The utilization of image fusion techniques, coupled with real-time ablation monitoring, increases accuracy in Ablative therapies (AT). We are pleased to present findings from a study involving men who have undergone MRFC, along with key factors to consider when selecting this treatment option for managing prostate cancer

Materials & Methods: Our Ethical Committee approved the MRFTC protocol, which started 10 years ago and registered as NCT02381990 on Clinicaltrials.gov. The registry focuses on treatment outcomes for PCa lesions using AT. We examined a consecutive cohort of men who received primary MRFC performed in the office using local anesthesia by a Urologist. Our evaluation included assessing Freedom from Progression (FFP) and survival metrics (Overall and Cancer-specific survival). Progression (P), a treated natural history event, was defined as conversion to WGM-surgery, radiation, or complete prostate ablation- hormonal suppression initiation, or metastasis development. We utilized Uni- and multivariate Cox Proportional-Hazards Model and Competing-Risk analysis to identify independent predictive factors. Additionally, a cross-validated recursive partitioning tree identified predictive levels based on relevant preoperative factors against the primary outcome: FFP.

Results: In MRFC, 1,168 completed the procedure, which took a median of 53mins (IQR: 47-60). A figure shows preop characteristics & analyses of P versus death by other causes (DOC); from year 1-9, individuals at risk is shown. The Cross validated RCT showed the prediction of progression based on significant factors: PSAD; MRI prostate volume(preMRIPV). After five years, 87% of individuals were free from progression, and 8% DOC.





Cross Validated Recursive Partition Tree

	Overall (N=1,168)
Age	
Mean (SD)	70.3 (7.57)
Median [IQR]	70.3 [65.7, 75.5]
prePSA	
Mean (SD)	7.62 (5.02)
Median [IQR]	6.20 [4.7, 8.8]
prePSAD	
Mean (SD)	0.18 (0.356)
Median [IQR]	0.135 [0.09, 0.19]
preMriPV	
Mean (SD)	53.5 (27.4)
Median [IQR]	46.1 [35, 63]
preGG	
3+3	497 (42.6%)
3+4	414 (35.4%)
4+3	172 (14.7%)
8-10	85 (7.3%)
prePiRADS	
1-2	60 (5.1%)
3	401 (34.3%)
4	403 (34.5%)
5	304 (26.0%)
preClinStg	
T1c	865 (74.1%)
T2a	141 (12.1%)
T2b	29 (2.5%)
T2c	133 (11.4%)
Events	
Disease Progression	63
Death Other Causes	45

Conclusions: Office-based MRFC is showing a noteworthy impact on the natural progression of prostate cancer. However, it is essential to verify these results by conducting a comprehensive assessment of randomized controlled trials.

10

External validation of a digital pathology-based multimodal artificial intelligence prostate biopsy biomarker in a prospective, real-world prostate cancer cohort treated with radical prostatectomy

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Introduction & Objectives: A multimodal artificial intelligence (MMAI) biomarker (ArteraAI Prostate Test) was developed using clinical trial data from North American men with localized prostate cancer (PCa) treated with definitive radiation with or without androgen deprivation therapy, using digital pathology images and key clinical information to generate prognostic scores. This study is an external validation of the MMAI biomarker on a prospective real-world dataset of European men who underwent radical prostatectomy (RP) for localized PCa at a tertiary referral center in Sweden.

Materials & Methods: The MMAI algorithm used digitized images from diagnostic H&E prostate biopsies at Skåne University Hospital, Malmö, age, PSA values, and tumor stage. The association between the MMAI model, continuously (per standard deviation increase) and categorically (based on pre-established cutoffs), and endpoints of interest were performed with Fine-Gray and cumulative incidence analyses for biochemical recurrence and logistic regression for adverse pathology (AP) at RP. Deaths without events were treated as competing risks for BCR. Men eligible for upstaging were considered evaluable for AP at RP.

Results: Of 749 men referred for biopsy between 2004-2010, 235 underwent RP, 230 had available clinical data for this study, and 154 had available digital pathology slides of the initial prostate biopsy. The validation cohort consisted of 143 patients who had sufficient tumor and complete clinical data to generate MMAI scores. Median follow-up for censored patients was 8.8 years. At diagnosis, median PSA was 7.5 ng/mL, median age was 64 years, 29% had grade group ≥3, 8% had cT3, and 88 men were evaluable for AP at RP. MMAI was significantly associated with BC[MS1] [AB2] [AB3] [MT4] R (subdistribution HR 2.45 [95% CI 1.77-3.38], p<0.001) and AP at RP (OR 4.85 [95% CI 2.54-10.78], p<0.001). Estimated 5-yr BCR rates for MMAI Intermediate-High vs Low were 25% (95% CI 15%-35%) vs 4% (95% CI 0%-8%), respectively.

Conclusions: We found the prostate biopsy MMAI biomarker, previously shown to be prognostic for distant metastasis and prostate cancer-specific mortality in men getting definitive radiation, to be prognostic for post-RP endpoints: BCR and AP. This biomarker validation study using a prospectively collected independent cohort further supports the use of MMAI biomarkers in men with prostate cancer outside North America and those treated with RP.

11

Does the percentage of Gleason 4 in targeted prostate biopsies predict the percentage of Gleason 4 at final pathology in prostatectomy specimen? Implications for active surveillance

European Urology Open Science 2024;567 (Supplement 1): S12

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Introduction & Objectives: Active surveillance has become standard of care of low risk prostate cancer. Its indication is more and more extended to the intermediate risk group with low volume Gleason 4 disease. Current EAU guidelines recommend active surveillance in patients with < 10% Gleason 4. This cut-off is based on radical prostatectomy data that suggest that prognosis of patients with <10% Gleason 4 is similar to patients with Gleason 3 only. There is little data available exploring the correlation between the percentage of Gleason 4 on biopsy specimen vs. whole mount sections after radical prostatectomy. The aim of the study was to do such correlation.

Materials & Methods: We retrospectively analyzed patients that underwent MRI targeted and systematic prostate biopsy for the diagnosis of prostate cancer followed by radical prostatectomy. In all patients, detailed information about the percentage of Gleason 4 was available for all individual biopsy cores (targeted and systematic) as well as radical prostatectomy specimens analyzed by whole mount sections. The percentage of Gleason 4 was cross-tabulated between targeted biopsies and whole mount pathology. Moreover, logistic regression analysis was used to predict clinically relevant underestimation of the percentage of Gleason 4 in targeted biopsies relative to whole mount sections. The cut-off for relevant underestimation was set at +10%.

Results: A total of 190 patients underwent biopsy and radical prostatectomy. Median age was 67 years, median PSA was 7.5ng/ml, clinical stage was T1c in 60%, median prostate volume was 48cc and median size of the MRI index lesion was 13mm. In patients with up to 5%, 5-10%, 11-20% and 21-30% of Gleason 4 on targeted biopsies, 91%, 50%, 14% and 28%, respectively, had clinically relevant underestimation of the percentage of Gleason 4. In the logistic regression multivariable model, percentage Gleason 4 on targeted as well as systematic biopsies were the only significant independent predictors of clinically relevant underestimation of the percentage of Gleason 4 (OR 1.03 (1.01-1.06), p= 0.004; OR 1.01(1.00-1.03), p=0.02, respectively).

Conclusions: The percentage of Gleason 4 on targeted biopsy, especially in the low percentage ranges (<10%) is poorly correlated with the percentage of Gleason 4 on whole mount pathology. The recommended 10% cut-off needs to be used with caution and alternative variables need to be taken into consideration to increase the use of active surveillance in intermediate risk patients.

