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1

INTRAVESICAL ADMINISTRATION OF CHECKPOINT INHIBITORS FOR NON-MUSCLE-INVASIVE BLADDER CANCER: THE STATE OF THE ART

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Background/Aim: New immunotherapy with checkpoint inhibitors is developing especially for advanced stages of bladder tumor and as second-line treatment; however, non-muscle-invasive bladder cancer (NMIBC) represents only a small proportion of all efforts in this field. Moreover, these new drugs are primarily administered intravenously and intravesical administration has not yet been fully explored. The expression of PD-L1, biomarker of checkpoint inhibition has been reported at the surface of both tumor cells and peritumoral immune cells; this may truly represent a potential cornerstone in the development of a new treatment for bladder cancer. *Materials and Methods:* To highlight the major ongoing trials on intravesical checkpoint inhibitors, we performed a search to identify reports for four ongoing trials focusing on patients with NMIBC (Figure 1). *Results:* Despite intense trial activity, no completed study has reported data on the results of intravesically administered checkpoint inhibitors to date. The major four identified ongoing trials are: NCT03759496, ACTRN12620000063910, NCT03167151 and NCT02808143 (Table I). *Conclusion:* PD-L1 has been identified as being

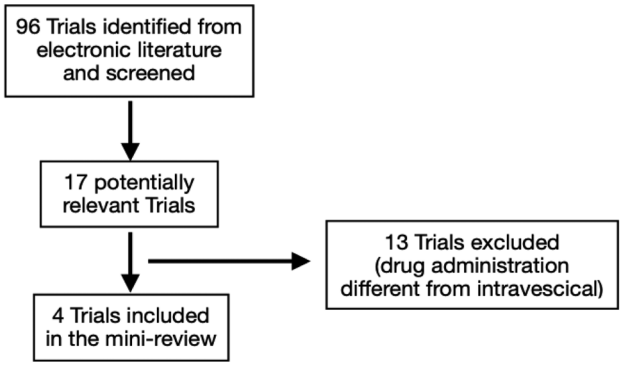

Figure 1. *Study flow chart.*

Table I. *Current ongoing trials on intravesical administration of checkpoint inhibitors.*

Registration number	Public title	Dosage (Administration)	Patients	Primary outcome measures	Phase	Status	Estimated study completion date
NCT03759496	Efficacy of Durvalumab in non-muscle-invasive bladder cancer	Up to 1,000 mg (intravesical)	BCG-refractory/ recurrent/ intolerant NMIBC	MTDHGRF toxicity	II	Recruiting	Dec. 2021
ACTRN1262 0000063910	A phase 1 open label dose escalation study to evaluate the tolerability, safety, and immunological efficacy of suburothelial durvalumab injection in adult subjects with muscle invasive bladder cancer or high risk non muscle invasive bladder tumours.	Not declared (sub-urothelial injection)	Muscle invasive or high risk NMIBC	Tolerability safety	I	Recruiting	Not declared
NCT03167151	Pembrolizumab in intermediate risk recurrent non-muscle invasive bladder cancer (NMIBC) (PemBla)	50-200 mg (intravesical)	Intermediate risk NMIBC	Safety tolerability toxicity	I, II	Recruiting	Aug. 2021
NCT02808143	Pembrolizumab and BCG solution in treating patients with recurrent non-muscle invasive bladder cancer	Not declared (intravesical)	High-risk or BCG refractory NMIBC	MTDDLTs	I	Recruiting	Jan. 2020

BCG: Bacillus of Calmette-Guerin; NMIBC: non muscle invasive bladder cancer; MTD: maximum tolerated dose; HGRF: rate of high-grade relapse free; DLTs: dose limiting toxicities.

related to prognosis in many neoplastic diseases, including NMIBC; the translation of this diagnostic tool in the treatment setting combined with the experience of standard intravesical therapy might benefit patients with NMIBC.

2
COULD HoLEP CHANGE THE FURTHER MANAGEMENT OF INCIDENTAL PROSTATE CANCER?

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Background/Aim: Holmium laser enucleation of the prostate (HoLEP) is effective in treating lower urinary tract symptoms from prostatic disease. We investigated the role of HoLEP in the management of patients with benign prostatic hypertrophy (BPH) and prostate cancer (PCa). *Materials and Methods:* Retrospective review of data regarding all patients undergoing HoLEP at a single institution was performed. Pre- and postoperative prostate-specific antigen, multiparametric magnetic resonance imaging, and pathology results were analyzed for those with PCa identified prior to HoLEP and incidentally at HoLEP. *Results:* A total of 147 patients underwent HoLEP. Eighteen patients had PCa diagnosed before HoLEP and 16 (10.9%) had PCa incidentally detected at HoLEP. The total prostate-specific antigen level at 3 months after HoLEP had dropped by 82.35% (8.27 ng/ml at initial evaluation to 1.46 ng/ml) in patients already diagnosed with PCa and by 91.03% (3.01 ng/ml at initial evaluation to 0.27 ng/ml) in the group with incidental detection; the values remained stable up to 12 months after HoLEP. All patients in both groups (including patients who underwent cancer treatment post-HoLEP) survived without cancer progression, including patients with PCa diagnosis at HoLEP and based on the initial PCa status. *Conclusion:* More than 10% of patients undergoing HoLEP might receive a diagnosis of PCa. HoLEP can be performed even in patients with PCa, at any disease stage, in order to relieve lower urinary tract symptoms. Whether PCa is diagnosed before or at HoLEP, the procedure does not affect the oncological outcomes. Further investigation is warranted to determine the durability of the success of these approaches.

3
ROBOT-ASSISTED, LAPAROSCOPIC AND OPEN RADICAL CYSTECTOMY: SURGICAL DATA OF 1,400 PATIENTS FROM THE ITALIAN RADICAL CYSTECTOMY REGISTRY (RIC) ON INTRAOPERATIVE OUTCOMES

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Background/Aim: The Italian Radical Cystectomy Registry (Registro Italiano Cistectomie; RIC) aimed to analyse outcomes of a multicentre series of patients treated with radical cystectomy for bladder cancer. *Materials and Methods:* An observational, prospective, multicenter, cohort study was carried out to collect data on radical cystectomy and urinary diversion via open (ORC), laparoscopic (LRC), or robotic-assisted (RARC) techniques performed at 28 Italian Urological Departments. Enrolment was planned from January 2017 to June 2020 (goal: 1,000 patients); it was discontinued early with inclusion of 1400 patients. The trial was registered on ClinicalTrials.gov on 01/14/2020 (NCT04228198). Data collection was conducted in accordance with the World Medical Association Declaration of Helsinki. This study was approved on 06/25/2020 by the Ethical Committee of the University of Padova (number: 0042389). Chi-square and *t*-tests were used for analysis of categorical and continuous variables. Statistical analyses were performed using Stata-SE 15. Medians and interquartile ranges (IQR) are reported. All tests were two-sided with a significance level set at $p<0.05$. *Results:* Overall median

operative time was longer in RARC [390 (IQR=335-465) min] than in ORC [250 (IQR=217-309) min] and LRC [292 (IQR=228-350) min] (p<0.001). The median duration of cystectomy was longer in RARC [140 (IQR=115-180) min] than in ORC [90 (IQR=60-120) min] and LRC [100 (IQR=72-135) min] (p<0.001). Lymph node dissection (LND) was performed more frequently in RARC (97.1%) and LRC (93.5%) than ORC (85.6%) (p<0.001). The rates of limited LND dissection were similar; extended LND was performed two-fold more frequently in RARC (61.6%) (p<0.001). The median duration of LND was higher in RARC [80 (IQR=60-100) min]. A nerve-sparing technique was performed in one-third of RARCs, while in LRC and ORC, almost no patients underwent it. In RARC, the neobladder rate was significantly higher (more than one-half) than in LRC and ORC, where non-continent diversion was preferred in 80% of cases. The diversion was performed with the same radical cystectomy approach in the majority of RARCs (79.7%) and LRCs (78.3%). The median urinary diversion time was significantly higher in RARC [134 (IQR=100-194) min] than LRC [100 (IQR=60-125) min] and ORCs [60, IQR=30-90) min] (p<0.001). The median estimated blood loss (ml) was lower in RARC [250 (IQR=165-400)] than ORC [400 (IQR=250-600)] and LRCs [330 (IQR=200-600)] (p<0.001). The intraoperative blood transfusion rate was 11.4%, 21.7% and 35.6% for RARC, LRC and ORC, respectively (p<0.001). The rate of conversion to open surgery was slightly higher in RARC (6.8%) than LRC (4.3%). Intraoperative complications occurred in 18/1,425 cases (1.3%) without statistically significant differences among the approaches. *Conclusion:* Data from the RIC confirmed the need to collect as much data as possible in a multicenter manner. RARC was proven to be feasible with perioperative complication rates that do not differ from other approaches

4
THE TREATMENT OF SYMPTOMATIC LYMPHOCELE POST-RADICAL PROSTATECTOMY IN THE ERA OF ROBOTIC SURGERY

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Background/Aim: Pelvic lymph node dissection (PLND) is an integral part of the surgical treatment of localized intermediate-risk and high-risk prostate cancer (PCa); the most common complication of PLND is lymphocele formation. In most cases the development of lymphoceles is clinically asymptomatic but in the case of infected/symptomatic lymphocele, an active treatment is required. The aim of this work was to analyze the current evidence on the treatment of infected/symptomatic lymphocele by a robotic approach. *Materials and Methods:* A search was carried out in PubMed, EMBASE, and Cochrane databases with the following terms: lymphocele, symptomatic, infected, robotic-assisted radical prostatectomy, robot-assisted, and treatment. *Results:* The search identified only three reports (Figure 1) focusing on treatment of symptomatic/infected

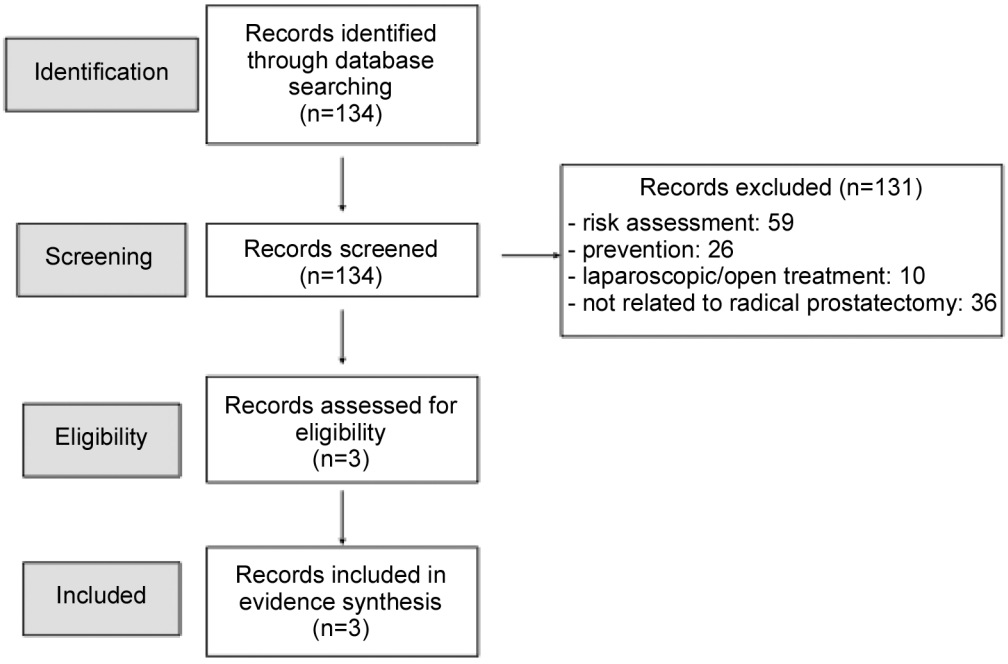

Figure 1. *Flow diagram of article selection process.*

lymphocele using a robot-assisted approach. The main and most frequent reason for performing robotic treatment was infected lymphocele. The median time from robot-assisted radical prostatectomy plus PLND to robotic treatment of lymphocele was 118 days (range=30-240 days). The robotic treatment approach was successful in all reports. *Conclusion:* The drainage of lymphocele with a robotic approach appeared safe, feasible, and with satisfactory outcomes for definitive treatment of an infected/symptomatic lymphocele sac.

5

COMPARISON BETWEEN THE EFFECTS OF MUSIC AND VIRTUAL REALITY ON PERCEIVED PAIN DURING TRANSRECTAL BIOPSY

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Aim: The aim of this study was to compare efficacy in reducing perceived pain between music and virtual reality in men undergoing transrectal prostate biopsies. *Materials and Methods:* A total of 95 men who underwent transrectal prostate biopsies at our institution, between January 2019 and February 2020, were randomly assigned to a music (group A) (n=53) or virtual reality (group B) (n=42) group. Patients assigned group A wore a virtual-reality headset and were shown a 360˚ 4k virtual-reality video of natural landscapes during the entire prostate biopsy while patients assigned to group B listened to their favorite music (chosen themselves) throughout the procedure. Pain was assessed multiple times utilizing a visual analogue scale (VAS). Pain evaluation was performed at the introduction of the transrectal probe (VAS1), during the administration of periprostatic lidocaine infiltration (VAS2), and during basal, equatorial and apex biopsy (VAS3a, VAS3b and VAS3c, respectively). Further evaluations were made on site at 1 hour after the biopsy (VAS4), and via phone in the same evening and the following morning (VAS5 and VAS6, respectively). Statistical analysis was performed using a Mann–Whitney *U*-test for non-parametric variables, assuming $p<0.05$ as statistically significant. *Results:* No significant differences were reported in baseline characteristics of patients between the two groups. Mean VAS1 was 3.51 for group A compared to 1.88 of group B (U=272.5, $p<0.0001$). Similarly, VAS2 was 2.17 *versus* 1 (U=251, $p<0.0001$), VAS3a was 1.46 *versus* 0.93 (U=557.5, $p<0.0001$), VAS3b was 1.70 *versus* 1.02 (U=469.5, $p<0.0001$), VAS3c was 2.91 *versus* 1.43 (U=222, $p<0.0001$). Slight differences were reported for VAS4 (0.89 *versus* 0.26, U=531.5, $p<0.0001$), VAS5 (0.53 *versus* 0.02, U=779.5, $p<0.0001$), although statistically significant; no clinically significant difference was reported for VAS6 (0.13 *versus* 0.05, U=1050, $p=0.119$). *Conclusion:* This study compared the efficacy in perceived pain reduction of virtual reality *versus* music, reporting overall superiority of the former. Pain reduction was particularly marked during the first steps of the prostate biopsy procedure (introduction of the probe, administration of periprostatic anesthesia) allowing the hypothesis that anxiety and discomfort also play a role in pain perception. Further studies are required to explore this correlation and to evaluate the influence of different aspects such as method of music delivery and volume. or video genre, in addition to the use of additional devices or procedures to reduce initial anxiety and stress.