12

Predicting pathological tumor volume in prostate cancer lesions using micro-ultrasound and MRI

European Urology Open Science 2024;567 (Supplement 1): S13

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Introduction & Objectives: Micro-ultrasound (microUS) is a novel imaging modality relying on high frequency at 29MHz which allows a three-time better resolution compared to conventional transrectal ultrasound. The high sensitivity to detect significant prostate cancer (PCa) in the peripheral area might be instrumental to enhance our ability to personalize surgery. In this study, we aimed to measure the ability of microUS to predict pathological tumour volume of significant PCa lesions against final pathology.

Materials & Methods: Single centre analysis of consecutive patients undergoing robot-assisted radical prostatectomy between August 2018 and October 2020. We selected patients with available pre-biopsy prostate MRI as well as microUS performed at our institute. Significant PCa lesions in the peripheral area were retrospectively annotated along with their volume on PIRADS 2.1 maps by the local expert radiologist, urologist and pathologist interpreting MRI, microUS and final pathology, respectively. The radiologist and the urologist were blinded to clinical and pathological data. Cognitive registration between the index modalities and final pathology was performed; disagreement was resolved by consensus. Clinically significant PCa was defined by the presence of Grade Group (GG) >/= 2 and/ or a volume >/= 0.5ml at final pathology. Linear regression was performed to assess the relationship between pathologic tumor volume with MRI and microUS volume.

Results: 65 men with a median age of 64 years (IQR 60-69) and a PSA of 8,5 ng/ml (6.3-13.5). 104 significant lesions were identified by final pathology; 42 were excluded as were in the transition area, leaving 62 for the analysis. GG 1, 2, 3, 4 and 5 was present in 16%, 49%, 26%, 1% and 8% lesions, respectively. 82% and 74% were visible on MRI and microUS, respectively. The median tumor volume on final pathology was 1.2 ml (0.2-3.9). Table 1 displays the relationship between microUS, MRI sequences and pathological tumor volume. The amount of underestimation tended to increase with larger tumor volume with the smallest deviation for microUS. Limitations include the retrospective nature, the reviewer bias and the registration error.

Variable	R^2	R^2corrected for grade group	Coefficient (95%-CI)	Coefficient corrected for grade group (95%-CI)	p-value
MicroUS	0.94	0.94	1.34 (1.25-1.43)	1.28 (1.18-1.39)	< 0.001
MRI T2WI	0.81	0.82	2 (1.81-2.19)	1.89 (1.69-2.09)	< 0.001
MRI ADC	0.68	0.7	1.98 (1.71-2.24)	1.83 (1.55-2.11)	< 0.001
MRI DWI	0.67	0.7	2.25 (1.93-2.56)	2.06 (1.74-2.39)	< 0.001

Conclusions: MicroUS seems to better predict pathological volume of clinically significant lesions. Combining microUS with MRI might be particularly important in focal therapy, where zonal stratification and treatment planning are key.

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Oncological and functional outcomes of robot-assisted radical prostatectomy in low-risk prostate cancer patients eligible for active surveillance

European Urology Open Science 2024;567 (Supplement 1): S14

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Introduction & Objectives: Many low-risk prostate cancer (PCa) patients which are considered eligible for active surveillance (AS) decline this strategy and immediately proceed to surgery. The aim of our study was to evaluate the outcomes of robot-assisted radical prostatectomy (RARP) in this patients' category.

Materials & Methods: Prospectively collected database of patients operated by RARP from 2012 to 2018 was reviewed, and low-risk PCa cases were selected with RARP performed within 6 months from diagnosis. We have assessed post-op pathology reports and biochemical recurrence (BCR) rate, as well as urinary continence (number of pads per day) and erectile function (EF) outcomes using Sexual Health Inventory for Men (SHIM).

Results: Out of 2114 RARPs performed, 549 (26%) patients were D'Amico low risk and 384 (18.1%) had prostate biopsy within 6 months (with median time to surgery 4.4 months). 249/384 (64.8%) men had pathological upgrading with 69.9% upgrade from ISUP 1 to ISUP 2 and 30.1% from ISUP 1 to ISUP 3 and 4. The maximal diameter of tumor <1 cc has been identified in 9.1% of men and 83% of patients had bilobar disease. On MVA age >70 years and clinical stage T2a predicted upgrading. 345/384 (89.8%) patients had available data for BCR, urinary continence and EF for 3 years with median follow-up of 40.2 months. Extracapsular extension was detected in 16.9% and positive surgical margins in 19% of cases. 57 (14.8%) men had BCR - with 89.5% of them having pathological upgrading. No pads use was achieved in 88%, 89.8% and 90.1% of patients at 1, 2 and 3 years respectively. 70% of men had SHIM>21 before surgery and underwent RARP with bilateral nerve-sparing: in this subgroup after 1, 2 and 3 years proportion of men with SHIM>21 was 51.7%, 54.2% and 53.2% respectively (with the use of PDE5 inhibitors allowed). There was no significant difference in functional outcomes between patients with versus without upgrade in final pathology.

Conclusions: RARP provided excellent functional outcomes of treatment in low-risk PCa patients, who declined active surveillance. At the same time, at retrospective analysis considerable rate of adverse pathology (including the maximal diameter of tumor) and BCR was noted, which highlights the need to re-assess treatment strategy selection protocols in low-risk disease.

14

PSA based intermediate endpoints to compare cancer specific survival difference between radiotherapy and radical prostatectomy for the treatment of localized prostate cancer

European Urology Open Science 2024;567 (Supplement 1): S15

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Introduction & Objectives: There is no validated PSA-based endpoint to compare oncological outcomes after radical prostatectomy (RP) and radiation therapy (RT). We aimed to define a novel PSA-based intermediate endpoint that leads to similar prostate cancer-specific mortality (PCSM) for primary treatment comparison.

Materials & Methods: This population-based study included all men with cT1-3, cN0M0 prostate cancer (PCa) in Stockholm who underwent RP or RT with PSA follow-up from 2003 to 2021. Competing risk regression, accounting for non-PCa mortality, was used to compare the cumulative incidence of PCSM in patients meeting different PSA-based endpoints after RP and RT. Endpoints were predefined by systematically increasing PSA cut-offs and PSA doubling times (PSA-DT) at recurrence. The analysis was adjusted for age at diagnosis, Charlson, PSA, ISUP Gleason at biopsy, cT stage, and treatment year, and was repeated to identify endpoint combinations that resulted in similar PCSM for RT and RP (subdistribution hazard ratio [SHR] of RT vs RP close to 1).

after RT (PSA ≥ nadir + 2) was 3.35 (95% CI 2.67, 4.23) compared to RP patients with a rising PSA≥0.2. Similar results were found when comparing PSA nadir + 2 with patients reaching higher PSA cut-offs after RP (≥ 0.5 and ≥ 1 ng/ml). Further comparisons were therefore performed by lowering the PSA cut-offs for the RT endpoint (nadir + 1-0.5 ng/ml).
The endpoint definition leading to similar survival rates was PSA nadir + 0.5 ng/ml after RT and PSA ≥ 0.5 ng/ml with PSA DT < 9 months after RP (SHR RT vs RP 1.00, 95% CI 0.78, 1.29). The adjusted cumulative incidence of the endpoint was higher after RT (Figure 1).

Conclusions: We performed a systematic analysis of PSA-based early endpoints following primary treatment for PCa and found that patients who underwent RT and reached a PSA ≥ nadir + 0.5 ng/ml had similar survival rates to patients with PSA ≥ 0.5 ng/ml and PSA DT < 9 months after RP. Our results highlight that current BCR definitions are suboptimal and present novel early endpoints for primary treatment comparison.