6

EFFECTS OF MUSIC ON PERCEIVED PAIN DURING TRANSRECTAL BIOPSY

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Aim: The aim of this study was to investigate the effects of music on perceived pain in men undergoing transrectal prostate biopsy. *Materials and Methods:* A total of 98 men undergoing transrectal prostate biopsies at our institution between February 2019 and January 2020 were randomly assigned to a music (group A, n=53) or control (group B, n=45) group. Patients assigned to group A underwent biopsy while listening to music, chosen by the patient, during the entire biopsy while patients assigned to group B represented the control group. Pain perception was assessed multiple times using a visual analogue scale (VAS) at predetermined checkpoints: introduction of the transrectal probe (VAS1); administration of periprostatic lidocaine infiltration (VAS2); basal, equatorial and apex biopsy (VAS3a, VAS3b and VAS3c, respectively); 1 hour after the biopsy (VAS4); and by phone the same evening and the following morning (VAS5 and VAS6, respectively). Statistical analysis was performed using a Mann-Whitney *U*-test for non-parametric

variables, assuming $p<0.05$ as statistically significant. *Results:* No significant differences in baseline characteristics of patients between the music and control group were reported. Mean VAS1 was 4.87 for the control group compared to 3.51 of group A (U=556, $p<0.0001$). Similarly, VAS2 was 2.71 *versus* 2.17 (U=726, $p<0.0001$), VAS3a was 4.53 *versus* 1.46 (U=59.5, $p<0.0001$), VAS3b was 4.87 *versus* 1.70 (U=17.5, $p<0.0001$), VAS3c was 6.42 *versus* 2.91 (U=63, $p<0.0001$). Slight differences were reported for VAS4 (1.91 *versus* 0.89, U=458.5 $p<0.0001$), VAS5 (0.82 *versus* 0.53, U=848, $p=0.006$) and VAS6 (0.33 *versus* 0.13, U=895, $p=0.001$). *Conclusion:* Clinically and statistically significant differences in perceived pain were reported between the two groups examined, favoring the music group compared to the controls. Although statistically significant, differences reported in VAS obtained after the biopsy were minimal. Further studies are required to evaluate the influence of music delivery, volume, and use of additional relaxation instruments.

7

IS HYPERURICEMIA A RISK FACTOR FOR BLADDER CANCER?

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Aim: The aim of this study was to evaluate the correlation between hyperuricemia and bladder cancer, as it is thought to be associated with carcinogenesis. *Materials and Methods:* Clinical data of 433 men who underwent transurethral resection of bladder tumor (TURBT) at our institution between 2017 and 2021 were collected and retrospectively analyzed. Serum levels of uric acid were obtained from preoperative blood analyses performed within 1 month from hospital admission. Patients were divided dichotomously according to a serum uric acid level compatible with hyperuricemia (>8 mg/dl). A further correlation was performed between serum uric acid levels and histological reports of TURBT. Statistical analysis was performed with Kruskal–Wallis test for non-parametric continuous variables and logistic regression for categorical variables, assuming $p<0.05$ as statistically significant. *Results:* A total of 372 patients were included in the study (82% males, 18% females), with a mean (± standard deviation) age of 70.51±11.18 years. Patients were divided by histological report into negative, benign, grade 1 tumor and grade 3 tumor groups. The mean serum uric acid levels were 5.47±1.44 mg/dl (mean rank 183.36), 5.25±1.23 mg/dl (mean rank 156.32), 5.56±1.44 mg/dl (mean rank 185.04) and 5.88±1.63 mg/dl (mean rank 203.6) [H(3)=8.179; $p=0.042$], respectively. Logistic regression indicated that patients with hyperuricemia presented a 3.35-fold increased risk of exhibiting bladder cancer compared to non-hyperuricemic patients ($p=0.21$). *Conclusion:* Patients with hyperuricemia are more likely to be diagnosed with bladder cancer, with a three-fold increased risk compared to non-hyperuricemic patients. Further studies are required to evaluate, prospectively, the role of hyperuricemia in bladder malignancies.

8

IMPACT OF MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING OF PROSTATE IN THE DETECTION OF CLINICALLY SIGNIFICANT CANCER BEFORE PROSTATIC BIOPSY IN BIOPSY-NAIVE PATIENTS

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Aim: To evaluate the detection rate of multiparametric magnetic resonance imaging (mpMRI) of clinically significant prostate cancer (PCa) [International Society of Urologic Pathologists (ISUP) grade ≥2] before biopsy in biopsy-naïve patients. Patients and Methods: The study was conducted as a retrospective observational study carried out at AOU Federico II, Naples, Italy, on 484 patients who underwent prostatic biopsy between January 2019 and July 2020. Inclusion criteria comprehended prostate-specific antigen >4 ng/ml or positive digital-rectal exam. A total of 157 patients underwent random biopsy (group 1) while 327 patients underwent cognitive biopsy due to a previous mpMRI (within 6 months of biopsy) (group 2). All mpMRI images were obtained with 3-Tesla instruments and interpreted according to PIRADS version 2.0. Pearson's chi-square test was performed for statistical analysis considering $p<0.05$ as statistically significant. *Results:* Mean age (± standard deviation) was 69.01±7.9 years for group 1 and 68.05±7.1 years for group 2. PSA was 11±9 ng/ml for group 1 and 8.91±7.31 ng/ml for group 2 and the number of cores obtained at biopsy was 12.56±1.59 ng/ml and

15.69±1.135 ng/ml, respectively. When the detection rate of clinically significant PCa was compared among groups, 60.5% of patients in group 1 had no PCa at biopsy compared to 47.4% of patients in group 2; 18.5% of patients in group 1 presented ISUP 1 PCa compared to 15.3% of patients in group 2, and, finally, 21% of patients in group 1 had an ISUP ≥2 PCa compared to 37.3% in group 2 (p=0.009). Furthermore, group 2 outcomes at biopsy were analysed to evaluate the impact of PIRADS score on the detection rate of PCa. Patients with PIRADS 2 had a negative result in 63.6% of cases, ISUP 1 in 27.3% and ISUP ≥2 in 9.1% of cases; results were similar for PIRADS 3, with a negative result in 62.1% of cases, ISUP 1 in 20.4% of cases and ISUP ≥2 in 17.5% of cases; PIRADS 4 had no PCa in 48.7% of cases, 12.6% ISUP 1 PCa and 38.7% ISUP ≥2 PCa; and finally,for PIRADS 5, there was no PCa in 8.3% of cases, ISUP 1 PCa in 1.7% and ISUP ≥2 PCa in 90% (p<0.0001). *Conclusion:* mpMRI was confirmed as a reliable diagnostic tool prior to performing prostate biopsy, avoiding unnecessary biopsies, with related complications, and detection of non-clinically significant PCa. In addition, previous mpMRI before performing a prostatic biopsy increased the overall detection rate of the standard procedure.

9

THE ROLE OF mpMRI IN DETECTING TARGETS FOR BIOPSY: COMPARING CONCORDANCE RATES REGARDING SIDE OF LESION AT IMAGING AND TARGETED BIOPSY

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Background/Aim: Targeted biopsy increases the overall prostate cancer detection rate and reduces the risk of detection of clinically insignificant prostate cancer. The aim of the study was to evaluate the diagnostic accuracy of multiparametric magnetic resonance imaging (mpMRI) in terms of the side of localization of the suspected lesion compared with that at biopsy. *Materials and Methods:* The study was conducted as a retrospective observational study at AOU Federico II, Naples, Italy. In all, 195 patients underwent systematic plus targeted transrectal ultrasound guided prostatic biopsy (12 cores + 4 targets), between January 2019 and July 2020. Inclusion criteria were prostate-specific antigen >4 ng/ml or positive digital-rectal exam and mpMRI acquired within 3 months from date of biopsy. All mpMRI images were obtained with 3-Tesla instruments and interpreted according to PIRADS version 2.0. Pearson's chi-square test was performed for statistical analysis considering p<0.05 as statistically significant. *Results:* The mean age of patients was 69.2±6.9 years while the mean prostate-specific antigen was 10.2±9.3 ng/ml and the mean number of cores obtained was 15.93±0.71. For bilaterally located lesions, mpMRI was concordant with biopsy in 65% of cases. For lesions located on the left side of the prostate gland at mpMRI, a concordance rate of 69.6% was obtained at biopsy, while for lesions located on the right side of the prostate gland, a concordance rate of 73.5 was obtained at biopsy (p<0.0001). *Conclusion:* mpMRI performed before biopsy increased the detection rate of targeted biopsy, with a concordance rate with side of lesion that reached 73.5%. Further data are required in order to evaluate the influence of other specific positions (e.g., apex, mid-gland and base) in order to achieve better results in terms of biopsy targeting.

10

ROLE OF NEUTROPHIL PERCENTAGE-TO-ALBUMIN RATIO AS A DIAGNOSTIC BIOMARKER IN BLADDER CANCER

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Aim: The aim of this study was to analyze the Neutrophil percentage-to-albumin ratio (NPAR) as a possible diagnostic biomarker for bladder cancer prior to transurethral resection of bladder tumor (TURBT). *Materials and Methods:* Clinical data of 433 men who underwent TURBT at our institution between 2017 and 2021 were collected and retrospectively analyzed. NPAR data were calculated from preoperative blood analyses obtained at the time of hospital admission and were successively correlated with histological reports obtained after TURBT. Statistical analysis was performed using a Kruskal–Wallis test for non-parametric variables, assuming p<0.05 as statistically significant. *Results:* Overall, 410 patients were included in the study (80.7% males, 19.3% females), with a mean age (± standard deviation) of 70.43±11.17 years. Among histological reports obtained, 76 were negative for bladder cancer, 69 reported a benign finding, 119 reported grade (G) 1 bladder cancer and 146 reported G3 bladder cancer. Mean NPAR rank was 186.45 for patients without bladder cancer, 178.43 for patients with

benign lesions, 211.61 for patients with G1 and 223.22 for those with G3 [H(3)=9.147; p=0.027]. The mean NPAR was 14.37±2.5, 14.25±2.95, 15.22±4.13 and 15.48±3.06, respectively. No other significant differences were reported in baseline characteristics. Although statistically significant, no clinically significant difference was reported between patients without bladder cancer and those with benign lesions (including inflammatory findings predominantly) compared to patients with G1 and G3 bladder cancer. *Conclusion:* The role of NPAR as a diagnostic biomarker for bladder cancer appears feasible as an increase of this ratio is associated with G1 to G3 bladder cancer. Further studies are required to properly evaluate and confirm our findings.

11
ABNORMAL PRESENTATION OF A BILATERAL, SYNCHRONOUS AND PLURIMETASTATIC TESTICULAR LYMPHOMA WITH MEDIUM AND LARGE CELLS

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Background/Aim: Primary testicular lymphoma accounts for 5% of all testicular cancer, with increased incidence in patients aged >60 years. Bilateral synchronous clinical presentation with brain metastases is an unusual clinical presentation. Echotomography shows complete structural subversion of the didymus from hypoechoic nodular lesions, with parenchymal hypervascularization on color-Doppler. Orchiectomy is essential for the histopathological evaluation of the disease and the definition of the immunophenotypic structure. The most common histotype is diffuse large-cell B lymphoma. Polychemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) protocol has changed the prognosis and history of the disease. *Case Report:* We report a case of a paucisymptomatic patient (53 years old) who presented with headache and erectile dysfunction. On ultrasound examination, tissue architecture of the didymes was found to be completely subverted and of hard 'wooden' consistency. Metastasis had spread to the lungs, abdomen, central nervous system, neck, and dental arches. He underwent bilateral orchifuniculectomy and subsequent antiblastic protocol.

12
THE AUTOPHAGY INHIBITOR DESMETHYLCLOMIPRAMINE REDUCES EPITHELIAL–MESENCHYMAL TRANSITION, PROLIFERATION, AND INVASION IN KIDNEY CARCINOMA CELL LINES

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Background: Renal cell carcinoma (RCC) is a lethal urological tumor that represents about 3% of all diagnosed cancers. RCC is divided into three main subtypes; clear-cell RCC (ccRCC) accounting for ~75%, papillary ~15% and chromophobe ~5% of cases (1). Many factors, such as smoking, obesity, hypertension, and germline mutations, are considered risk factors for the onset of this disease (2). At an early stage, RCC is often asymptomatic; therefore, it may be diagnosed when the disease is in an advanced stage or a metastatic form. In these conditions, patients are difficult to treat; in fact, overall survival of patients with metastatic RCC at 5 years from diagnosis is lower than 10% (2). Currently, pharmacological treatment for metastatic RCC targets biological pathways involved in tumor growth and metastasis, including the mammalian target of rapamycin (mTOR) and tyrosine kinase receptors (2). However, many patients treated with mTOR, and tyrosine kinase inhibitors acquire drug resistance making the therapy ineffective and without clinical benefits (3). Therefore, research for new early diagnostic and prognostic markers, as well as novel therapeutic options, is crucial for improving overall survival and quality of life of patients with advanced RCC. The investigation of the molecular basis of RCC has led to the detection of mutation/dysfunction of different genes involved in renal carcinogenesis including Von Hippel Lindau, BRCA1-associated protein-1, polybromo-1, SET domain-containing 2, phosphatidylinositol-4.5-*bis*phosphate 3-kinase catalytic subunit alpha, hepatocyte growth factor receptor and tumor suppressor p53 (1, 4). We found that p53 may be degraded through the activation of autophagy in different ccRCC cell lines (1). Autophagy sustains energy homeostasis by eliminating damaged proteins and organelles during stress and aging and is involved in different pathologies including cancer (5). Autophagy may have a dual function in cancer: as a tumor-suppressive mechanism, especially in the early stage of tumorigenesis; conversely, in later stages, autophagy enhances

growth, survival, tumorigenesis and causes resistance to therapeutic agents (5). Here we analyzed the effects of autophagy inhibition in different ccRCC cell lines. *Materials and Methods:* Caki-1, Caki-2 and KJ29 ccRCC cell lines were used as *in vitro* models of ccRCC. Normal kidney epithelial transformed cells (4/5) and embryonic kidney cells (HEK 293) were used as controls. Autophagy was inhibited by treating cells with desmethylclomipramine (DCMI), an antidepressant that inhibits autophagosome–lysosome fusion. Cell proliferation assay was performed by seeding 25.000 cells per well in 24-well plates and cultured for 24 h in Dulbecco's modified Eagle's medium (DMEM)/F12 supplemented with 1% fetal bovine serum with/without DCMI at different concentrations (1, 5 and 10 μM). After staining with trypan blue, cell numbers were calculated using a Burker chamber. Cell invasion assay was carried out using Costar Transwell permeable polycarbonate supports (8.0-mm pores) coated with Matrigel, in which 2×10^5 cells in serum-free DMEM/F12 were seeded. After 48 h of treatment with 5 and 10 μM DCMI, cells that passed the permeable support were fixed and stained with 0.1% of crystal violet solution. Finally, cells were counted by using the cell counter plugin available on Fiji software. Proteins associated with autophagy and the epithelial-mesenchymal transition such as microtubule-associated protein 1A/1B-light chain 3 (LC3), E-cadherin and vimentin were analyzed by western blotting using specific antibodies. Statistical analysis was performed by GraphPad Prism software using analysis of variance or *t*-test as appropriate; values of