15

Proteome signatures in urinary extracellular vesicles enable prostate cancer detection

European Urology Open Science 2024;567 (Supplement 1): S17

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Introduction & Objectives: Prostate cancer (PCa) diagnosis faces limitations, including invasiveness, inaccuracy and limited resources highlighting the need for non-invasive diagnostic methods. Due to the distal location of the prostate to the urinary bladder, PCa protein markers can be detected in urine. Urine contains extracellular vesicles (uEVs), which are secreted by various cell types, including PCa cells. However, little is known about how to use urine for biomarker detection, for example stability. In the current study we aimed to investigate the longitudinal stability of the uEV proteome, and the presence of protein signatures that can be used for the detection of significant PCa.

Materials & Methods: uEVs were isolated using the Microvesicle Enrichment Kit. Proteins were measured using in-depth LC-MS/MS-based proteomics profiling. Urine was collected from healthy donors for up to 6 months. Prostate cancer profiles were studied in a multicenter cohort of uEVs from 222 individual patients. We generated 4 datasets using 2 different Mass spectrometry based proteomics acquisition methods, first data dependent acquisition (DDA) (n=43/D43, n=94/D94) and secondly data independent acquisition (DIA) (n=85/D85, and longitudinal collected samples) and identified 2025, 2693, and 3891 proteins (30% data presence). (Single sample) gene-set-enrichment analysis was performed using the Genepattern tool. An EV-score was calculated based on the top 100 EV proteins from Vesiclepedia and were correlated to the identified proteins in the dataset.

Results: Prostate-specific proteins (e.g. KLK3, FOLH1) and EV-associated proteins (e.g. CD9, CD63) correlated to the EV-score, confirming the presence of EVs and prostate-proteins within the isolated uEVs. Longitudinal collected samples showed that the uEV proteome is highly stable in time, though there was variation in uEV proteins between the different donors. The uEV proteome is stable over a prolonged time-period, underscoring its potential for reliable non-invasive diagnostic/prognostic biomarkers. To further investigate the biomarker potential, we selected significantly up and downregulated proteins from the 3 datasets (D43, D94, D85). Gene set enrichment analysis shows a highly similar function of deregulated proteins in all 3 datasets, with proteins involved in immunity, metabolism and cell adhesion. In uEVs of PCa patients, 15 proteins were significantly upregulated, and 17 significantly downregulated, in 2 or 3 datasets. Many of these proteins are involved in the same protein-complex-function. Gene-Set-Enrichment-Analysis showed enrichment of immune-related processes, and decreased cell cycle pathways/signaling. These pathways were also deregulated in the uEV dataset of Khoo et al (2024).

Conclusions: In conclusion, uEVs have a stable proteome over a prolonged time, and are a potential source for the detection of significant PCa.

16

Can we "smell" something important?

European Urology Open Science 2024;567 (Supplement 1): S18

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Introduction & Objectives: Urinary volatile organic compounds (VOCs) are small molecule products of metabolism found in all bodily fluids. They are proving to be promising biomarkers for a range of diseases, including prostate cancer. Understanding the variables that influence expression of VOCs in urine is important in metabolomic studies for biomarker discovery. Assessing how storage time, osmolality, and acidity affect expression is important to ensure appropriate profiles are available within the limit of detection of laboratory equipment and can be reliably measured.

Materials & Methods: Patients with suspicion of prostate cancer were recruited from biopsy clinic and urine samples collected immediately prior to the procedure. Urine osmolality was measured using a point of care refractometer. Samples were frozen to -20oC immediately and underwent one freeze-thaw cycle to generate two 1ml aliquots in 10ml vials which were re-frozen until analysis. Prior to analysis, 200µl of 2.5M H2SO4 or NaOH were added as changing the acidity level alters which VOCs are released from the urine. Samples were analysed using SPME-GC-MS (solid phase microextraction gas chromatography-mass spectrometry). A subset of samples were analyzed using a prototype gas chromatography-sensor system which can detect smaller VOC abundances.

Results: 949 men have been recruited although only 416 patients were included in this preliminary analysis. Median number of VOCs detected in acidified urine was 47 (IQR 40-54) and 32 (IQR 24-39), respectively. We identified 189 compounds in the whole cohort. On chi squared analysis of the acidified samples, 18 compounds had significantly higher prevalence in patients with PC. In the alkalinized samples, 4 VOCs were prevalent in the samples from PC patients and 2 VOCs appear to be at lower concentration. Storage time does not appear to alter VOC expression. Median urine osmolality was 420mOsmol/l (IQR 410-790 mOsmol/l) A positive correlation was observed between urine osmolality and the number of VOCs detected in both acidified and alkalinised urine. VOC count increased in a linear fashion up to 600mOsmol/l before plateauing.

Conclusions: This study demonstrates the reproducibility of urinary VOC analysis. It has allowed the development of a platform to assess the use of a urinary VOC analysis in the detection of clinically significant prostate cancer and might permit correlation with clinically meaningful prostate cancer outcomes although data is limited at this moment.

17

The risk of venous thromboembolism after cystectomy and prostatectomy with or without a pelvic lymph-node dissection

European Urology Open Science 2024;567 (Supplement 1): S19

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Introduction & Objectives: While pelvic lymph-node dissections are associated with increased risks of side effects such as lymphocele and lymphedema, the oncological benefit of adding a lymph-node dissection to a prostatectomy or cystectomy remains controversial. In this study, we have used a large historical population-based database in Sweden to investigate the 90-day risk of deep venous thrombosis and pulmonary embolism after prostatectomy and cystectomy with special focus on the risks associated with adding a lymph-node dissection to the procedure.

Materials & Methods: Using nationwide healthcare databases, we identified all 11 850 patients who underwent prostatectomy for prostate cancer or cystectomy for bladder cancer in Sweden from 1997 through 2016, and followed them up for the occurrence of a fatal or non-fatal pulmonary embolism or deep venous thrombosis 90 days from the date of index hospital admission. We calculated propensity-score adjusted ORs and 95% Cis for the association between lymph-node dissection and each of the outcomes using logistic regression.

Results: The overall 90-day cumulative incidence of PE was 1,24% and 1,65% for DVT among patients operated with lymph-node dissection, and 0,56% and 0,64%, respectively, for those without lymph-node dissection. The 90-day adjusted ORs for PE and DVT in bladder cancer were both 0,99 (95% CIs; 0,67 – 1,47 for PE and 0,68 – 1,43 for DVT). The absolute risks for DVT or PE were also similar after cystectomy with and without a pelvic lymph-node dissection.
In prostate cancer, adding a lymph-node dissection was associated with a significantly increased risk of PE (OR, 2.29; 95% CI, 1.68 to 3.11) and DVT (OR, 2.95; 95% CI, 2.25 to 3.88). While the absolute risk for PE and DVT was higher after open surgery, the relative risk associated

with adding a lymph-node dissection to the procedure was higher in laparoscopic surgery.

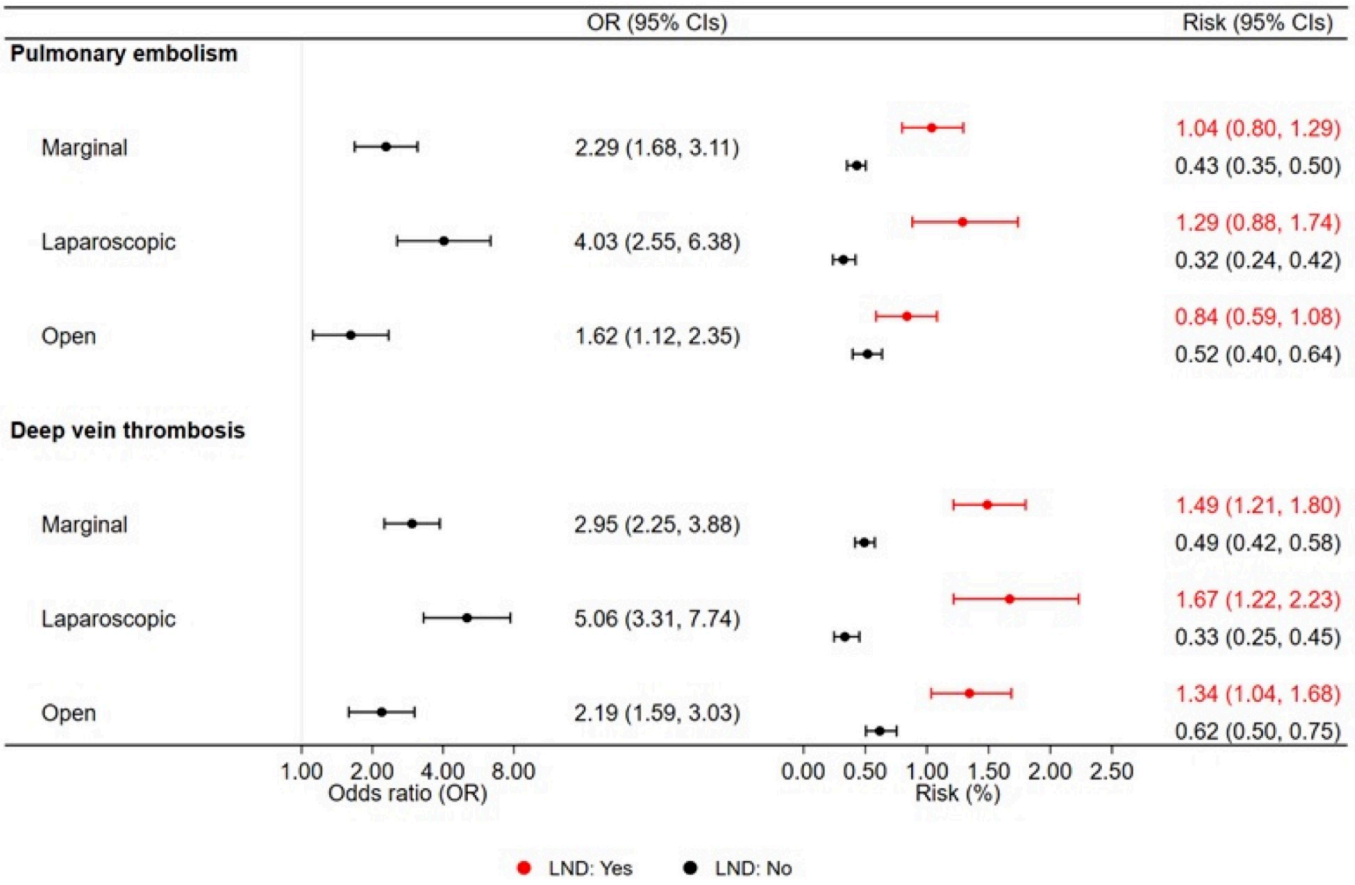

Figure 1. Forest plot for absolute risks and odds ratios for PE and DVT in patients with prostate cancer with or without lymph-node dissection.

Conclusions: We found that adding a lymph-node dissection to increases the risk of both PE and DVT. Adding a lymph-node dissection to a laparoscopic prostatectomy was associated with a fourfold increase of risk of VTE. On the other hand, there was no increased 90-day risk associated with an added lymph-node dissection during cystectomy.

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The role of PSMA expression in predicting aggressive disease phenotypes in patients with prostate cancer

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Introduction & Objectives: Prostate-specific membrane antigen (PSMA) has been proposed as a biomarker for prostate cancer (PCa) aggressive phenotypes. Despite advances in imaging and biomarker technology, existing models for predicting disease outcomes, such as progression in active surveillance (AS), extracapsular extension (ECE), seminal vesicle invasion (SVI), and lymph node involvement (LNI), are characterized by suboptimal accuracy. This study investigates the role of PSMA expression, measured by immunohistochemistry (IHC) and PSMA-PET SUVmax, in predicting these adverse disease outcomes in different settings, aiming to enhance the clinical decision-making process for PCa management.

Materials & Methods: This analysis incorporated data from two patient cohorts: 1) 71 PCa patients under AS from 2019 to 2022, of whom 25 underwent PSMA-IHC quantification via H-score and 47 underwent PSMA-PET SUVmax measurement, 2) 550 patients staged with 68Ga-PSMA-PET/CT who underwent radical prostatectomy (RP) with or without pelvic lymph node dissection (PLND) at 7 referral centers. Disease progression in AS was defined as ISUP grade group upgrading at confirmatory biopsy or the need for radical treatment during follow-up. ECE, SVI, and LNI were assessed based on histopathological data post-RP. Kaplan-Meier survival analyses and multivariate models were used to assess PSMA biomarkers' (namely, H-score and SUVmax) predictive value for AS progression, ECE, SVI, and LNI.

Results: When considering the AS cohort (n=71), the progression-free survival rate was 53% after a median follow-up of 30 months. Patients with an H-score ≥130 were significantly more likely to discontinue AS ($p<0.01$). Higher PSMA SUVmax values (≥10) were associated with an increased risk of ISUP grade upgrading at confirmatory biopsy (OR 5.25, $p=0.04$).When considering patients undergoing RP (n= 550), the median SUVmax was 11 (IQR: 7-19). A total of 315 (57%), 83 (15%) and 58 (11%) had ECE, SVI and LNI. PSMA-PET SUVmax was associated with ECE (OR 1.09, $p<0.01$), SVI (OR: 1.11, $p < 0.01$) and LNI (OR 1.01, $p = 0.05$). Incorporating SUVmax into predictive models improved their accuracy, increasing the ROC-derived area under the curve (AUC) for ECE, SVI and LNI from 63 to 68%, 71 to 77% and 71 to 73% with improved calibration and decision-curve analyses (DCA).

Conclusions: PSMA expression, measured through IHC on biopsy specimens and PSMA-PET SUVmax, is a valuable biomarker for predicting aggressive disease features across multiple scenarios in PCa management. Elevated PSMA levels are associated with a higher risk of AS discontinuation, ECE, SVI, and LNI. These findings suggest that incorporating PSMA-based biomarkers into existing predictive models significantly enhances the ability to identify patients at high risk for adverse outcomes, improving clinical decision-making and individualized patient care.

19 Optimizing oncologic outcomes in high-grade non-muscle invasive bladder cancer: The impact of a surgeon-led treatment pathway

European Urology Open Science 2024;567 (Supplement 1): S22

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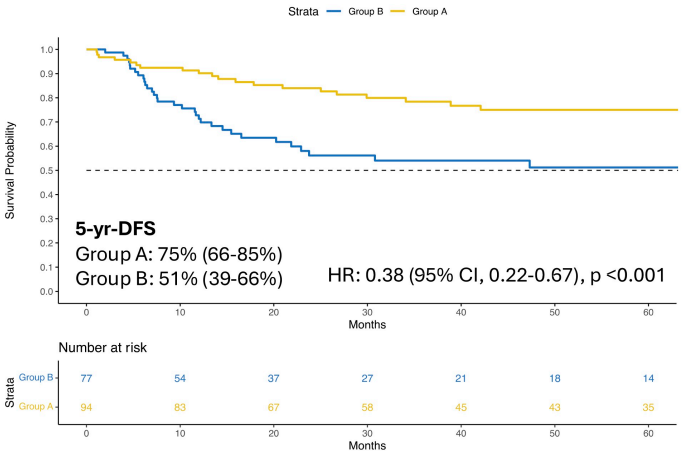
Introduction & Objectives: The management of high-grade non-muscle invasive bladder cancer (HG-NMIBC) is complex, requiring accurate transurethral resection of bladder tumors (TURBT), intravesical therapy, and diligent follow-up. We hypothesized that centralizing patient care from the first diagnosis, performed by an experienced surgeon, could improve oncological outcomes.