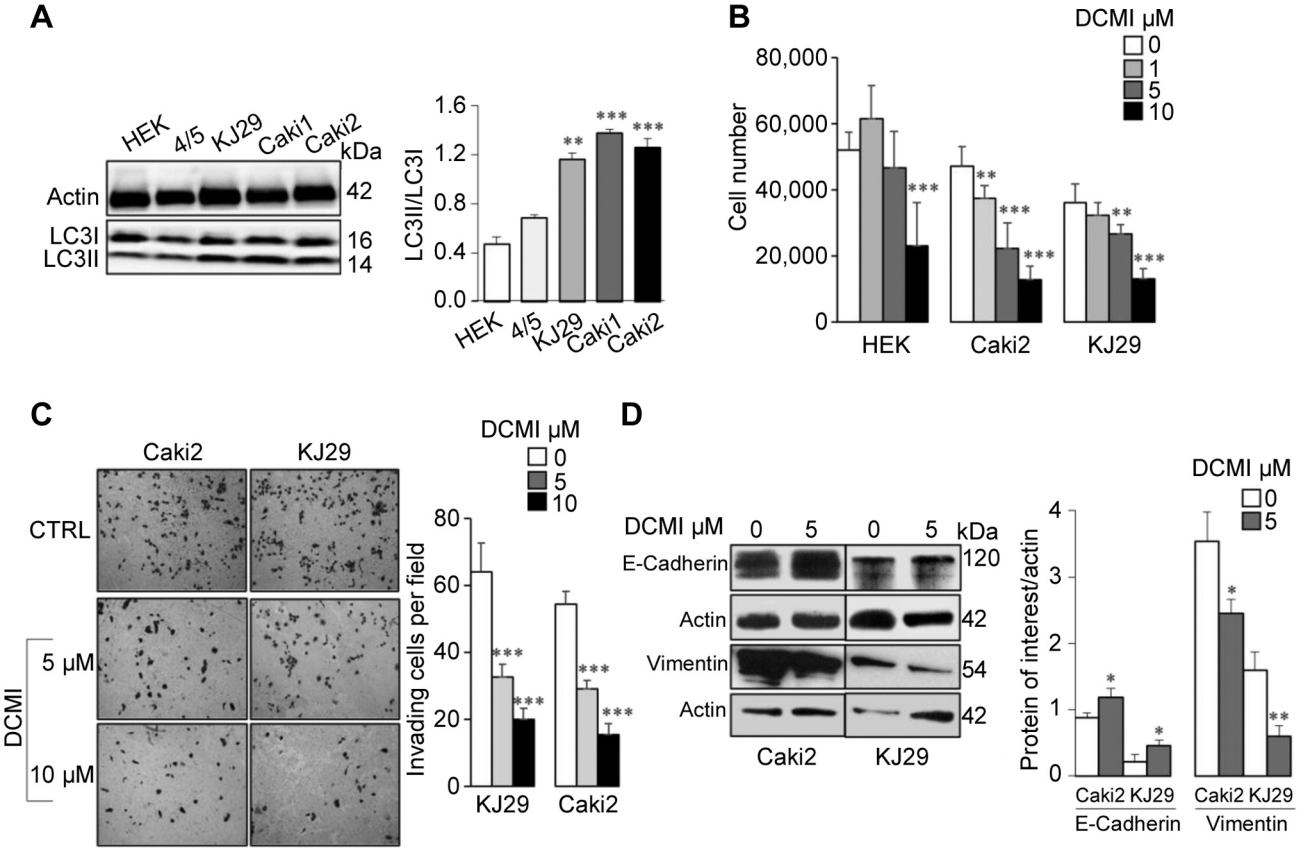

Figure 1. *The inhibition of autophagy reduces cell growth, invasion and epithelial–mesenchymal transition in kidney cancer cells. A: Western blot analysis of autophagy marker Microtubule-associated protein 1A/1B-light chain 3 (LC3) was performed in control (4/5 and HEK 293) and in clear-cell renal cell carcinoma (Caki1, Caki2 and KJ29) cells cultured in basal conditions (Dulbecco's modified Eagle's medium/F12 10% fetal bovine serum). Levels of the light form of LC3 (LC3II) were greater in ccRCC than in control cells (**p<0.01 and ***p<0.001). B: Control (HEK 293) and ccRCC (Caki2 and KJ29) cells were cultured for 24 h with/without the autophagy inhibitor desmethylclomipramine (DCMI). DCMI strongly reduced cell proliferation in Caki2 and KJ29 cells compared with untreated cells (**p<0.01 and ***p<0.001). In HEK293 cells, DCMI reduced the cell number only at 10 μM (***p<0.001). C: Caki2 and KJ29 cells were cultured for 48 h in serum-free medium with or without DCMI using Transwell permeable supports coated with Matrigel. Cell invasion was inhibited by DCMI treatment (***p<0.001). D: The expression of E-cadherin and vimentin in Caki2 and KJ29 cells treated with/without DCMI were analyzed by western blotting. The inhibition of autophagy by DCMI increased the levels of E-cadherin and reduced those of vimentin (*p<0.05 and **p<0.01). Values are the mean±standard deviation and the statistical significance was calculated from at least three independent experiments.*

$p<0.05$ were considered statistically significant. *Results:* Western blot analysis performed in control and ccRCC cells cultured in basal conditions (DMEM/F12 10% FBS) showed that the levels of autophagic marker LC3II were higher in ccRCC (Caki1, Cak2 and KJ29) cells than in control (4/5 and HEK) cells (Figure 1A). Therefore, autophagy appeared to promote and sustain cell growth and invasion in these cell models for ccRCC. To test this hypothesis, cell proliferation and invasion assays were carried out in control and ccRCC cells treated with different doses of the autophagy inhibitor DCMI. Treatment with DCMI reduced cell proliferation, especially in Caki-2 and KJ29 ccRCC cells, while in control cells, this compound affected cell growth only at the highest concentration (Figure 1B). Moreover, the inhibition of autophagy by DCMI strongly prevented invasion in Caki2 and KJ29 cells compared with those cultured without DCMI (Figure 1C). Consistent with this, the expression of the epithelial marker E-cadherin was greater while the level of the mesenchymal protein vimentin was lower in both Caki2 and KJ29 cells treated with 5 μM DCMI compared with untreated cells (Figure 1D). These data indicate that the inhibition of autophagy blocks epithelial–mesenchymal transition in different ccRCC cell lines. *Conclusion:* Our findings suggest that autophagy promotes cell proliferation, invasion and epithelial–mesenchymal transition in ccRCC cells. Therefore, these data support the assumption that autophagy may affect tumor progression in kidney cancer. Since the inactivation of autophagy after DCMI treatment leads to the inhibition of cell growth and invasion, the use of this compound could be a promising option for the treatment of metastatic kidney carcinoma.

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13
UPDATE ON THE TRANSPERINEAL IMPLANTATION OF FIDUCIAL MARKERS FOR IMAGE GUIDED PROSTATE RADIOTHERAPY

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Background: The prostate gland is subject to frequent displacements that can lead to the target being missed in external beam prostate cancer radiation treatments; therefore, various positioning control methods have been developed. The transrectal implantation of intra-prostatic fiducial markers to enable accurate targeting of the prostate before and during radiation delivery (image-guided radiotherapy, IGRT) is widely used. This procedure places patients at risk for complications such as infections and rectal bleeding (1, 2). We report an update on our experience in implantation of prostate fiducial markers by a transperineal approach. *Patients and Methods:* We retrospectively reviewed the features and outcomes of 133 consecutive patients subjected to ultrasound-guided implantation of prostate fiducial markers through a transperineal approach for prostate IGRT between September 2011 and March 2022. The median age of the 133 patients was 76 (range=53-84) years. A transurethral prostatic resection for obstructive benign prostatic hypertrophy had been undergone by 27 (20.3%) patients prior to fiducial implantation. Fifty-five (41.3%) patients were on oral antiplatelet or anticoagulant therapy. Twenty patients of this group (36.4%) stopped these medications, 32 (58.2%) patients replaced oral therapy with low molecular weight heparin 7-10 days before the implant, and 3 (5.4%) patients did not disrupt oral antiplatelet therapy, according to individual cardiovascular risk. After local anesthesia performed by subcutaneous and transperineal periprostatic Mepivacaine injection, three markers were inserted into the prostate gland through the perineum using transrectal ultrasound guidance in a sterile field. Antibiotic prophylaxis was not used. In 128 (96.2%) patients, three gold seed markers (1.2×3 mm or 1×5 mm) for tumor kV/mV X-rays or cone-beam computed tomography localization were implanted, and three Beacon® transponders (1.3×8.7 mm) were used in five (3.8%) patients for tumor electromagnetic localization and tracking through a Calypso® System (Varian Medical Systems, Pablo Alto, CA, USA). *Results:* In two patients, two episodes of self-limiting urinary bleeding occurred immediately after the procedure. No other complication was recorded. At the evaluation before discharge, all patients reported no pain or dysuria. No complications, such as urinary obstruction or infection, hematospermia, or rectal bleeding were reported in the following days. No marker loss or migration was reported.

Discussion and Conclusion: IGRT with intra-prostatic markers can cause serious complications if the insertion of the fiducials is done through the rectum, as is usually the case. It can lead to a rate of urinary infection of 7.7% and a total of 2.8% of patients requiring hospital admission for infective complication despite antibiotic prophylaxis (1). Rates of 4-9.1% of rectal bleeding, 18.5% of hematospermia and 3.8-15% of hematuria are reported (2). In our series, only two patients (1.5%) experienced a single episode of self-limiting hematuria after gold marker implantation and no worsening of baseline urinary obstruction symptoms was recorded. The larger current series confirm our previous experience (3) showing that a transperineal approach for prostate implantation of fiducial markers is safe and should be preferred to limit patient morbidity and to avoid excessive use of antibiotics, thus reducing the risk of developing antibiotic-resistant bacteria. In our series, previous transurethral prostatic resection did not increase the risk of seed loss.

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14

MULTIPARAMETRIC MRI IN DIFFERENTIATING BETWEEN MUSCLE-INVASIVE AND NON-MUSCLE-INVASIVE URINARY BLADDER CANCER WITH VESICAL IMAGING REPORTING AND DATA SYSTEM (VI-RADS) APPLICATION: OUR INITIAL EXPERIENCE

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Aim: Our goal was to describe initial experience in our Center in using multi-parametric magnetic resonance imaging (mpMRI) to differentiate muscle-invasive (MIBC) from non-muscle-invasive bladder cancer (NMIBC). Patients and Methods: Patients with finding of >15 mm suspicious bladder cancer at ultrasound, computed tomography scan or flexible cystoscopy underwent mpMRI before tumor resection. We used a five-point VI-RADS score, derived using T2-weighted MRI, diffusion-weighted imaging, and dynamic contrast enhancement. MRI was 1.5 T. Images were analyzed by a dedicated MRI radiologist with no previous experience in bladder MRI, and all transurethral resections of bladder were performed by expert urologists. Accuracy was determined using histopathology as the reference standard. *Results:* A total of 70 tumors were analyzed, both primary and recurrent. Overall accuracy of the complete mpMRI protocol was 88% in differentiating NMIBC from MIBC. Better accuracy was achieved for >25 mm (93%) and lateral wall sided (91%) lesions, while a lower rate was recorded for domed tumors (85%). Hematuria, cytology, focality and patient features did not affect results. No differences were recorded for histological variants. *Conclusion:* mpMRI is considered effective for determination of muscle invasion in cases of urinary bladder cancer, in our initial experience. The VI-RADS scoring system represents an easy-to-learn tool. An increasing experience and better instrumentation (for example use of 3 T-MRI) can further improve our preliminary results.

15

MULTIPARAMETRIC MRI OF THE BLADDER AS A PREDICTIVE FACTOR OF HISTOPATHOLOGY AT REPEAT TUR: COULD IT HAVE A ROLE?

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Aim: We present our experience on the use of multi-parametric magnetic resonance imaging (mpMRI) for bladder cancer in the setting of repeated transurethral resection (reTUR) to predict absence of residual tumor (T0), persistence or progression at second resection. *Materials and Methods:* Patients with indication at reTUR following European Association of Urology guidelines [after incomplete initial transurethral resection of bladder (TURB), or in case of doubt about completeness of a TURB; absence of detrusor muscle in the specimen after initial resection, with the exception of Ta low-grade/grade 1 tumors and primary carcinoma *in situ*; T1 tumors] underwent a bladder MRI

before second resection. Results were classified as no evidence of residual tumor, evidence of residual tumor or suspected progression (lesions classified as VIRADS 4 or 5, according to standard VI-RADS score, derived using T2-weighted MRI, diffusion-weighted imaging, and dynamic contrast enhancement). MRI was 1.5 T. Images were analyzed by a dedicated MRI radiologist. Accuracy was determined using histopathology as the reference standard. *Results:* A total of 25 MRI evaluations were performed: 18 were classified as no residual tumor, five as residual tumor and two as suspected progression. Concordance with histopathology was 88%. Only in three cases did MRI not correctly predict the results of reTUR: in two cases MRI was classified as no residual tumors but histopathology found persistence of disease (of high grade), and the remaining case was classified as residual tumor but reTUR was negative. All three cases were intraoperatively macroscopically negative and primary cancers were on the posterior wall. *Conclusion:* mpMRI is considered effective for prediction of histopathology at reTUR. Better instrumentation (3T-MRI), increasing experience and integration of modern predictive models can further improve our preliminary results, even including accurate cost analysis.

16
THE ROLE OF THREE-DIMENSIONAL VIRTUAL MODELS (3DVMS) IN PARTIAL NEPHRECTOMY FOR HIGHLY COMPLEX RENAL TUMORS

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Background: New technologies are leading to an era of precision surgery. The development of augmented reality in three-dimensional virtual models (3DVMs) has been the key to improving the spatial understanding of bidimensional images (*e.g.,* computed tomography and magnetic resonance imaging). The aim of this study was to evaluate the usefulness of 3DVMs in the intraoperative management of highly complex renal masses during minimally invasive partial nephrectomy. *Materials and Methods:* We prospectively enrolled patients diagnosed with organ-confined unilateral complex renal masses (with PADUA score >10) for treatment with minimally-invasive (laparoscopic or robot-assisted) partial nephrectomy between August 2017 and August 2021. 3DVMs were used as a tool both for preoperative strategy planning and intraoperatively, when needed. The control group retrospectively included all patients burdened with highly complex renal masses surgically removed without the use of 3DVMs. Data collected before, during and after surgery were recorded, including serum creatinine and glomerular filtration rate (eGFR). Specific multivariable logistic regression models were used to predict the Margins Ischemia and Complications (MIC) achievement. *Results:* A total of 222 patients were recruited (79 in the 3DVM group, 143 in the control group). Postoperative eGFR values were significantly lower in the 3DVM group (p=0.03). Data showed the postoperative eGFR value for the 3DVM group was significantly low (p=0.03). Overall, MIC was achieved in 65.8% and 55.2% for the 3DVM group and control group, respectively). Nonetheless, the control group recorded a higher rate (p=0.03) of major post-surgical complications (Clavien–Dindo grade >3. Moreover, due to the ability of 3DVMs to independently predict the success of the procedure (odds ratio=2.7, p=0.001), a significantly higher proportion of patients in the 3DVM group achieved MIC (p=0.01). *Conclusion:* 3DVMs are increasingly becoming an essential and useful tool for planning a tailored surgical approach in cases of surgically complex renal masses. They can be used in different ways, matching the surgeon's needs from the planning phase to pedicle management, tumor resection and reconstruction phase, leading to maximum safety and efficacy outcomes.

18
COMBINATION TARGETED AND RANDOM SAMPLING *VERSUS* TARGET-ONLY SAMPLING IN MRI-GUIDED FUSION PROSTATE BIOPSY: ANALYSIS OF PROSTATE CANCER GRADING CONCORDANCE WITH SURGICAL HISTOLOGY

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Background: Ultrasound-guided biopsy (SB) is the gold standard in prostate cancer (PCa) diagnosis. In recent decades, magnetic resonance imaging-guided biopsy (MRI-B) has been employed as an alternative to SB, with PCa detection rates that reach up to 70 % (1). In particular, MRI-

B was shown to be superior to SB in terms of detection of clinically significant PCa (2). Fusion biopsy (FB) is one of three models of MRI-B and represents the most widely used technique on an outpatient basis with limited costs. It is unclear whether MRI-B should be performed with target samplings alone or in combination with random samplings. To settle this issue, some authors evaluated the concordance of PCa Gleason grade (GG) in patients undergoing radical prostatectomy (RP) and previously subjected to MRI-B (2, 3). Similarly, the aim of this study was to define the best approach to obtaining the greatest GG concordance between MRI-B and RP, by targeted samplings alone or in combination with random ones. *Materials and Methods:* From March 2016 until July 2021, 103 patients were enrolled consecutively. All patients received a PCa diagnosis after trans-rectal FB (Toshiba Aplio 500 Smart Fusion System). Each procedure provided the combination of target and random samplings. Then, they underwent laparoscopic or robot-assisted RP. PCa grading was defined according to the 2014 classification system. We also discriminated clinically significant PCa (GG≥2) and clinically insignificant PCa (GG<2). The first aim of the study was to detect concordance of GG results between FB and RP obtained after target sampling alone, after random sampling alone and after combination samplings. Qualitative data were tested with the chi-square test. Statistical significance was considered at $p<0.05$. *Results:* The median age of patients at RP was 66.2 (range=47-75) years. The median PSA was 8.02 (range=2.04-46) ng/ml with PSA density of 0.17 (range=0.02-1.12). The median prostate volume was 58.8 (range=16-183) ml with a median number of biopsy samplings per patient of 14.4 (range=8-19). All baseline characteristics of the population are described in Table I. Concordance of PCa GG between RP and FB was greater with the combination of targeted and random samplings (68/103, 66%) than with random sampling alone (54/103, 52%, $p=0.047$) or with targeted sampling alone (58/103, 56%, $p=0.15$). We also observed no statistical differences ($p=0.12$) in terms of detection rate of clinically significant PCa after RP (83.5%) or FB (combination approach: 74.7%), as described in Table II. Conversely, there was statistical relevance when RP was compared with targeted samplings alone (67%, $p=0.0061$) and with random sampling alone (56.3%, $p<0.001$). Discussion: It is unclear whether MRI-B should be performed with targeted sampling alone or in combination with random sampling. Some authors came to the same conclusion: A combination approach obtains the greatest PCa GG concordance. Similarly, our study showed highest concordance using the combination approach. Moreover, we did not find a statistical difference for detection of clinically significant PCa comparing RP and combination approach FB. *Conclusion:* Combination approach FB showed the best PCa GG concordance with RP although there was no statistical difference compared with targeted sampling alone. These findings suggest that the combination approach FB is the most accurate method in PCa diagnosis.