Materials & Methods: We conducted a retrospective analysis of 175 consecutive HG-NMIBC patients who underwent TURBT performed by a highly experienced surgeon at a tertiary center (2012-2023). All patients received Bacillus Calmette-Guérin (BCG) therapy. Group A included patients treated solely by the experienced surgeon from diagnosis, while Group B consisted of patients initially treated elsewhere before undergoing TURBT at our center. Propensity score-based overlap weighting was used to balance the groups. Kaplan-Meier curves were used to estimate disease-free survival (DFS), progression-free survival (PFS), and cancer-specific survival (CSS). Univariable Cox regression models were used for comparisons.

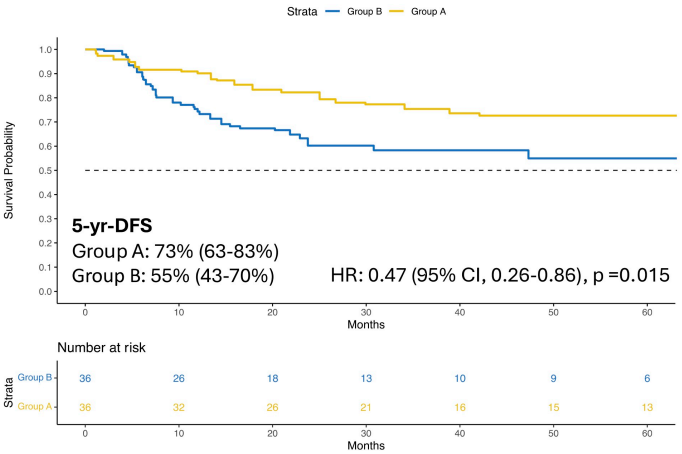
Results: Group A included 94 patients, while 81 in Group B. Median age was 71 years. T1HG disease was present in 126(72%) patients and equally distributed (p=0.7). Early epirubicin instillation (EI) was given to 52% in Group A vs. 37% in Group B (p=0.045). Median tumor size was 3.00 cm in Group A vs. 1.50 cm in Group B (p<0.001), with multifocal disease in 33% vs. 62%, respectively (p<0.001). The T0 rate at second-look TURBT was 59% in Group A vs. 36% in Group B, with HG disease in 31% vs. 52%, respectively (all p<0.01). The 5-year DFS was 75% in Group A vs. 51% in Group B (HR:0.38, p<0.001). Group A had superior PFS (HR:0.31, p=0.01) and CSS (HR:0.23, p<0.001). After weighting (Figure 1), DFS (HR:0.47, p=0.015), PFS (HR:0.36, p=0.032), and CSS (HR:0.20, p<0.001) remained significant. Results were consistent when restricting the analyses to patients with only one prior TURBT. Outcomes between those who received EI and those who did not were similar (p>0.05).

Conclusions: HG-NMIBC patients treated exclusively at a tertiary referral center by an experienced surgeon achieved superior short- and long-term oncological outcomes compared to those initially treated elsewhere. Surgeon experience from first diagnosis, adherence to intravesical therapy, and follow-up protocols are crucial for improving oncological outcomes in HG-NMIBC patients.

DFS (progression and recurrence) – before weighting



DFS (progression and recurrence) – after weighting



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Ablation of recurrent bladder tumors by cold plasma - First in human study

European Urology Open Science 2024;567 (Supplement 1): S23

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Introduction & Objectives: Bladder cancer (BC) is one of the most common cancers in humans. Therapy options for low-burden recurrent LG tumors include surveillance, office fulguration, and TURBT. Office-based fulguration is an attractive option concerning its minimal invasiveness, quality of life, and economic aspects. The specific fulguration preference method and protocol are not determined as office procedures. One of the promising new technologies is a non-thermal cold plasma that can serve as an alternative to TURBT, office thermal fulguration, and laser ablation.

Materials & Methods: This is a prospective, multicenter, open-label, non-randomized, first-in-human (FIH) study held between March 2022 and May 2024. The study population included patients who were confirmed to have LG low-to-intermediate risk NMIBC and were scheduled for a TURBT. Tumor and tissue responses were assessed by follow-up cystoscopies held three weeks thereafter and then 3, 6, 9 and 12 months after the procedure. The single-use procedure kit is designed for endoscopic NTAPTM treatment. It features a flexible NTAP™ probe (Fig 2) and a pressure transducer that monitors the working pressure. The flexible NTAP™ probe was inserted into the bladder through a rigid cystoscope that requires the use of general anesthesia.

Results: 39 patients diagnosed with recurrent bladder NMIBC have been screened for the study, in two medical centers. Of the patients screened, 30 were enrolled in the study, eight were screen failures, and one withdrew consent before the procedure date. The study population included 25 (83%) males, and the average age was 67 years. Altogether, 67 tumors were treated in 36 NTAPTM procedures. Sixteen adverse events (AEs) in 11 patients were reported throughout the study, of which none were related to the study device. The NTAPTM treatment was found to be tolerable and safe. The post-procedure length of stay was shorter compared to the standard TURBT procedure. Most patients were discharged on the same day. Twenty-four of the 30 patients showed a complete response in the first check cystoscopy held three weeks post-procedure. In total, 67 tumors were treated by NTAPTM. 56 tumors were completely ablated, which corresponds to 83.6% success rate of the NTAPTM treatment. When asked to choose between NTAPTM treatment or TURBT for a repeat procedure, all patients chose NTAPTM.

Conclusions: Endoscopic NTAPTM treatment for recurrent low-intermediate NMIBC is safe and effective and can potentially serve as a local office therapy alternative to TURBT for low-burden recurrent tumors.

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FBXW7 loss-of-function is associated with worse overall survival and leads to the accumulation of MYC in muscle-invasive bladder cancer

European Urology Open Science 2024;567 (Supplement 1): S24

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Introduction & Objectives: Loss-of-function mutations in FBXW7 occur in up to 10% of muscle invasive bladder cancer (MIBC). Although FBXW7 is known to play a critical role in the proteasome degradation of oncogenic proteins including NOTCH, mTOR, and MYC, suggesting that loss of its function could be oncogenic, its significance in MIBC has not been studied. Here, we investigate the oncogenic role of altered FBXW7 function and explore strategies for targeting FBXW7-deficient tumours.

Materials & Methods: The MSK-IMPACT and TCGA (2017) MIBC cohorts were analyzed for FBXW7 genomic alterations and mRNA expression levels in relation to clinical outcomes. FBXW7 was knocked out (KO) in basal (UM-UC3) and luminal (RT112) MIBC cell lines. Two hotspot-mutations in FBXW7 (R479G and R505G) were introduced to assess their functional impact. Phenotypic assays, downstream pathway analysis, and pharmacologic inhibition of the FBXW7-MYC axis were carried out on these cell lines, as well as in an in vivo orthotopic MIBC model.

Results: In patients, low expression or genomic alteration of FBXW7 was associated with increased MYC signalling and shorter survival. In cell lines, FBXW7 KO resulted in elevated expression of MYC and cell cycle genes (CCNE1, CCND1, CDK2, CDK4 and CDK6). Re-transfection of a wild-type FBXW7-coding plasmid in these KO cell lines normalized the expression of MYC and cell cycle genes. FBXW7-KO cells transfected with R479G and R505G mutants retained the KO-induced phenotype and downstream signaling. We confirmed that FBXW7-deficient (mutated and KO) cell lines displayed enhanced sensitivity to MYC inhibition (MYCi) using two different compounds (VPC70619, and KSI-3712). Furthermore, we demonstrated the increased efficacy of KSI-3712 in an orthotopic mouse MIBC model harboring the R479G and R505G mutants compared to the wild-type FBXW7-rescued control.