Table I. *Baseline characteristics of study population.*

	Overall (n=103)
Median age at RP (years)	66.2 (47-75)
Median PSA value (ng/ml)	8.02 (2.04-46)
PSA density	0.17 (0.02-1.12)
Median prostate volume (ml)	58.8 (16-183)
Median biopsy samplings (n)	14.4 (8-19)
FB (target + random) grade group, n (%)	
GG1	26 (25.2%)
GG2	46 (44.7%)
GG3	17 (16.5%)
GG4	10 (9.7%)
GG5	4 (3.9%)
RP grade group	
GG1	17 (16.5%)
GG2	47 (45.6%)
GG3	23 (22.3%)
GG4	8 (7.8%)
GG5	8 (7.8%)

PSA: Prostate-specific antigen; RP: radical prostatectomy.

Table II. *Comparison of the rate of detection of clinically significant prostate cancer (csPCa) and Gleason grade group concordance between radical prostatectomy (RP) and random, target and combination fusion biopsy (FB).*

	csPCa detection rate, n (%)			Concordance, n (%)	*p*-Value
	csPCa	cisPCa/neg	*p*-Value		
RP	86/103 (83.5%)	17/103 (16.5%)			
Target FB	69/103 (67%)	34/103 (33%)	0.0061	58/103 (56%)	
Random FB	58/103 (56.3%)	45/103 (43.7%)	<0.001	54/103 (52%)	0.15
Combination FB (target + random)	77/103 (74.7%)	26/103 (25.3%)	0.12	68/103 (66%)	0.047

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19
TARGET PROSTATE BIOPSY ALONE *VERSUS* TARGET PLUS STANDARD BIOPSY: PROSPECTIVE RCT IN BIOPSY-NAIVE PATIENTS

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Background: The aim of this study was to compare the detection rate of clinically significant prostate cancer (PCa) in biopsy-naïve patients with positive mpMRI undergoing FB alone (group A) compared with those undergoing FB with ultrasound-guided biopsy (SB) (group B) for the incidence of complications, overall detection of PCa and biopsy results with the final pathological findings after robotic prostatectomy (RARP). *Materials and Methods:* A two-arm (1:1) parallel non-inferiority randomized control trial took place from 4/2019 to 10/2021. Eligible participants were aged <75 years, naïve for biopsy, with serum prostate-specific antigen <15 ng/ml and positive multi-parametric magnetic resonance imaging (mpMRI) (Pi-RADS lesion v.2 >3). FB was performed using a BioJet fusion system; in group B, SB was performed according to Rodriguez-Covarrubias. RARP with total anatomical reconstruction was carried out when indicated. Detection of PCa and csPCA (Gleason score >7) were assessed. Post-biopsy complications were recorded according to Clavien–Dindo. The concordance between the pathological findings of biopsy and RARP was assessed. Fisher's exact test and Mann–Whitney test were applied; Logistic principal component analysis (LogPCA) and Pearson's correlation, in terms of correlation funnel plot, were performed to explore the data in a multivariate manner. *Results:* Overall, 201 and 193 patients were enrolled in groups A and B, respectively. PCa and clinically significant PCa were detected at 63.7% and 60.2% *versus* 71.0% and 60.6% in groups A and B (p=0.12 and p=0.93), respectively. The type of biopsy approach did not influence nerve-sparing or positive surgical margins during RARP (p=0.89 and p=0.67, respectively), nor the rate of significant improvement (12.1% *versus* 23.1% in groups A and B, respectively; p=0.12). The LogPCA model showed no distinction between the two cohorts. In group B, lesion diameter <10 mm was the only predictor of positive SB only for PCa (p=0.04). Especially in this context, the addition of ipsilateral SB was useful (increasing detection of PCa by 3%). There were no differences in terms of complications. *Conclusion:* In biopsy-naïve patients, the FB approach alone was not inferior to FB+SB in detecting PCa or csPCa. The addition of sampling in the grey area homolaterally to the mpMRI index lesion improved the detection rate of the FB-only approach to almost the level of the combined approach. The omission of SB did not affect post-surgical outcomes in terms of nerve sparing, positive surgical margins, and upgrading/downgrading approach.

20
THE APLIO I700 ULTRASOUND CANON MEDICAL SYSTEM® IN PROSTATE FUSION BIOPSY: EASY TO LEARN, FAST TO RUN

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Background/Aim: Our Division of Urology has adopted the Aplio i700 Canon Medical System® because it was the ultrasound machine available at our hospital radiology service. We evaluated the efficiency, detection rate and reproducibility of the Aplio i700 Canon Medical System® with dedicated software in prostate fusion biopsy. *Materials and Methods:* A retrospective observational study was conducted between October 2019 and August 2021 on freehand and elastic fusion prostatic biopsies performed transrectally with an Aplio i700 Canon Medical System®. Through data from our prospectively collected database, we compared the experience of four surgeons divided into two groups: Group 1 consisted of two attending physicians with experience of over 50 fusion biopsies with the elastic method; group 2 consisted of two residents with good capacity in transrectal ultrasound and standard biopsies but naive for the elastic fusion method biopsy. Baseline patient characteristics (age, prostate-specific antigen, prostatic volume, digital rectal examination, PIRADS and volume lesion at the magnetic resonance imaging), number of samples and postoperative parameters (histology, pain, and complications) were evaluated in the two groups. The overall rate of detection and detection stratified for PIRADS ranges, for prostate volume and for lesion dimension were compared. We evaluated the loading and the fusion of the image time in the two groups. *Results:* A total of 100 patients per group were considered. The two groups appeared homogeneous for the variables considered. The overall detection rate was 61%: 63% in group 1 and 59% in group 2. Splitting the lesions according to the PIRADS score, the detection rate in group 1 (34 lesions PIRADS 3, 41 PIRADS 4 and 25 PIRADS 5) was 32% for PIRADS 3, 70% for PIRADS 4, 92% for PIRADS 5 lesions; in group 2 (29 lesions PIRADS 3, 42 PIRADS 4, 29 PIRADS 5) it was 31% for PIRADS 3, 64% for PIRADS 4 and 79% for PIRADS 5 lesions. In prostates with volume ≤40 cc, detection was excellent in both groups (92% for group 1 and 88% for group 2). In lesions ≤6 mm, the detection rate was 45.5% in group 1 and 41% in group 2. In group 1, the loading time was 2 minutes, and the fusion time was 6 minutes and 45 seconds. In group 2, the loading time was 2 minutes and 20 seconds, and the fusion time was 7 minutes and 10 seconds. There were no differences in terms of complications and pain. *Conclusion:* The Aplio i700 Canon Medical System® allows high detection rates, comparable with other fusion systems, with extremely low loading and fusion times. The learning curve is fast, and results are independent of the operator's experience, especially for PIRADS 3 and 4.

21

PROSTATIC FUSION BIOPSY: EXPERIENCE AND RESULTS WITH APLIO I700 CANON MEDICAL SYSTEM®

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Background/Aim: The use of magnetic resonance imaging (MRI)-guided prostate biopsy is spreading throughout the urological world. The primary objective of this study was to evaluate the prostate cancer detection rate and its trend over time according to the experience of the fusion biopsy method with the help of Aplio I700 Canon Medical System®. A secondary objective was the evaluation of operating times and complications associated with the methodology. *Materials and Methods:* in this study, the data of the first 300 fusion biopsies performed with the elastic method with the aid of an Aplio I700 Canon Medical System® were considered. We considered the patient's age, prostate-specific antigen, digital rectal examination, previous execution of prostate biopsy, prostatic volume, size, number and PIRADS of the lesion. We divided patients into two groups in order to assess how the detection rate changed according to the increase in experience. Then we performed a multivariate logistic regression analysis to evaluate the interactions between the aforementioned variables and the detection rate. Finally, we analyzed the operating times and complications in the two groups. *Results:* Overall, 300 patients were analyzed, first evaluated in their entirety, and then divided into two groups, the first consisting of the first 150 patients subjected to fusion biopsy and the second by the remaining 150 patients subjected to fusion biopsy. The two groups were homogeneous for patient age, prostate-specific antigen, digital rectal examination, prostate volume, size, number and PIRADS of the lesion and number of lesions in the anterior region. The detection rate overall for prostate cancer was 57.3%. No differences in detection rates were detected between the two groups. As the operator's experience of the maneuver increased, the chance of finding a tumor increased by 0.002. Only the PIRADS score was found to be related to the rate of prostate cancer detection ($p<0.001$). The operating times significantly decreased from a total of 14 minutes and 30 seconds to a total of 9 minutes in the second group. There were 13 complications in the study period, with a stable trend

over time. *Conclusion:* The approach to fusion biopsy with Aplio I700 Canon Medical System® was shown to be feasible, safe and effective, even in the early implementation. With a significantly reduced operating time over the years, the few complications and competitive detection rate have remained stable over time.

22
GENITAL-SPARING RADICAL CYSTECTOMY IN WOMEN: IS IT REALLY WORTH IT? OUR EXPERIENCE

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Background/Aim: The aim of the study was to evaluate genital organ-sparing radical cystectomy surgery in female patients both from the point of view of oncological and functional (urinary and sexual) results. The operations were performed at a single high-volume center for the treatment of muscle-invasive and non-muscle-invasive bladder cancer. *Materials and Methods:* Between January 2015 and January 2018, eight female patients underwent radical cystectomy and bilateral pelvic lymphadenectomy with preservation of genital organs (the entire vagina, uterus, fallopian tubes, and ovaries) and orthotopic urinary neobladder (Padua Neobladder). Inclusion criteria were recurrent T1G3 tumors; refractory tumors after Bacillus Calmette-Guerin therapy without associated carcinoma *in situ*; T2 or T3a tumors entirely resected at endoscopic transurethral resection of the bladder and not involving urethra/bladder trigone. Exclusion criteria were: T3b or higher bladder cancer, associated carcinoma *in situ* and involvement of urethra or bladder trigone. Oncological and histopathological outcomes (overall survival, recurrence free survival), urinary outcomes (day and night incontinence, intermittent catheterization use, Sandvik score) and sexual outcomes (Female Sexual Function Index 19) were considered. The average follow-up time was 46 months. *Results:* Regarding oncological results, histopathological examination reported urothelial carcinoma in seven patients of whom 3/8 patients (37.5%) had low grade T1 stage, 2/8 patients (25%) had high grade T2 stage and finally 2/8 patients (25%) had high-grade T3 stage. No patient developed local or metastatic relapse (recurrence-free survival 100%); overall survival was 100%. Out of the eight patients, continence was preserved during both day and night in seven (87.5%), and only one patient (12.5%) complained of urinary leakage during the night. The Sandvik score showed complete continence in five patients (62.5%); a mild degree of incontinence in two patients without using devices for incontinence (25%); and moderate degree of incontinence in one patient (12.5%). The Female Sexual Function Index Questionnaire (FSFI) administered at 1 year from the surgery showed sexual desire in all patients (100%); subjective arousal, achievement of orgasm, sexual satisfaction in 7/8 patients (87.5%); and sufficient lubrication in 6/8 patients (75%). Only one patient (12.5%) complained of dyspareunia during sexual intercourse. *Conclusion:* Our study demonstrates that genital-sparing radical cystectomy is a safe surgery in terms of oncological results, and, above all, is beneficial in terms of urinary and sexual function, quality of life, psychological and emotional health of the patients. However, it is a treatment reserved for selected female patients strongly motivated to preserve fertility and sexual function, and who are informed about the benefits and complications of such a procedure.

23
NUTRITIONAL AND INFLAMMATORY STATUS AS PREDICTIVE BIOMARKERS IN OLIGORECURRENT PCA (RADIOSA TRIAL) – AN UPDATE

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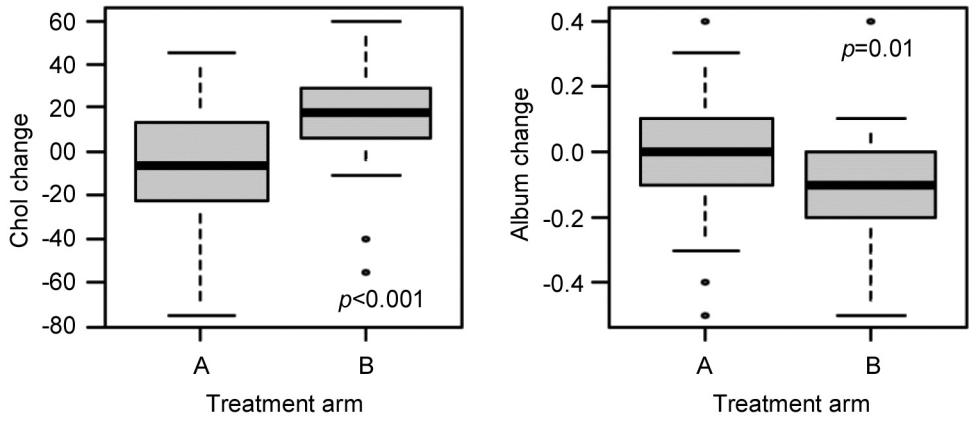

Figure 1. *Box plots showing changes in cholesterol (left) and albumin (right) at 6 months in the cohort of patients stratified according to treatment without (arm A) and with androgen deprivation therapy.*

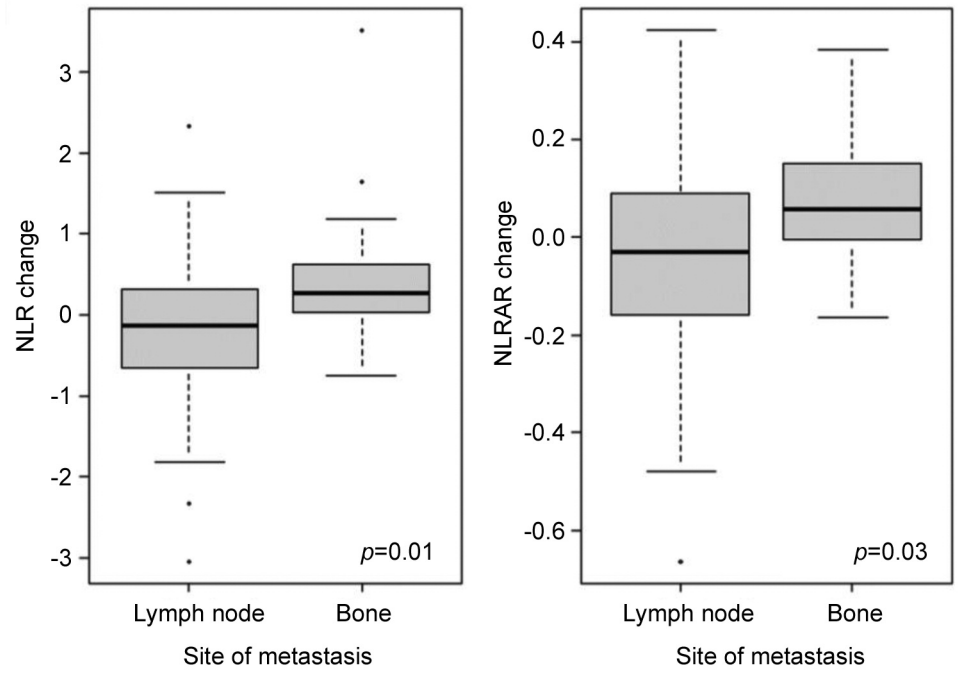

Figure 2. *Box plots showing changes in neutrophil-lymphocyte ratio (NLR) (left) and the NLR-albumin ratio (NLRAR) (right) at 6 months in the cohort of patients stratified according to the site of metastases.*

Aim: Stereotactic body radiotherapy (SBRT) represents a low-toxicity treatment for prostate cancer localizations that may allow delaying the start of androgen deprivation therapy (ADT) in the oligometastatic setting. In the RADIOSA phase II randomized clinical trial (NCT03940235), the biology task entails the identification of predictive and prognostic biomarkers in the context of oligorecurrent, castration-sensitive prostate cancer in order to distinguish polymetastatic from oligometastatic disease subsequently laying the groundwork for personalized treatments for those who may really benefit from metastasis-directed therapies. *Materials and Methods:* According to the administration of ADT and the location of the metastases, patients who matched the inclusion criteria were divided into two treatment groups: SBRT to all lesions: arm B with ADT *versus* arm A without. Serum-derived biomarkers, namely albumin, neutrophil and lymphocyte count, and total cholesterol, were measured at baseline, and at 3 and 6 months after radiotherapy. The prognostic nutritional index, an immune and nutrition-based prognostic score, and the controlling nutritional status

(CONUT) score, a scoring system for evaluating patient's nutritional status, were calculated in accordance with the body of available literature (1, 2). As inflammatory indicators, neutrophil-lymphocyte ratio (NLR) and the NLR-albumin ratio (NLRAR) were assessed. Changes in these parameters between baseline and 6-month timepoint were evaluated both in absolute and relative values. By grouping patients according to ADT administration (arm B *versus* A, yes *versus* no) and site of metastases (bone *versus* lymph node), significant differences in the trend of these parameters between the groups were assessed using the non-parametric Wilcoxon rank-sum test. *Results:* The current analysis comprised 62 patients (33 in arm A and 29 in arm B. When patients were stratified by ADT administration, the absolute changes in albumin and cholesterol levels (Figure 1) were significantly different according to the two groups (p=0.01 and p<0.001, respectively). The absolute changes in inflammatory scores (NLR and NLRAR) were also different when patients were stratified according to the site of metastases (p=0.01 and p=0.03) (Figure 2). As bone localizations are linked to a lower response rate than lymph node-only sites, this outcome is consistent with the well-known fact that a higher inflammatory status results in a worse prognosis. *Conclusion:* The addition of ADT appears to have an impact on changes in cholesterol and albumin, two markers of a deteriorating quality of life. Additionally, it appears that the site of metastases and inflammatory status are associated. The examined parameters seem to represent intriguing candidates for possible use in clinical decision-making to group patients according to whether they would benefit more from less aggressive therapies. The validation of these potential biomarkers requires further evaluations, correlations with clinical outcomes and extended follow-up data.

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24
ACTIVE SURVEILLANCE IN FAVORABLE INTERMEDIATE RISK PROSTATE CANCER: A 15-YEARS' SINGLE CENTER EXPERIENCE

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Background/Aim: Active surveillance (AS) has been used in selected favorable intermediate risk (FIR) prostate cancer (PCa) patients, but it is still undervalued due to concerns about its oncologic safety. International guidelines formalized the inclusion of FIR patients in AS protocols as an option. The aim of our study was to evaluate the outcomes of selected patients with FIR features enrolled as off-protocol cases over the last 15 years. *Patients and Methods*: We analyzed the prospectively collected data of 75 patients with FIR-PCa enrolled as off-protocol cases within AS studies between 2005 and 2020. Patients were classified as FIR as a consequence of prostate specific antigen (PSA) 10-20 ng/ml or Gleason Grade (GG) Group £2, with <50% positive cores. Follow-up consisted of PSA measurements every 3 months. Physical examination including digital rectal exam was planned every 6 months, and reclassification biopsy at 12 months and then every 2 years. Multiparametric Magnetic Resonance Imaging (mpMRI) was introduced since 2016 and performed at 12 months and according to clinical indication thereafter. Discontinuation rate and rate of progression to GG≥3 as well as to metastatic disease were analyzed. Fisher's exact test was used to compare categorical variables. *Results:* Median (interquartile range, IQR) age was 66 (IQR=61-74) years. Median PSA was 11.48 ng/ml (IQR=10.48-14.47 ng/ml). Median PSA density was 0.21 ng/ml/cm^3 (IQR=0.13-0.30 ng/ml/cm^3). Patients had GG 1 cancer and PSA >10 and <20 ng/ml in 62/75 (82%) of cases (Group A) and GG 2 and PSA <20 ng/ml in 13/75 (18%) of cases (Group B). Median follow-up was 39 months (IQR=24-73). Median time in AS was 30 months (IQR=12-49). Overall, 41% (31/75) of patients did not undergo active treatment (AT), with a median duration time without AT of

31 months, including patients who switched to watchful waiting (WW). The rate of withdrawal from AS was 72% (54/75): 59% in Group A and 77% in Group B. Twenty/54 (37%) underwent AT (median time to AT: 11 months), 10/54 (18%) carried on in WW and 24/54 (44%) of patients followed an AS program in other centers (median follow-up: 31 months). Progression to GG≥3 occurred in 10/75 (13%) patients (median time: 36 months), with no difference between the two groups (p=0.3). No progression to metastatic disease was reported. Finally, 1 non-PCa-related death was recorded. *Conclusion:* We did not record any excess of unfavorable pathology at follow-up biopsy among patients with FIR PCa undergoing AS. Pathology progression occurred in just 13% of all cases within a median time of 36 months since diagnosis. Total numbers and numbers of GG2 cases are limited as well as follow-up duration. We will further report the follow-up and the outcomes of the prospective cohort recently started (INT-FIR protocol) to validate these data. Nonetheless, our small series does not seem to exclude AS as a possible option in selected patients with FIR PCa.

25
STEREOTACTIC BODY RADIOTHERAPY FOR BONE OLIGORECURRENT CASTRATION SENSITIVE PROSTATE CANCER DETECTED BY PSMA-PET

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Aim: The aim of the current study was to evaluate the outcomes of patients affected by oligometastatic prostate cancer (PC) with bone metastases detected by prostate specific membrane antigen – positron emission tomography (PSMA-PET) and treated with stereotactic body radiotherapy (SBRT). *Patients and Methods*: From 2017 to 2021, 56 bone metastases in 40 patients were treated with SBRT. All patients were affected by oligorecurrent PC diagnosed by PSMA-PET without ongoing androgen deprivation therapy (ADT). Median disease-free interval from the primary treatment was 39 months (2-244 months) and patients presented with median PSA of 0.60 ng/ml (0.16-15.2 ng/ml), with PSA doubling time (PSAdt) of 6.7 months (1.1-40.8 months). Most oligometastatic patients had a single lesion (70%), 22.5% presented with two lesions, 5% with three lesions, and 2.5% with four lesions. *Results:* The 56 lesions were divided as follows: 39 (69.7%) were non-spine metastases and 17 (30.3%) were spine-metastases. SBRT was delivered in 3-5 fractions with a median dose of 30 Gy (24-40 Gy); median EQD2 was 85 Gy. Median local control (LC) was 18 months (2-28 months), considering a median follow up of 22 months. One- and two-years LC were 96.3% and 93.9% respectively, with a disease progression-free survival (DPFS) of 45.3% at 1 year and 27.3% at 2 years. Median time of DPFS was 9 months (3-37 months). The median nadir PSA (nPSA) after the treatment was 0.9 ng/ml and twelve patients had a biochemical progression with no PSA drop after SBRT. At univariate analysis, factors which favorably impacted on DPFS were: lower number of lesions (p=0.003), longer disease-free interval (p=0.0003), lower PSA pre SBRT (p=0.0013) and nPSA after SBRT (p<0.0001). Also, ADT-free survival was significantly related to the same parameters: lower number of metastases (p=0.0001), longer time to oligometastases onset (p=0.009) and PSA values before and after SBRT (p<0.0001 and p=0.004, respectively). At multivariate analysis, the correlation was maintained between number of metastases treated and ADT-free survival (p=0.04) and between nPSA after SBRT and DPFS (p=0.03). After progression, a further course of SBRT in association with ADT was proposed in 7 patients; instead, 11 patients became polymetastatic, and thus received ADT alone. Median ADT-free survival was 13.5 months (2-45 months) with 1- and 2-years ADT-free survival of 67.5% and 61.8%, respectively. *Conclusion:* PSMA-PET guided SBRT presented in our experience with excellent results as a way to postpone the start of ADT in the setting of bone oligorecurrent PC patients.

26
ACUTE AND LATE TOXICITY AND QUALITY OF LIFE REPORT OF THE FIRST 100 PATIENTS WITH PROSTATE CANCER TREATED WITH STEREOTACTIC BODY RADIOTHERAPY USING 1.5T MR-LINAC

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Aim: To assess preliminary acute and late toxicity of the first 100 patients treated with stereotactic body radiotherapy (SBRT) 1.5T MR-Linac for prostate cancer. *Patients and Methods*: This study enrolled and evaluated the outcome of the first 100 patients treated with MR-guided radiotherapy (MRgRT) with 1.5T MR-linac from October 2019 to December 2020. All the patients were registered in a prospective study (MR Linac n°XXXX). Before radiotherapy, an optional insertion of a rectal spacer was proposed to all patients; however, it was applied just in 37 patients. Androgen deprivation therapy was prescribed in 32 patients according to international guidelines. Toxicity was prospectively collected and evaluated according to Common Terminology Criteria for Adverse Events (CTCAE v5.0). Quality of life was assessed using IPSS, ICIQ-SF, IIEF-5, EORTC QLQ-C30, QLQ-PR25, and EPIC-26 questionnaires. *Results:* A total of 100 patients received the treatment: 34 with low risk, 29 with favorable intermediate-risk, 31 with unfavorable intermediate-risk, 2 with high risk, and 4 with a low-volume M1 disease. The median age was 71 years (range=52-84 years) and the median IPSS was 3 (range=0-7); 1.5T MR-guided daily adaptive SBRT was performed in 5 sessions for a median total dose of 35 Gy (35-36.25 Gy) on consecutive (n=75) or alternate days (n=25). Adaptive workflow consisted of: adapt to shape in 96% fractions and adapt to position in 4% treatment sessions. Median treatment duration was 40 min (range=33-83 min) and the median PTV volume was 105.8 cc (range=13.98-196.4 cc). The median follow-up was 12 months (range=3-20 months). Acute urinary and gastrointestinal toxicities consisted of five acute G2 genitourinary tract pain events and two cases of urethral stenosis requiring catheterization, and four cases of GI G2 events, such as rectal tenesmus or proctitis. All the G≥2 events occurred after an average time of 30 days from the end of RT. For late GU toxicities, we observed three G2 events consisting of urinary tract pain and one G3 event in a patient who received TURP 8 months after radiotherapy. G≥2 GI events were represented by three patients, including one patient who required argon laser procedure for radiation-induced proctitis. A transient decline in fatigue, fully regained after the first follow-up, was observed in the preliminary quality of life (QoL) assessment. All patients are currently alive with disease control, except for one patient with a diagnosis of M1-low volume disease that evolved into distant progression two months from the end of the RT. *Conclusion:* This preliminary study in a cohort of 100 patients demonstrates that SBRT with 1.5TMR-linac is feasible and safe with good results with regard to acute and late toxicity and has minimal effect on QoL. More mature data are warranted.

27

A TOXICITY COMPARISON OF STEREOTACTIC BODY RADIOTHERAPY IN LOCALIZED PROSTATE CANCER: 1.5T MR-GUIDED RT *VERSUS* LINAC-BASED VMAT

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Aim: to evaluate acute toxicity of stereotactic body radiotherapy (SBRT) in patients with a diagnosis of prostate cancer (PCa), delivered by MR-guided radiotherapy (MRgRT) with 1.5T MR-linac *versus* Linac-based volumetric modulated arc (VMAT). *Patients and Methods*: A total of 137 patients with a diagnosis of low-to-intermediate risk class PCa received exclusive SBRT. We delivered 35 Gy in 5 fractions to the low-risk class and 36.25 Gy in 5 fractions to the intermediate risk class. All the patients treated with MRgRT were enrolled in an ongoing Ethical Committee (EC) approved trial (n° 23748), differently from patients treated with CBCT-IGRT linac-based SBRT, who were enrolled in an EC approved PCa SBRT phase II trial (n° SBRT PROG112CESC). The primary end-point was acute toxicity, evaluated according to Common Terminology Criteria for Adverse Events (CTCAE v5.0). International Prostatic Symptoms Score (IPSS) was also collected. An exclusion criterion was less than at least 6 months of follow-up for the acute toxicity end-point assessment. *Results:* We included 137 patients in this report; MRgRT was delivered in 57 (41.6%) and volumetric modulated arc (VMAT) with conventional Linac in 80. The median initial prostate specific antigen (PSA) level was 6.5 ng/ml (range=1-19 ng/ml). The median IPSS before and after SBRT was 3 (1-16) and 5 (1-18). Globally, acute toxicity occurred as follows: G1 in 32 (23.3%), G2 in 20 (14.5%), and G3 in 4 (2.8%). At the univariate analysis, there were no significant differences in term of acute G1 toxicity between MRgRT and Linac-based VMAT (23.75% *versus* 21%; p=n.s.), whereas G2 toxicity was significantly lower in the MRgRT group (4.5% *versus* 10%; p=0.032). Acute G2 gastrointestinal (GI) toxicity was reported in 7% and 7.5% of the MRgRT and Linac-based VMAT group (p=0.61), respectively, while acute G2 genitourinary (GU) toxicity was registered in 10.5% and 15% of the MRgRT and Linac-based VMAT group, respectively (p=0.004). Acute G3 toxicity was observed in 2 in the MRgRT group and 2 in the Linac-based VMAT group

(*p*=n.s.). *Conclusion:* Prostate SBRT is feasible and safe. Compared to Linac-based SBRT, in the MRgRT group we observed a lower incidence of grade 2 toxicity. In order to further confirm the preliminary data of this study, a longer follow-up and a larger population are warranted.