Conclusions: Our findings suggest that FBXW7 functions as a tumor suppressor through its regulation of MYC signalling in MIBC. Tumours with FBXW7 mutations have high MYC activity, which can be effectively abrogated pharmacologically, both in vitro and in vivo. This suggests that MYCi may represent a promising treatment strategy for select FBXW7-alterated tumors.

22

EORTC GUCG 2418 STARBURST: Strategies for treatment adaptation following re-evaluation of the bladder after using primary neoadjuvant systemic therapies: An EORTC platform trial

European Urology Open Science 2024;567 (Supplement 1): S25

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Introduction & Objectives: The standard treatment for patient with muscle-invasive bladder cancer (MIBC) consists of neoadjuvant systemic therapy (NAT) followed by radical cystectomy (RC) or trimodal therapy (TMT). Currently, patients are not routinely reassessed after NAT and proceed directly to local treatment, leading to a missed opportunity for patients with complete or near complete response to benefit from bladder sparing strategies. On the other hand, for the non-responders, it is a missed opportunity to early systemic escalation. The platform will involve multiple steps. First, Starburst-1 (SB-1) is a single arm phase II trial that aims to create an effective multimodal signature that can predict effectively pathological complete response to NAT. Once the signature is validated, we will develop Starburst-2 (SB-2) as a platform in which we will test different risk-adapted strategies based on the response post NAT. This includes new combination of neo-adjuvant therapy, but also de-escalation therapies and escalation therapies according to patients' response to NAT.

Materials & Methods: In SB-1, we will enroll in a phase II, single arm, prospective cohort, patients with newly diagnosed MIBC (pT2-T4a N0-1 M0). All patients will be treated with standard of care (SOC) NAT followed by RC. All patients will be assessed before NAT by a cystoscopy, TURBT, urine cytology, bladder multiparametric MRI (mpMRI) using the NacVi-RADS score, blood and urine liquid biopsy. After completing the NAT, each patient will undergo a cystoscopy (+/- biopsy), SOC clinical and radiological workup (TAP CT +/- PET-FDG), a mpMRI and blood/urine collection. The primary endpoint of SB-1 is to prospectively evaluate the accuracy of the NacVI-RADS score to predict the pathological complete response defined as the absence of muscle invasive disease (ypT≥2 vs ypT0/a/1). Kappa score agreement between the MRI staging and RC pathological staging will also be addressed. Secondary endpoints include the assessment of new biomarkers including blood circulating tumor DNA (ctDNA) and urine tumor DNA (utDNA), urine multiplex biomarkers, pathomics, radiomics and molecular alterations that could predict pathological response. We also want to assess the added discriminative ability of a multimodal clinic-radiological-genetic score (CRGS) that include cystoscopy, MRI and liquid biopsies over SOC clinic-radiological evaluation. NCT number: to be obtained in the upcoming weeks

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Efficacy and safety of trans-obturator tape vs. urethral bulking in female stress urinary incontinence. A randomized controlled trial

European Urology Open Science 2024;567 (Supplement 1): S26

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Introduction & Objectives: Urinary incontinence affects up to 46% of adult women, markedly reducing the quality of life. When conservative treatments for stress urinary incontinence (SUI) fail, different surgical options are available. Controversy has been raised regarding the best surgical procedures worldwide, due to the balance between efficacy and complications. The aims of this study were to compare the outcomes and safety of the Trans-Obturator-Tape (TOT) vs polyacrylamide hydrogel intraurethral Bulking agent (BA) treatment.

Materials & Methods: This is a RCT comparing TOT and BA (Bulkamid®) in women with naive SUI. The study was approved by local Ethics Committee and pts provided written consent. Inclusion criteria: age over 18 years, SUI not responsive to conservative treatment, no previous SUI surgery, no bladder obstruction. Exclusion criteria: previous POP surgery; diabetes or neurological disease; POP≥ stage II. Pre-op work-up: history; pelvic examination; urodynamic study, trans-labial ultrasound, self-administered UDI-6, IIQ7, FSFI questionnaires. Patients were followed up at 1, 3, 6, and 12 months after surgery. At 6 and 12 months pts underwent clinical, urinary and sexual symptoms evaluation, uroflowmetry with PVR measurement, UDI-6, IIQ-7, FSFI and PGI-I questionnaires. The complications were classified using both the ICS/IUGA and Clavien–Dindo classification. Statistical analysis: the non parametric Mann-Whitney U test used for analysis of continuous variables and the categorical data were analyzed by using X2 test. All calculations were performed using IBM-SPSS® version 22.0 (IBM Corp., Armonk, NY, USA, 2013).

Results: 55 women have been randomized to TOT and 49 to BA. The mean follow-up was 15±2.3 months. No significant inter-group differences emerged in the pre-op evaluations for age and BMI. Objective cure rate at 3 months was 96% after TOT and 85% after BA. The rate remained constant at 1-year f-up for TOT while it decreased significantly for BA after 6 months reaching 36% at 1 year. In the BA group 30% of the pts underwent new BA infiltration, 32% opted for a definitive TOT implant. Only 2 grade III complication has been reported in the TOT group (vaginal mesh exposure 2AaT3S2).

Conclusions: Both BA and TOT can be used in naive SUI patients. On the basis of this study the results on efficacy and safety should be included in a share decision making process so as patients can choose the type of surgery according to their expectations and on the basis of potential benefits, risks, and side effects of each treatment option. Women may prefer a minor and safer procedure (no prosthesis, no deeper anesthesia, reuptake of daily activity after 1-2 days) even if it means a lower success rate.

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Developing new approaches to stress urinary incontinence treatment in women during early phase research into artificial muscle technology

European Urology Open Science 2024;567 (Supplement 1): S27

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Introduction & Objectives: In the US, UK, Canada, Australia, and France, the use of vaginal mesh implants is discontinued or paused. In Europe they are subject to Medical Device Coordination Group Guidance on the vigilance system. Hence, new solutions are needed for interventional therapy of stress urinary incontinence (SUI) in women. Developments in soft robotics, smart materials, and bio-interfacing suggest the possibility of implanting artificial muscles to replace or augment biological muscles, restoring mobility, body functions and quality of life.

Materials & Methods: emPOWER is a UK Research Council (EPSRC) clinical engineering project initiating foundational technologies and proof-of-concept for implantable artificial muscles to recover lost functions in clinical settings. The indication target areas are SUI, musculoskeletal (sit-to-stand transfer) and vocal cord paralysis. The project is developing prototype contractile mechanisms (“actuators”), attachment techniques and control interfaces.

Results: The SUI project is based on the current autologous sling operation, to ensure that no artificial material is in contact with the urethra. It envisages incremental development, modelling a series of comparatively small changes, which include near-term components already in development. An adhesive to join fibrous and artificial materials has been developed, which bonds quickly, and can be dissolved in ethanol if adjustment is needed (1). The attachment methods are being developed to remain future-compatible should more complex technology (actuators) become available in the longer term. The first quantitative estimates of engineering performance requirements for actuators have been completed. Crude working models have been developed, which could increase tension in a sling. These can be usable in the context of sling tension adjustment post operatively, and patient control when the user anticipates clinical need (for example, physical exercise). Using a “latch-state” model, energy is only used when transitioning between states. Next steps include evaluation of current imaging approaches for better planning of operations (scan under strain, e.g. imaging in the upright position using EOS skeletal scanners). In addition, intraurethral ultrasound to guide accurate placement of slings per-operatively and to remove the need for vaginal incision (to reduce infection risk).