28
TOXICITY AND EFFICACY OF POSTOPERATIVE MODERATE HYPOFRACTIONATED RADIOTHERAPY IN A SERIES OF 304 PROSTATE ADENOCARCINOMA CASES

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Aim: Adjuvant radiotherapy (aRT) has been shown to reduce biochemical relapse in prostate cancer (PC); early salvage RT (esRT) has similar efficacy and is a better tolerated treatment compared to immediate RT after surgery. As a standard treatment, postoperative RT is delivered with conventional fractionation, but given the low α/β ratio of PC, hypofractionation may also be considered in this setting. End point of the study were toxicity, progression-free survival (PFS), overall survival (OS) and biochemical relapse-free survival (BRFS). *Patients and Methods*: A total of 304 PC patients treated at our hospital were retrospectively analyzed, and subdivided into: aRT (105 patients), esRT (77 patients), and salvage RT (sRT) (122 patients). Treatment doses were 66 Gy in the aRT cohort and 67.5 Gy in the sRT and esRT groups. All treatments were delivered in 30 daily fractions. *Results:* With a median follow up of 33 months, the 3-year PFS and BRFS were 85.2% and 82%, respectively. Eight patients died and only 2 deceased from PC progression. At the univariate analysis, factors unfavourably related to PFS were also risk factors for diagnosis (high Gleason Score and pT≥3), concurrent androgen deprivation therapy (ADT), and esRT. In fact, the esRT group had a significantly lower 3-year PFS compared to the aRT and sRT groups. At the multivariate analysis, Gleason Score, tumor stage at diagnosis, and ADT maintained the negative correlation with PFS. At relapse, main treatments were found to be equally spread between ADT and SBRT (43% each group), whereas an association of ADT with SBRT was only found in 14% of patients. Thirteen patients had grade 3 toxicity, due to incontinence in 10 (3.2%) patients and urgency in 3 (1%) cases. Most patients reported Grade 1-2 genitourinary toxicity: urgency (36%), frequency (12.1%), dysuria (23%), and acute urinary retention (11.9%), and the majority of patients presented with the same symptoms at baseline. SRT was significantly better tolerated than aRT and esRT: in fact, it had a lower incidence of any-grade GU toxicity compared with other groups. *Conclusion:* Moderate hypofractionation appears safe and is associated with similar oncological results compared to conventional fractionation. EsRT demonstrated similar results to adjuvant regimen, with better tolerance.

29
THE PROGNOSTIC VALUE OF THE SIZE AND SUB-SITE OF LOCAL FAILURE AT DCE-MRI BEFORE SALVAGE RADIOTHERAPY FOR PROSTATE CANCER

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Aim: To investigate predictors of biochemical failure after salvage radiotherapy (sRT) in the context of a presumed local failure at dynamic contrast-enhancement-magnetic resonance imaging (DCE-MRI) post radical prostatectomy (RP). *Materials and Methods:* All patients referred for sRT at our Institution with a biochemical failure after RP were consistently offered restaging with both positron emission tomography/computed tomography (PET/CT) and multiparametric MRI since January 2014. Those with a presumed local failure at DCE-MRI as well as no regional/distant disease at PET/CT (either choline and/or PSMA) were selected for the present study. Exclusion criteria were history of androgen deprivation (AD) before sRT and positive nodes at RP. All patients underwent 3T DCE-MRI without endorectal coil and the lesion(s) transferred to the planning CT after co-registration. sRT consisted of 73.5 Gy to the presumed local lesion and 66-69 Gy to the prostatic bed in 30 fxs. Pelvic nodes (PN) were irradiated with 54 Gy/30 fxs in selected patients. The endpoint of the study was the development of a biochemical failure after sRT defined as a 0.2 ng/ml prostate specific antigen (PSA) rise above the

nadir. Various covariates (age, pre-RP PSA, pT and pN stages at RP, margins status at RP, ISUP grade group, time from RP to sRT, PSA doubling time, PSA detectability after RP, PSA at sRT, the location, number and volume of the detected recurrence(s), AD use, PN coverage, EUA risk category) were investigated using univariate analysis (UVA) at the time to biochemical failure [biological no evidence of disease (bNED)- survival]. Covariates with a *p*-value <0.2 at UVA were analysed by a Cox proportional hazards regression analysis. *Results:* Up to June 2020, 146 patients satisfying all selection criteria were treated with sRT. Median (IQR) PSA at sRT was 0.60 ng/ml (0.38-1.05 ng/ml) and only 17 patients (11.6%) received AD along with sRT. A total of 168 local lesions were detected, 92 (54.8%), 40 (23.8%), and 36 (21.4%) at the vesicourethral anastomosis (VUA), bladder neck, and retrovesical space, respectively. At the median (IQR) follow-up of 48.1 months (31.3-60.6 months), 22 biochemical failures were observed for a 4-yr bNED survival of 84.4% (95%CI=77.9-90.9%). On UVA, bNED-survival after sRT was significantly more likely for patients with VUA-only lesions (VUA-only *vs*. others, HR=0.307, 95%CI=0.120-0.784, *p*=0.014) and with smaller lesions (for every cc, HR=1.071, 95%CI=1.025-1.119, *p*=0.002). These associations remained significant ($p<0.01$) on multivariate analysis as well. For patients with VUA-only disease or with lesions smaller than 0.5 cc, 4-yr bNED survival rates were 90.7% (95%CI=83.4-98.0%) and 90.6% (95%CI=83.9-97.3%), respectively. The 46 patients with both favorable features had a 4-yr bNED rate of 94.6% (95%CI=87.3-100%). *Conclusion:* These data support local restaging with DCE-MRI before sRT in the setting of a biochemical failure after RP. Patients with VUA-only and/or small volume lesions have an excellent outcome after dose-escalated sRT.

31
THE RELEVANCE OF RADIOMIC FEATURES IN PREDICTING PROSTATE CANCER PATHOLOGY OUTCOMES

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Background/Aim: Using radiomic and clinical features to predict prostate cancer (PCa) pathology can facilitate better treatment decisions and personalization. However, it is often

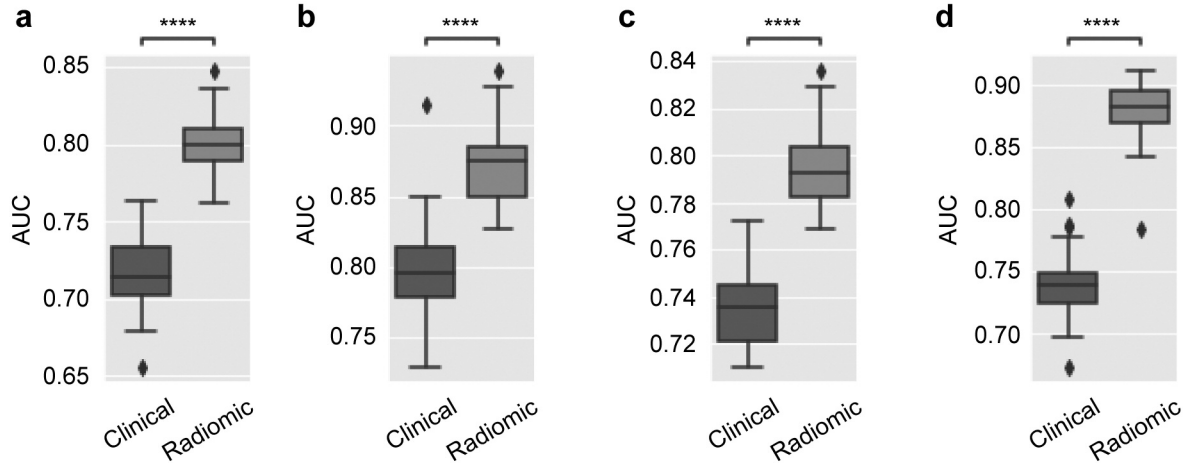

Figure 1. *Out-of-bag area under the curve values for the predictions of different outcomes over 32 repeated validation folds. (a) Surgical marginal status; (b) Lymph node status; (c) Tumor stage; (d) ISUP grade group.*

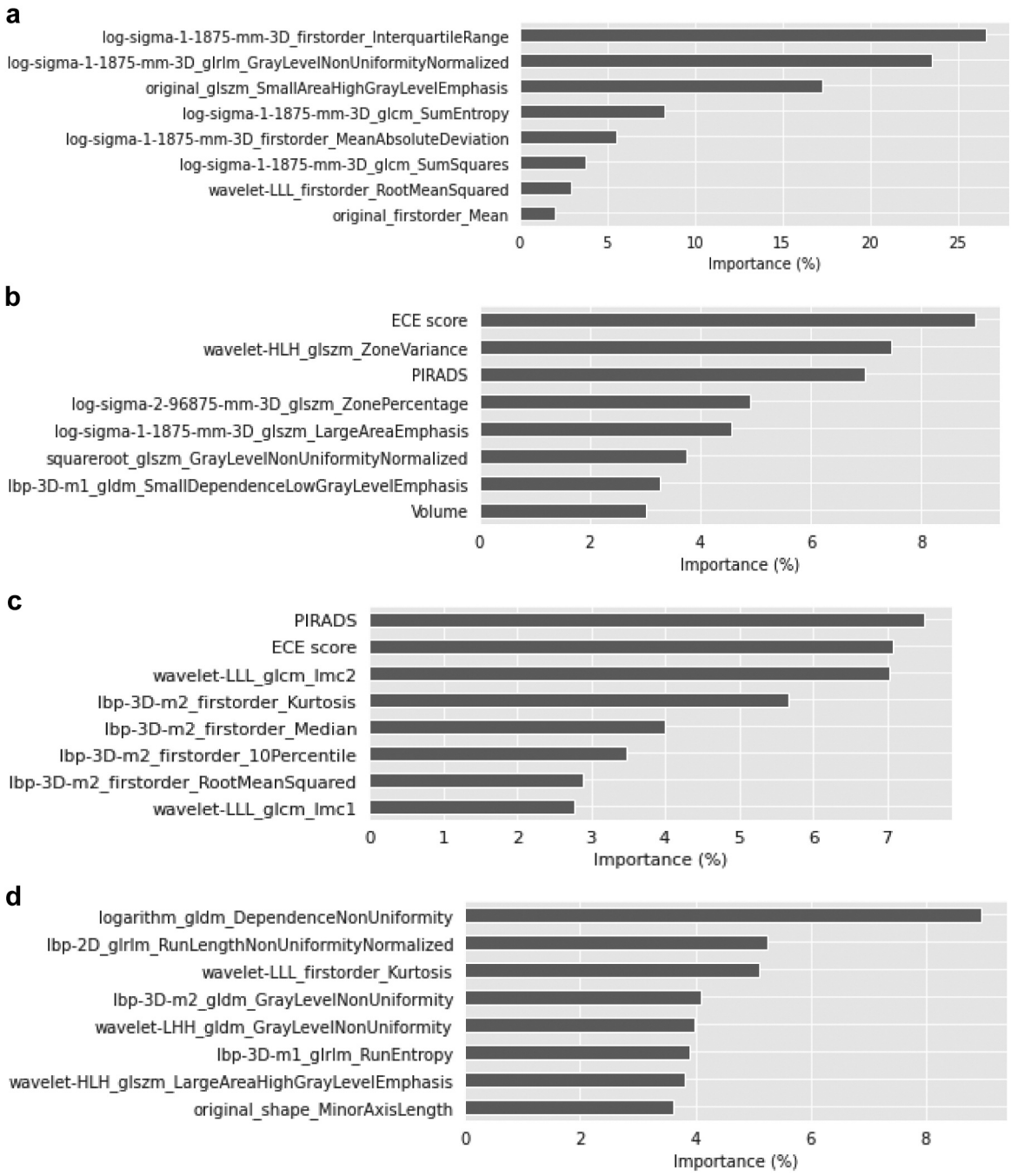

Figure 2. *The top eight features in terms of output value change when predicting different pathological outcomes. (a) Surgical marginal status; (b) Pathology-based lymph node status; (c) Pathology-based tumor stage; (d) Pathology-based ISUP grade group.*

unclear which radiomic features contribute and how they differ when modeling pathologic features. A radiomic signature was compared with prostatectomy as a confirmatory method in this study in order to predict PCa features. *Patients and Methods*: A representative subset of 100 patients were selected from a cohort of approximately 1,500 patients undergoing magnetic resonance imaging (MRI) and prostatectomy at our institution since 2015. The prostate of each patient was segmented from T2-weighted axial MRI images by an expert radiologist, and 1,810 radiomic features were extracted (PyRadiomics v3.0.1, AIM-Harvard). The radiomic feature set was reduced to 50 features using a

hierarchical clustering procedure based on absolute rank correlation. The feature with the highest absolute rank correlation with the target variable was selected in each cluster. Gradient-boosted decision-tree models were separately trained using clinical variables (age, prostate volume, initial prostate-specific antigen (iPSA), extraprostatic extension (EPE) score, Prostate Imaging-Reporting and Data System (PI-RADS) category, biopsy-based total Gleason score, International Society of Urological Pathology (ISUP) grade, and risk class) alone and in combination with the selected radiomic features to predict: surgical marginal status (R0 *vs*. R1), pathology-based lymph node status (pN0 *vs*. pN1), tumor stage (pT2 *vs*. pT3) and ISUP grade group (≤3 *vs*. ≥4), and validated with repeated 5-fold cross validation. Based on the mean prediction value change over validation folds, the mean feature importance in the clinical + radiomic feature models was assessed. *Results:* The validation AUC values (±95%CI) were 0.800 (±0.007) for surgical marginal status, 0.871 (±0.010) for pathological lymph nodes, 0.795 (±0.006) for pathological tumor stage, and 0.877 (±0.009) for ISUP grade group, respectively (Figure 1). The contributions of the top eight radiomic features in each model can be seen in Figure 2. Both EPE score and PI-RADS category had a great impact on the predictions in the pathological lymph node status and tumor stage models, whereas none of the clinical variables appeared in the top eight for predicting the surgical marginal status or pathology-based ISUP grade group. The most important radiomic features were Laplacian of Gaussian ("log") features for surgical marginal status, local binary pattern ("lbp") features for pathological tumor stage, and wavelet features for ISUP grade group. *Conclusion:* Radiomics can have a considerable impact on the prediction of pathological features of PCa. Moreover, radiomic and clinical features, particularly the radiological features of PI-RADS category and EPE score, seem to complement each other, with varying degrees of importance in different prediction scenarios. The important radiologic features may vary in different contexts and should not be judged on an absolute utility scale.

32
THREE-DIMENSIONAL VIRTUAL MODELS ASSISTANCE PREDICTS HIGHER RATES OF "SUCCESSFUL" MINIMALLY-INVASIVE PARTIAL NEPHRECTOMY

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Background/Aim: 3D virtual models (3DVMs) are nowadays under scrutiny to improve partial nephrectomy (PN) outcomes. Over the year, five different Trifecta definitions have been proposed to optimize the framing of "success" in the PN field (Table I). The aim of the study was to analyze whether the use of 3DVMs could impact the success rate of minimally-invasive PN, according to the currently available definitions of Trifecta. *Patients and Methods*: Two hundred and fifty patients with cT1-2N0M0 renal masses who were treated with minimally-invasive PN at our institution, were prospectively enrolled. Inclusion criteria were the availability of contrast-enhanced computed tomography (CT) from which a 3DVM was obtained, baseline and postoperative serum creatinine, and eGFR. These patients were then compared with a control group of 710 patients who underwent minimally-invasive PN with the same renal function assessments, but without 3DVMs. Trifecta rates were tabulated according to the currently available definitions, after stratification according to 3DVMs availability. Multivariable

Table I. *Current TRIFECTA definitions and their metrics.*

Authors	Oncologic	Complications	Renal function preservation
Definition (1)	NSM	CD ≤III	WIT <20 min
Definition (2)	NSM	Absence of complication up to 3 months after surgery	WIT <25 min
Definition (3)	NSM	Absence of urological complications	Post-op eGFR decrease <10% compared to the predicted post-op eGFR [predicted postop eGFR=pre-op eGFR × kidney tissue preserved (%)]
Definition (4)	NSM	CD ≤III	Decline of eGFR <30% from the baseline
Definition (5)	NSM	CD ≤II	No post-op AKI (defined according tothe RIFLE criteria)

NSM: Negative surgical margins; CD: Clavien-Dindo classification; WIT: Warm ischemia time; AKI: acute kidney injury.

logistic regression (MLR) models were used to predict the trifecta achievement according to the different trifecta definitions. *Results:* Among the definitions, Trifecta rates ranged between 70.8% to 97.4% in the 3DVM group *vs.* 56.8% to 92.8% in the control group. 3DVMs showed better postoperative outcomes in terms of ΔeGFR, postoperative complications, and major complications. At MLR, the use of 3DVMs independently predicted higher rates of successful PN across all the available definitions of Trifecta (OR=2.7, $p<0.001$; OR=2.0, $p=0.0008$; OR=2.8, $p=0.02$; OR=2.0, $p=0.003$). The main limitation is the lack of mid-term follow up functional assessment. *Conclusion:* There was large variability in the rates of Trifecta according to different definitions, but always in favor of those PNs assisted by 3DVMs. Their availability was found to be the constant predictive factor of successful PN, with a 2-fold higher probability of achieving Trifecta regardless of the different definitions available in literature and justifying their introduction in clinical practice.