Conclusions: Development of usable artificial muscles is decades away, but preparation at this stage can offer modifications which foreseeably could be introduced clinically, and will pave the way should artificial muscle technology progress to regulatory approval.

1. Hagemann MJL, Chadwick L, Drake MJ, Hill DJ, Baker BC, Faul CFJ. High-Performance Dopamine-Based Supramolecular Bio-Adhesives. Macromol Rapid Commun. 2024:e2400345.

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Novel biomaterials for stress urinary incontinence: development of a clinically relevant large animal model to mimic suburethral implantation

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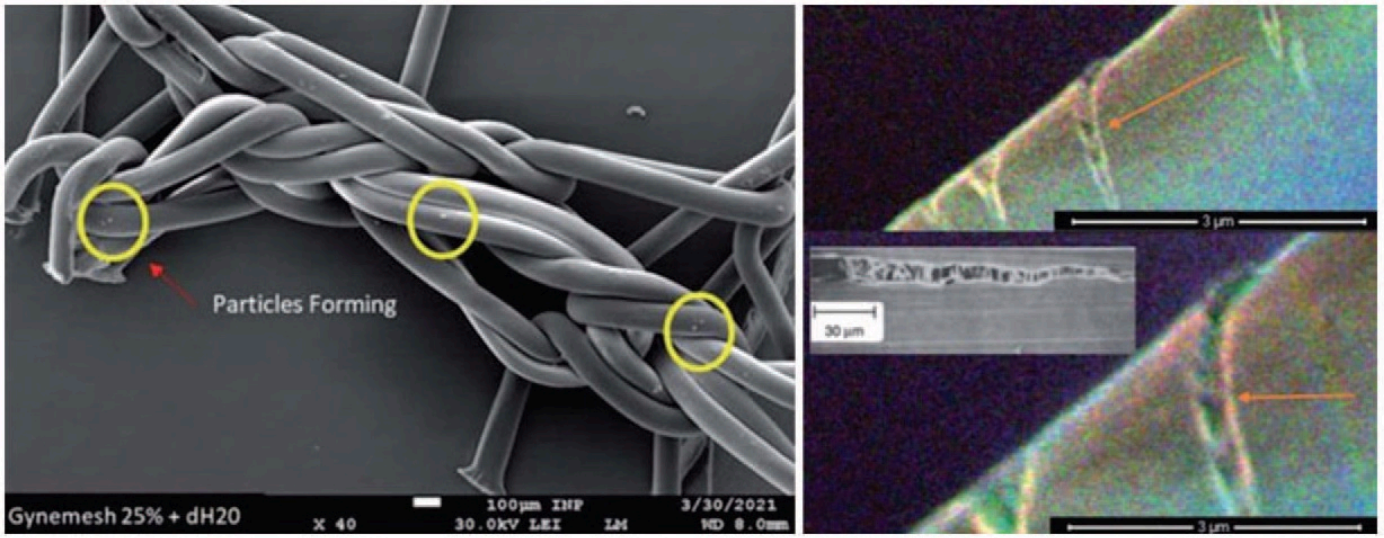
Introduction & Objectives: The serious complications of polypropylene mesh for stress incontinence are well recognised. We previously demonstrated that polypropylene reacts to mechanical distension and oxidative stress with surface alterations resulting in cracks visible using a surface analysis technique (figure 1). Such stressed polypropylene leads to activation of macrophages and expression of profibrotic genes. It is clear that prior to introduction of new biomaterials careful preclinical study is essential. An animal model that accurately reproduces surgical technique, include clinical and histochemical assessment, and predicts tissue responses to suburethral biomaterial in man is required. The objectives of this work are to develop and evaluate a relevant animal model of suburethral implantation of a novel biomaterial for stress incontinence.

Figure 1



Materials & Methods: Fourteen parous ewes of 30-40 kg were anaesthetised and placed in lithotomy position. A 12-Fr catheter was inserted. The ventral vaginal wall was longitudinally incised. The space between the vaginal wall and urethra was developed, with lateral retropubic dissection. Either a standard polypropylene tape (7 animals) or a fascia-mimetic microfibre spun polyurethane tape (n=7) was inserted using an introducer either via suprapubic (7 animals) or a transvaginal approach (n=7) into the sub-urethral and retropubic space. Postoperatively, animals were observed for pain and local complications and allowed access to water and food under continuous veterinary supervision adhering to animal welfare protocols.

Results: All animals passed urine freely. No complications were observed. At 3 months, tissue harvesting was undertaken. Examination of the vagina at harvest time showed good healing of the vaginal incision in all animals. The grafts were identified and excised with the surrounding tissue. One set of samples was snap-frozen in liquid nitrogen for immunohistochemical examination. The other set of samples were preserved in 10% formalin for histopathological examination. The preliminary results of histological and immunochemical analysis at 3 months will be presented and discussed.

Conclusions: This is large animal model for sub-urethral biomaterial implantation accurately reproduces surgical technique used to treat stress incontinence in women and can be used for the pre-clinical evaluation of novel biomaterials

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The development of a novel, multi-dimensional tool for the assessment of sexual dysfunction following radical prostatectomy: The RPQ

European Urology Open Science 2024;567 (Supplement 1): S30

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Introduction & Objectives: Current inventories for the assessment of post-radical prostatectomy (RP) sexual dysfunction are limited and are either overly focused on erectile function (IIEF, SHIM) or are too non-specific (EPIC). A tool that assesses, not alone erectile function, but also orgasm, libido, sexual incontinence and penile morphology is lacking and has impaired our ability to quantify the impact of such post-RP problems on patients' quality of life.

Materials & Methods: Constructs were developed based on literature review and expert panel consensus. Interviews were then conducted with prostate cancer patients until thematic saturation was achieved (n=10). Doing this, domains were verified and changes made to instructions, wording, order and definitions provided. The initial two drafts contained 41-items which was winnowed down to 32 questions over the course of validation. The draft instrument was administered to men who had undergone RP broken into four pre-determined groups (i) pre-RP (ii) < 1-year postop (iii) 1-2 years postop and (iv) 2-3 years postop Participants completed the RPQ plus the EPIC, IIEF, Self Esteem and Relationship (SEAR) and PROMIS Sexual Satisfaction questionnaires. All participants completed the RPQ alone again within two weeks to assess test-retest reliability. Absolute measures for goodness-of-fit included: Comparative Fit Index (CTI), Tucker Lewis Index (TLI) and root mean square error of approximation (RMSEA). Scale properties were evaluated using: Cronbach's α and intraclass correlation coefficient analysis (ICC) to assess internal consistency as well as test-retest reliability of subdomains. Cronbach's alpha and ICC ≥0.7 were considered acceptable. Convergent, discriminant, and divergent validity were assessed by correlational analyses of the subdomains with the other measures.

Results: 300 men were enrolled; 33% had not yet received RP, 34% were <12m, 18% 1-2 years and 15% or 2-3 years postop. Mean age was 62 (SD 7) years. The final measure is sub-divided into 6 domains: erectile function (erectile satisfaction and erectile hardness sub-domains), sexual desire, sexual incontinence, orgasm (orgasm satisfaction and orgasmic pain subdomains), sexual satisfaction, and penile morphology. Cronbach's α (internal consistency) was high for across all domains (0.78-0.92). The best-fit model had CFI and TLI values of 0.89 and 0.82 indicating good fit and the final measure demonstrated excellent convergent and discriminant validity.

Conclusions: This first-of-its-kind, multidimensional tool will help facilitate more effective research and clinical care by providing more accurate assessments of sexual functioning after RP.

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Phoenix Study: An EAU Research Foundation prospective registry on penile prosthesis implantation in 1000 patients (EAU-RF 2018-01)

European Urology Open Science 2024;567 (Supplement 1): S31

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Introduction & Objectives: According to the EAU guidelines, there is a strong recommendation to use Penile Prosthesis Implants (PPIs) if pharmacological treatments fail or depending on patient preference. At present, there are no clear recommendations which patient factors would identify the best surgical treatment options. The Phoenix registry aims to provide insight in daily urological practice in Europe and to evaluate outcomes. Objectives are to evaluate the effects of surgical treatment of erectile dysfunction with currently available certified PPIs and to determine prognostic factors which may help to identify clinical and surgical variable[KV2] that correlate with outcomes.

Materials & Methods: We have collected data from 1000 patients treated with a PPI. After signing informed consent that is approved by the local ethical committee, patient visits are conducted before- and after the surgical procedure at 2, 6, 12 weeks, and 1-year post-surgery. Long term follow-up will consist of a visit at 2 years and 2-yearly visits up to 10 years. Details of the surgical procedure and complications and revisions were collected. Various PROMS will be used at all visits for a) patients: the IIEF-5 (erectile function); the EQ-5D-5L and QoLSPP (Quality of Life & sexual function); 2 Sexual Encounter Profile questions (sexual function); and b) for patients & partners: 3 satisfaction questions and EDITS (satisfaction).

Results: At present moment, the recruitment is completed, and the projected 1000 patients have been included in the database. We present the data of the last cut off point including 915 patients. 23 centers across Europe actively participated in the registry. Except 3 centers which included more than 100 patients (one included 199 patients Belgium, KVR) the remaining 20 centers included a mean of 20 patients each. This give a perspective of high, medium and low volume centers which are very representative of the actual landscape across Europe. Median age was 62 years Type of device used was AMS 700 3-piece (3p) (55%), Titan 3p (22%), Titan Touch 3p (11%), Titan Narrow Base 3p (1%), Genesis malleable (m) (2%), Tactra m (1%), other (2%). The main aetiologies of ED were vascular (49%,) radical prostatectomy (RP) (31%), other pelvic surgery (4%) diabetes (18%), Peyronie's disease (13%), neurogenic (6%), other (10%). PROMS were completed in 94% of the patients at baseline.

Conclusions: Data collected so far indicate high use of 3-piece PPIs in Europe, with only less than 5% of patients were implanted with a malleable prosthesis. Main etiologies of ED are vascular, pelvic surgery (RP), diabetes and Peyronie's disease. Important information about surgical approach, use of drains, data on penile length, etc., are available and will be presented.

28 Efficacy vs. cost effectiveness, a timely discussion in onco-urology

European Urology Open Science 2024;567 (Supplement 1): S32

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Introduction & Objectives: Cost of treating metastatic prostate per EAU guidelines increased in the past ten years by 25-to-50-fold, reaching up to 50-100,000 international dollars (I$) per year in the 5 EU-states analyzed (Martini, Eur Urol 2022). Health amounted in 2023 in F to 8.9% of Gross Domestic Product (GDP), with €4.6 billion for innovative drugs and €250 million for PEMBRO alone. Unbalanced budgets across Europe further question the sustainability of overlooking costs in the advancement of care, particularly of cancer drugs.

Materials & Methods: Literature review, individual data survival extraction from survival curves according to Guyot [4] by OLTRE Medical Consulting (https://www.oltremc.com/) and arithmetic, to question:
Q1: the threshold of cost effectiveness (CE)
Q2: the use of the published literature to estimate the cost of innovative drugs and assess their CE

Results: R1: Although invaluable the human life has monetary value:
- A common medical benchmark is dialysis, routinely offered to a cost of $130,000 € per QUALY and $60,000 per year, (Lee, Value Health 2006).
- The WHO-CHOosing Interventions that are Cost-Effective (WHO-CHOICE) 1998 initiative proposed that treatments ensuring one year of “good quality life” are cost effective up to 3 times the GDP per capita, that is in France up to I$181,000 (I$60,340x3) per year, approximately €128,510 https://www.imf.org/external/datamapper/profile (accessed on 3 October 2024).
R2: The PROpel trial - ABI+OLA vs. ABI and placebo in patients with mCRPC in all-comers- that showed a significant benefit with a delay of 8 months (16.6 vs. 24.8 months) in imaging-based progression (Clarke, Lancet Oncol 2018) later translated into a benefit in overall survival (Saad, Lancet Oncol 2023) -exemplified the second question
- 399 patients received 6,093 months of OLA to ensure 404 cumulated additional months of delayed progression, that is collectively 15.1 months (6,093:404) of OLA per month of delayed progression, or 180 months of OLA (15.1 x 12) per year of delayed progression.
- Threshold for CE of OLA in France would amount to €128,510:180 months, that is 714 €/month.
- OLA is EMA-approved in BRAC1/2-mutated mCRPC patients at €39.4/150mg tablet in F. Amouting in the PROpel context (300mg b.i.d) to €4,732 per month (€39.4x4x30d), approximately 7 times the WHO-CHOICE threshold.
- Alternately, €851,760 (€4,732x180months) would be required for one cumulated year of delayed progression in all-comers.

Conclusions: 1. WHO-CHOICE is a simple metric to assess CE.
2. CE analysis should complement efficacy as key objective in the design of clinical trials.
3. Measurable effect after long exposure to costly treatment may not be adapted to the current economical constraints.
4. That may be remedied by adjusting the cost to the measured benefit.
5. Less costly treatments showing a sustainable measurable effect should be supported (e.g. surgery?)

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Artificial Intelligence (AI) in the management of prostate cancer - Current state of the art

European Urology Open Science 2024;567 (Supplement 1): S33

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Introduction & Objectives: With AI winning the Nobel Prize for Chemistry, the importance of this technology for prostate cancer (CaP) has become of considerable importance. We present the current state of the art in this field.

Materials & Methods: A review of AI in CaP from our own research collaborative and other international groups.

Results: AI interventions have been proposed for every stage in the management of CaP. The PANDA (Prostate Cancer Grade Assessment) challenge represents a framework whereby international collaboration and publicly available datasets have accelerated AI model development. It was joined by 1,290 developers from 65 countries for Gleason grading using 10,616 digitised, publicly available prostate biopsies. Several submitted algorithms performed as well as expert pathologists. AI algorithms have targeted MRI for cancer detection, staging, and segmentation of the prostate. We proposed a comprehensive system, AutoProstate, for automated reporting of CaP MRI, which achieved a high accuracy in the detection of clinically significant cancer. AI systems can improve situational awareness, surgical approaches, and patient outcomes during Robotic Assisted Radical Prostatectomy (RARP). Surgeons' Automated Performance Metrics have been used to predict functional outcomes post RARP. AI models such as MonaAI Label also enables the use of interactive 3D imaging systems for intra-operative planning. A real-time 3D augmented reality system can identify prostatic lesions at neurovascular bundle (NVB) level to enhance nerve sparing during RARP. Studies have explored using Generative AI (GenAI) models to create MRI based synthetic CT (sCT) scans and thus enable MRI only radiotherapy workflows. Commercial solutions already exist and have demonstrated high agreement between sCT based predicted radiation doses and real CT based dosage. Finally, the idea of AI driven automation has returned. Although a machine can perform certain steps of an operation such as suturing more accurately than a human being, surgical judgement is unlikely to be replaced by AI anytime soon. These advances must be safe and regulated. The set-up of UK Research and Innovation (UKRI) funded Responsible AI and the Trustworthy Autonomous Systems (TAS) Hub are steps in the right direction for the ethical and responsible development of AI in CaP.

Conclusions: AI is transforming CaP management from diagnosis to treatment. This progress underscores the need for regulation and the development of safe, ethical and non-biased software.