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33
EARLY TOXICITY AND DIFFUSION-WEIGHTED MRI ASSESSMENT AFTER SINGLE-DOSE ABLATIVE RADIATION THERAPY FOR UNFAVORABLE PROSTATE CANCER

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Background/Aim: To investigate diffusion-weighted (DWI) magnetic resonance imaging (MRI) changes and early gastrointestinal (GI) and genitourinary (GU) side effects in patients with organ-confined unfavorable prostate cancer (PCa) following single-dose ablative radiation therapy (SDART). *Patients and Methods*: Ten patients included in the prospective clinical trial "ABRUPT" (NCT04831983) were treated with a single fraction of 24 Gy to the whole prostate with urethra sparing in association with androgen deprivation therapy (ADT) as per standard of care. Treatment was delivered on linac platform with a volumetric modulated arc therapy (VMAT) and a real-time organ-motion electromagnetic tracking system. Multiparametric MRI was performed before SDART (time 0), one-hour post-SDART (time 1), and 3-months after treatment (time 2). Acute toxicity was evaluated with Common Terminology Criteria for Adverse Events version 5 (CTCAE_v5) scale. IPSS score and quality of life (QoL) metrics assessed with EORTC questionnaires QLQ-PR25/-C30 were also measured. *Results:* Median age was 76 years (range=62-82 years). Median prostate volume was 35.4 cc (range=10-59 cc). At 3-months follow-up none of the patients experienced GI toxicity, while GU side effects were observed only in three patients (two G1 and one G2). Median IPSS score decreased from 6 (range=2-8) at baseline to 5 (range=2-17) 3 months after treatment. At the same timepoints, no significant changes in EORTC-QoL score were documented. An increase in ADC value of the tumor lesion by about 26% (range=7%-66%) and 51% (range=21%-81%) was registered at time 1 and time 2, respectively, compared to the baseline. Median prostate volume was found unchanged at time 1, while decreased by about 25% (range=9%-59%) at time 2. At the last follow up,

all patients had biochemical no evidence of disease and four of them had a complete response. *Conclusion:* SDART irradiation of the whole prostate with urethra sparing was feasible and well tolerated. Our findings showed a correlation between early changes in ADC values after SDART and later tumor response in patients with unfavorable PCa. Long-term results are needed to confirm whether DWI can be used as an early biomarker of treatment outcome in this setting.

34
SHORT-TERM RT FOR EARLY PCA WITH CONCOMITANT BOOST TO THE DIL (PHASE II TRIAL AIRC-IG-13218)–UPDATES

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Background/Aim: The aim of the present work was to provide an updated report on toxicity and oncological outcomes at 5 years of the Phase II prospective trial "Short-term high precision radiotherapy with simultaneous boost to the dominant intraprostatic lesion (DIL) for patients with early-stage prostate cancer (PCa) (AIRC-IG-13218)". *Patients and Methods*: The study cohort consists of 65 patients, with low and intermediate risk PCa, enrolled since June 2015. Included patients underwent extreme hypofractionated radiotherapy to the prostate (36.25 Gy in 5 fractions) and a simultaneous integrated boost of 37.5 Gy to the DIL. Multiparametric magnetic resonance imaging (mpMRI) co-registered with the planning computed tomography (CT) was used to identify the DIL. The Common Terminology Criteria for Adverse Events (CTCAE) v4.0, the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) criteria were used to evaluate toxicity. All included patients have been evaluated by a medical visit and/or phone call. For contacted and alive patients, quality of life (QoL) was assessed by International Prostate Symptoms score (IPSS), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 (EORTC QLQ-C30), EORTC QLQ prostate specific (QLQ-PR25), and sexual activity by International Index of Erectile Function (IIEF-5). Prostate-specific antigen (PSA) values for all patients with no evidence of disease (NED) were gathered and analyzed. *Results:* Among the 65 patients enrolled, an updated 5-years follow-up was available for 50 of them. After a median follow-up of 4.8 years [interquartile range (IQR)=3.8-5.2 years], out of the 50 reachable patients, 40 (73%) resulted alive with NED, 3 (8%) alive with disease, and 7 (19%) died of other causes. Five-years biochemical progression-free survival was 73% when calculated on all patients and 90% on patients still alive. Five-year overall survival rate was 81%. Median PSA across the 40 NED patients was 0.36 ng/ml (IQR=0.18-0.63 ng/ml). One grade (G) 1 and two G2 gastrointestinal (GI) and 8 G1 and 2 G2 genitourinary (GU) toxicities were reported, with no G≥3 events recorded. Patients' overall QoL was satisfactory at last available follow-up, according to questionnaires. *Conclusion:* Earlier findings that extreme hypofractionated schedule with concurrent boost on the DIL is a safe and effective method are confirmed by our updated data. Results show that increasing the dose to the DIL does not worsen the RT toxicity and consequently does not impact on the QoL of patients, opening up the opportunity for an even more escalated treatment.

35
A RANDOMIZED CONTROLLED TRIAL ON LIFESTYLE AND INTERACTION WITH MICROBIOTA IN PROSTATE CANCER PATIENTS UNDERGOING RADIOTHERAPY: MICROSTYLE STUDY

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Background/Aim: The standard non-surgical approach for localized prostate cancer (PCa) is radiotherapy (RT) but one of the limitations of high-dose RT is the potential increase in gastrointestinal (GI) and genitourinary (GU) toxicities. Recent findings point to an improvement in GI and GU toxicities profile and fatigue by healthy lifestyle approaches. Thus, we designed a clinical trial for PCa patients undergoing RT to investigate whether changes towards a healthy lifestyle are able to modify the microbiome, improve quality of life, and decrease the side effects of RT. *Patients and Methods*: According to the study protocol, 300 PCa patients undergoing salvage or curative RT will be recruited in two comprehensive Italian Cancer Centers (Milan and Naples). Participants will be randomized into two arms: Intervention Group (IG) and Control Group (CG); the ones allocated to the IG will receive personalized counseling on diet and exercise to improve overall lifestyle and to reduce eventual RT-related toxicities and a pedometer device (steps counter) to monitor and increase physical activity and reduce sedentary behavior. Participants included in the CG will receive baseline general advice and materials available for patients undergoing RT. The primary outcome will be assessed at the end of a 6-month intervention, by measuring the change in adherence to a healthy lifestyle. As secondary outcomes, the change from baseline in fasting serum metabolic and inflammatory biomarkers such as lipid profile, glucose, PSA, insulin, HOMA index, testosterone, estradiol, sex hormone binding globulin, highly sensitive C-reactive protein (hs-CRP), adiponectin, 25-hydroxy vitamin D and interleukin 6 (IL-6) will be monitored. Intestinal microbiome composition will be evaluated through fecal samples analyses. According to the cross-over design, the CG will cross to the IG after 6 months, to actively enhance compliance towards suggested lifestyle recommendations for all patients. *Results:* To date, we have enrolled 19 patients (10 allocated to IG and 9 to CG) in the two centers. Median age was 70 (range=55-80 years). Of them, 58% are former smokers and 26% smokers. Median body weight was 81 kg (range=60-112 kg), BMI was 28 (range=20-38 kg/m^2) and Waist to Hip Ratio was 1.0 (0.9-1.3). *Conclusion:* This innovative trial proposes a lifestyle intervention during RT, which includes both dietary and physical activity counselling, as well as monitoring changes in the microbiome and serum biomarkers. The promotion of healthy behavior will be started before initiation of standard care, to achieve long lasting impacts, control side effects, coping with feelings of anxiety and depression, and improve the effectiveness of RT.

37

MONO-INSTITUTIONAL SERIES OF 46 PATIENTS TREATED WITH SBRT RE-IRRADIATION FOR ISOLATED LOCAL RECURRENCE OF PROSTATE CANCER AFTER PRIMARY SURGERY AND SALVAGE RADIOTHERAPY

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Background/Aim: Re-irradiation by stereotactic body radiotherapy (SBRT) represents a valid option for locally recurrent prostate cancer (PCa) treatment. The aim of this retrospective study was to determine the efficacy and safety of such treatment. *Patients and Methods*: The study included patients who underwent salvage hypofractionated radiotherapy for isolated PCa local recurrence after primary surgery and previous salvage/adjuvant radiotherapy or brachytherapy at our Institution between 2010 and 2021. Patients who received hormone therapy and those who underwent more than one local re-irradiation were also

included. Histological confirmation was not mandatory. Local relapse in the prostate bed was assessed by magnetic resonance (MR) and/or choline/prostate-specific membrane antigen (PSMA) positron emission tomography (PET). Salvage SBRT re-irradiation was delivered with image-guided radiation therapy (IGRT) using the BrainLab VERO System. *Results:* Forty-six patients met the inclusion criteria and were considered for the analysis. Most lesions were peri-anastomotic. Patients and treatment characteristics are listed in Table I. PET was available for 26 (56.5%) and MR for 40 (87.0%) patients. Six patients (13.0%) received more than one re-treatment and two of them (4.3%) received three re-irradiation treatments for prostate bed recurrence. Five patients (10.9%) were lost at follow-up. Among the 41 patients with updated follow-up data, 14 (34.1%) resulted free from disease. Progression of disease (PD) was observed in 27 out of 41 patients (66%) with 16 (39.0%) clinical and 11 (26.8%) biochemical progressions. Median time to biochemical and clinical progression was 14 (interquartile range, IQR=6.0-37.5) and 14.4 months (IQR=6.7-16.7), respectively. Regarding toxicity outcomes, no acute GU events higher than G1 occurred. One patient experienced grade (G) 3 genitourinary (GU) late toxicity with implantation of an artificial urinary sphincter after worsening of urinary incontinence; another patient had late G4 GU event with acute urinary retention and underwent bladder catheter positioning. No acute or late G ≥2 gastrointestinal (GI) toxicity events were reported in the whole cohort. *Conclusion:* Salvage stereotactic re-irradiation treatment for locally recurrent PCa seems to be a promising strategy to control bed recurrence. Further studies and longer follow-up are warranted to confirm these preliminary findings.

38

U-CHANGE PROJECT: APPROACHING THE NEW UROTHELIAL CANCER SCENARIO AMONG CLINICIANS, PATIENTS AND CAREGIVERS. A MULTIDIMENSIONAL CONSENSUS DOCUMENT

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Background/Aim: The complex management of advanced urothelial carcinoma, in spite of current progress in the treatment, continues to show how this disease remains aggressive and difficult to cure. However, the upcoming availability of innovative treatments, with the promise to prolong survival and improve quality of life, will challenge clinicians and payors of healthcare organizations (1). *Patients and Methods*: The U-CHANGE Project, has been designed with the aim to provide a full picture of the current model of care of advanced urothelial carcinoma patients in order to identify limitations (AS IS Scenario) and recommend actions for the future (TO BE Scenario). Twenty-one experts analyzed the different scenarios in a multidimensional and multiprofessional Consensus of three different dimensions (tables): clinicians (epidemiologists, oncologists, and urologists), patients (patients' associations, nurses, journalists, physiotherapists), institutions (hospital pharmacists, economists, responsible of healthcare units). Each table developed a series of statements related to specific domains of the disease (awareness, diagnosis, treatment, patient support, integrated care pathway, multidisciplinary teams, economic model) and a simplified, two-steps Delphi methodology was used to establish consensus among all the panel experts voting for all statements in the following plenary session. An appropriate cut-off of 75% was chosen, according to Loblaw *et al*. (2) and using a 5-points Likert scale; statements not meeting 75% agreement were modified and reproposed for a second vote. *Results:* For the AS IS Scenario, after plenary discussion, 16 statements were submitted to vote; 15 statements overpassed the 75% agreement, 1 statement was reformulated and approved in the second round, 1 statement was withdrawn because it was finally considered not acceptable by the proponents. For the TO BE Scenario, after plenary discussion, all the 19 statements were submitted to vote, and successfully overpassed the prespecified cut-off point. All the contents of the sessions, after audio-video recording, were circulated along with a detailed report among the participants after the meetings, reporting all the most relevant comments and proposed solutions for improving the overall outcome of the patients with advanced urothelial carcinoma, in any possible dimension. Examples

of recommended actions, supported by the Consensus, were: importance to increase awareness of this tumour in the population, develop educational programs for several healthcare professionals, promotion of R&D strategies in the biomarkers area, support for having a PDTA (integrated care pathway) in each Region, and activation of multidisciplinary teams and patient/caregiver support programs with the inclusion of new services in the social, labor and psychological areas. *Conclusion:* The U-CHANGE Project set up the ambitious objective to put on the same level of importance, for the first time, all the potential key stakeholders involved in the standard care of the patient with advanced urothelial carcinoma: not only eminent clinicians but also representatives of patients and other direct and indirect impacted stakeholders such as caregivers, nurses, pharmacists, healthcare managers of public hospitals. The new innovative, targeted agents (such as avelumab, enfortumab vedotin, erdafitinib and sacituzumab) may have the potential to significantly change the clinical approach to the treatment of this very aggressive disease; however, the U-CHANGE Project experience, shows that, to do so, it will be necessary to redesign the entire model of care in order to take into consideration: sustainability, possibility to anticipate the benefits of certain treatments, and the ability to target the right patient with the right agent, depending on the different stage of the disease. In this regard, the opportunity of such a multidimensional Consensus sets a new standard of collaboration and partnership among different stakeholders in the uro-oncology area in order to share information, best practices, and utilization of resources, with the final objective to increase the probability to obtain better outcomes and quality of life of these patients. The U-CHANGE Project takes place under the patronage of the Italian Association of Medical Oncology (AIOM), Italian Society of Uro-Oncologists (SIUrO), Italian Association of Hospital Pharmacists (SIFO), PaLiNUro Association of Patients, Italian Federation of Voluntary Association in Oncology (FAVO).

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39

ONE-CARBON METABOLISM ENZYMES ACTIVITY MODULATION AS A POTENTIAL THERAPY IN KIDNEY CANCER

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Background/Aim: Serine and one-carbon unit (SOC) metabolisms are essential biochemical pathways implicated in fundamental cellular functions such as proliferation, biosynthesis of important anabolic precursors, and the availability of methyl groups. Recent evidence has highlighted a critical role of many serine metabolism enzymes in the activation of the immune system as in the case of MTHFD2, whose deficiency promoted regulatory T cell differentiation as well as a decrease in mTORC1 signaling. Further evidence of a possible clinical interaction has been shown in advanced metastatic patients; administration of an immune-modulatory vaccine against IDO1/PD-L1 in combination with Nivolumab induced prolonged survival. The present project aimed at deciphering the role of the activity of key enzymes involved in SOC metabolism on the regulation of the proliferation of kidney cancer cell lines and the modulation of the expression of immune regulatory molecules. *Materials and Methods:* The effect of phosphoglycerate dehydrogenase (PHGDH) chemical inhibition with CBR-5884 on the cell cycle was evaluated *in vitro* using propidium iodide staining and clonogenicity assay. The subsequential transcriptomic changes were analyzed though quantitative polymerase chain reaction (qPCR). *Results:* The chemical blockage of PHGDH enzyme resulted in decreased cell proliferation after treatment of ACHN and 786-O kidney cancer cell lines, without altering the cell cycle, while incrementing cell death. The inhibition of the enzyme also decreases the ability of forming colony in a dose-dependent fashion on both cell lines. Combined inhibition with a specific serine hydroxy

methyl transferase 1/2 inhibitor, SHIN1, also showed synergistic activity with PHGDH inhibition. Moreover, the analysis of gene expression after PHGDH inhibition, showed decreased of mRNA transcripts of key genes involved in the pathogenesis of kidney cancer such as HIF1α, HIF1β, VHL, and VEGFA. Regarding immune checkpoint molecules, low doses of PHGDH increased expression of tumor-related immune modulatory molecules such as B7H4, CD70, CD276, and PD-L1. *Conclusion:* Altogether, our results document the effect of the inhibition of SOC metabolism on the proliferation of kidney cancer cells, with alteration of the expression of genes involved in its pathogenesis and immune escape suggesting its possible therapeutic role.

40
THE RISK OF BLADDER RECURRENCE AFTER RADICAL SURGERY FOR UPPER TRACT UROTHELIAL CANCER IS ASSOCIATED WITH THE PRECEDING RESECTION OF THE URETERAL MEATUS

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Background/Aim: Upper tract urothelial carcinoma (UTUC) is a relatively rare disease usually involving the pyelocaliceal structures rather than at the ureter and accounting for less than 10% of all urothelial cancers (1). While numerous risk factors have been recognized as being associated with UTUC, data regarding risk factors for bladder recurrences are still lacking (2). Considering that bladder recurrences occur in about one third of patients affected by UTUC (3), it is fundamental to identify any predisposing condition to improve clinical strategies and treatments after UTUC surgery. A possible risk factor for bladder recurrence could be the transurethral resection of the bladder cuff. In our work, we evaluated any possible associations between the transurethral resection of the ureteral meatus preceding the surgical treatment of the UTUC and the subsequent risk of bladder recurrences. *Materials and Methods:* In our retrospective study, all patients with a diagnosis of UTUC from 2 high volume centers were enrolled. The period evaluated was from January 2016 to December 2019. Clinical records of every patient, including cancer characteristics, age, comorbidities, and previous surgery were recorded. Patients were classified according to the treatment of the UTUC: terminal ureterectomy (TU) *vs*. radical nephroureterectomy (NU) and surgical technique of bladder cuff removal (extravesical *vs*. endoscopic excision). Site and timing of any eventual previous vesical TransUrethral Resection (TUR) of bladder tumors were recorded, together with patients' outcome, including the characteristics of the bladder recurrences (T stage, grading, number of lesions). For the univariate analysis, the continuous variables were summarized using the median and interquartile range (IQR). Categorical variables were defined as absolute numbers and percentages (%). For the quantitative variables, comparisons between patients were made through the Mann-Whitney test, whereas for the qualitative variables the Chi-square test was used. A p-value <0.05 was considered statistically significant. Statistical Software R version 3.4.2 was adopted for statistical analysis. *Results:* A total of 139 patients were enrolled in the study (64 patients from center A and 75 patients from center B). In total, 30 women and 109 men with a mean age of 74 years (range=37-98 years) were selected. No statistically significant difference in patients' characteristics was detected between the two study centers. Thirty-eight patients with UTUC not undergoing surgery for advanced age, poor general status or refusing surgery, were excluded. Fifty-eight out of 139 patients (41.7%) were previously treated with transurethral resection of the homolateral ureteral meatus before surgery, due to a tumor located at or emerging from the ureteral meatus with a median time interval with the subsequent ureteral surgery of 6.4 months (range=2-11 months). A total of 101 patients (72.6%) were treated surgically after UTUC diagnosis: 18 patients (12.9%) underwent terminal ureterectomy with ureteral reimplantation, and 83 patients (59.7%) radical nephroureterectomy. Endoscopic bladder cuff removal was performed in 57 of the 101 patients (56.4%), whereas 44 patients (43.6%) underwent extravesical bladder cuff excision. During the follow-up, bladder recurrence occurred in 39 (28%) out of 139 patients, with a median follow-up of 17.6 months. Histological characteristics of bladder recurrences, including number of lesions, grading, staging, and any eventual concomitant carcinoma *in situ* (Cis) are shown in Table I, while the differences in bladder recurrence characteristics between patients who were previously treated with resection of the ureteral meatus and patients treated with endoscopic bladder cuff removal are shown in Table II. 9 patients out of 39 with bladder recurrence (23%) underwent endoscopic resection of the bladder cuff. There was no statistically significant association between recurrence and endoscopic bladder cuff (p=0.23). Twenty-six patients with recurrence (66.6%) had previously undergone resection of the ureteral meatus for urothelial cancer, that resulted in a statistically significant association ($p<0.01$). The median time interval between the TUR of the ureteral meatus and the subsequent surgery was 6.4 months. Bladder disease progression requiring radical cystectomy was observed in 9 (6.4%) of the 139 patients analyzed, 4 (44%) with a previous history of ureteral meatus TUR. *Conclusion:* Previous endoscopic resection of the

ureteral meatus appears to represent a risk of bladder recurrence, independent from the strategy adopted in the subsequent surgery for UTUC. Our study does not reveal any correlation between the risk of bladder recurrence and the surgical approach or the method of excision of the bladder cuff (extravesical *vs*. endoscopic). Current international guidelines (1) recommend a single instillation, only for patients with high-risk UTUC. Our results, although requiring confirmation by larger studies, could indicate the adoption of a prolonged adjuvant treatment and a stricter endoscopic follow-up in patients previously treated with TUR of the ureteral meatus.

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41
THE ROLE OF TERT PROMOTER MUTATION IN ADVANCED UROTHELIAL CARCINOMA TREATED WITH IMMUNOTHERAPY

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Background/Aim: Immune checkpoint inhibitors (ICI) are revolutionizing the treatment of advanced urothelial carcinoma (aUC). Currently, several ICIs are approved for the treatment of aUC in different settings. However, only a small fraction of patients responds to immunotherapy (20-25%) and there is a lack of reliable predictors of response to ICIs. Genomic profiling performed through next-generation sequencing (NGS) may help to identify predictive or prognostic markers able to guide therapeutic choices. Among the genomic alterations being studied, Telomerase reverse transcriptase promoter (TERTp) mutations have been identified as a promising predictive marker of response to treatments in several types of tumors (*e.g.,* melanoma, glioblastoma). A retrospective study on aUC patients treated with ICI showed that TERTp mutation is associated with an improved progression-free survival (PFS). We analyzed tissue samples of patients with aUC treated with ICI to assess the status of TERTp and the effect of its mutations on survival outcomes. *Patients and Methods*: We performed a single-center retrospective analysis on 18 patients (pts) with aUC of the bladder or upper tract treated with an ICI, according to different settings, to assess the status of TERTp, type of mutation and co-mutations, and to evaluate its prognostic value. Tumor DNA was extracted from formalin-fixed paraffin-embedded (FFPE) specimens and then analyzed using a laboratory-developed NGS multi-gene panel. The panel analyzes a total of 343 amplicons in 27 oncogene/oncosuppressor markers (human reference sequence hg19/GRCh37, 21.77 kb), including *TP53*, *BRAF, RAS*, and *TERT* genes among others. *Results:* We evaluated FFPE tumor samples from 18 pts eligible for the study. A total of 11 of the 18 (61.1%) pts had tissue samples adequate for genomic profiling analysis. One of these was not evaluable for survival outcome since ICI treatment was not started. All patients received an ICI as a second line of treatment for aUC from January 2020 to April 2022. The most frequently altered genes were the *TP53* (63.6 %) and TERT promoter (36.3%). The only type of TERTp mutation was c.124C>T (100%). In 50% of the cases, we found a concomitant mutation in *TP53*. In our exploratory analysis, pts with TERTp mutation had a lower median PFS compared with TERTp wild-type (wt) pts (3.8 *vs*. 9.4 months - mo, respectively). *Conclusion:* TERTp mutation is quite frequent in aUC and seems to be a potential prognostic and predictive factor. Our small pts sample supports this hypothesis and highlights the need to further evaluate TERTp alteration in a wider cohort. Our results seem to show a negative prognostic role of TERT promoter mutations, in contrast to other previous studies. In addition, the value of co-mutations, especially the frequently altered *TP53*, should be further explored, also in association with PD-L1 expression.

42

NEW NOMOGRAM TO CORRECTLY EXECUTE PELVIC LYMPH NODE DISSECTION IN PATIENTS WHO UNDERWENT TARGET BIOPSY ONLY

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Background/Aim: In the current urological armamentarium, a tool able to predict the risk of lymph node invasion (LNI) in prostate cancer diagnosed through target biopsy (TB) only before radical prostatectomy (RP) is not available. The objective of this study was to create a multiparametric Magnetic Resonance Imaging (mpMRI)/TB based nomogram to predict the risk of LNI. Patients and Methods: A retrospective analysis of data from April 2014 to March 2020 of patients with positive mpMRI and TB who subsequently underwent robot-assisted radical prostatectomy (RARP) with extended lymph-node dissection (ePLND) was carried out, drawing on our database maintained prospectively. A logistic regression model and a model discrimination, using an area under the receiver operating characteristic (ROC) curve, were created to assess how pre- and intra-operative factors influence the risk of LNI. At last, a logistic model-based nomogram able to estimate the risk of LNI was generated (Figure 1), together with its calibration plot. Using a similar cohort, the model was also validated. *Results:* Overall, 461 patients, of which 52 (11.27) had LNI, were included. Digital rectal exploration (DRE), Prostate Imaging Reporting and Data System (PI-RADS), seminal vesicle invasion (SVI), PSA and worst GS at I and II target lesions resulted to be significant predictors of LNI, in accordance with the logistic regression analysis performed and with the multivariable model. The AUC was 0.74 [95%CI=0.67-0.81]. As shown by the calibration plot, the model proved to be close to the ideal one, which is within the 95%CI. A visual nomogram was developed and a Youden index at 60 points (corresponding to a risk of LNI of 7%) was set, to discriminate between the risk or not of LNI. On a similar cohort, the model showed a LH+ of 2.58 (95%CI=2.17-2.98). *Conclusion:* In patients undergoing MRI-TB only, a score higher than 7% calculated with our novel nomogram can recognize patients with risk of LNI, considering the clinical stage, SVI at MRI, biopsy Gleason pattern, and PSA.

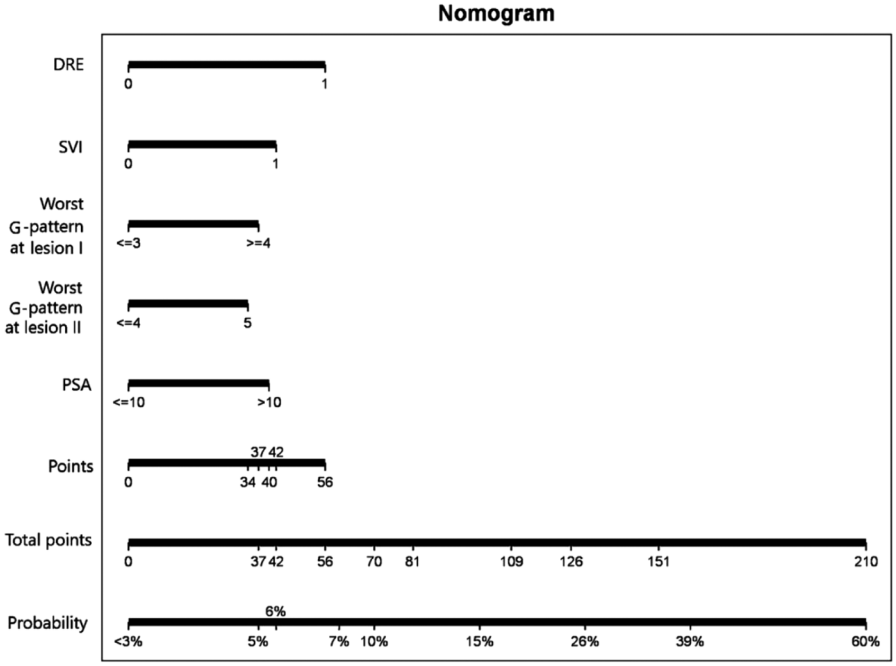

Figure 1. *Nomogram to predict the risk of lymph node invasion in patients who underwent prostate multiparametric-magnetic resonance imaging and target biopsy.*

43

MULTIDISCIPLINARY UNIT FOR THE MANAGEMENT OF UROTHELIAL CARCINOMA

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Background/Aim: Localized urothelial carcinoma (UC) of the bladder or of the upper tract (UTUC), independently from muscular invasion, requires a multidisciplinary evaluation in order to obtain the best clinical outcomes. In fact, given the high aggressiveness of this type of cancer, the only treatment with curative intent is the approach chosen to treat the localized disease. Neoadjuvant cisplatin-based chemotherapy is a highly effective treatment for T2-4 N0 M0 UC, and it is associated with prolonged disease-free survival (DFS) and overall survival (OS), but patient selection is of pivotal importance considering therapy side effects and risk of acute renal failure that could compromise surgical outcomes. Adjuvant treatment could be evaluated for cisplatin fit patients with pT3-4 any N or any pT N+. Treatment of non-muscle invasive tumors is still challenging, and it is crucial to select the best sequence of intravescical instillations (Bacillus Clamette-Guérin or chemotherapy) and endoscopical restaging or to address the patient to radical surgical treatment when resistance to these approaches arises. To date, in several uro-oncological Centers, only a small percentage of patients (10-12%), even with the correct staging characteristics, undergo neoadjuvant chemotherapy. *Patients and Methods:* In our Center, we established a multidisciplinary team composed of a urologist, medical oncologist, radiotherapist, radiologist, pathologist, and case manager nurse dedicated to the diagnosis and treatment of UC of the bladder and UTUC (Multidisciplinary Unit for the Management of Urothelial Carcinoma). In a weekly scheduled meeting, all newly diagnosed cases and re-assessment of disease are discussed, with revisions of the radiologic imaging, and treatment approaches are collegially selected. We studied the implementation of surgical and clinical outcomes of patients multidisciplinary evaluated in our Center between July 2020 and December 2021. *Results:* In this period of time, 62 meetings took place, and 289 patients were collegially discussed (247 UC of the bladder and 42 UTUC). Of these, 202 patients were addressed to surgical treatments: 118 radical cystectomies, 40 nephrouretherectomies, 19 diagnostic ureteroscopies, 28 transurethral resections of the bladder (TURB) with cytoreductive or palliative intent. Fifty-seven patients underwent conservative approaches (second endoscopical resections, intravesical instillations). After multidisciplinary discussion, non-surgical indications were: 18 patients were addressed to neoadjuvant treatment, 8 to adjuvant chemotherapy, 3 to first line definitive oncologic treatment and 20 patients underwent other diagnostic exams (10 computed tomography, 7 positron-emission tomography, 3 biopsies). We evaluated the outcomes of the multidisciplinary unit by assessing the percentage of patients addressed to neoadjuvant or adjuvant chemotherapy before and after the start of the meeting. In our Center, we witnessed a significant increase of neoadjuvant chemotherapy rate comparing the years 2018-2019, when there was no multidisciplinary discussion of the cases (0%), to 2020-2021, after the start of the multidisciplinary unit (18%). The rate of adjuvant treatment increased by 62%, from 5 in the years 2018-2019 to 8 in the years 2020-2021. *Conclusion:* The development of a Multidisciplinary Unit for the Management of Urothelial Carcinoma allowed to improve patients' care by achieving a better diagnostic accuracy and therapeutic strategy tailored on the single patient, taking into account oncological, surgical, radiological, and anatomo-pathological aspects of the case by different points of view. This strategy increases adherence to guidelines in the choice of diagnostic and therapeutic decisions, thus improving management accuracy, optimizing available resources, and reducing hospital visits wait-lists, which is strictly correlated to oncological and surgical outcomes. In addition, the tight collaboration between different specialists creates a multidisciplinary coordination of the scientific research activity and allows to select patients evaluable for enrollment in clinical trials.

44

BLADDER CANCER IN THE ERA OF IMMUNE CHECKPOINT INHIBITORS: THE ROLE OF PD-L1? A META-ANALYSIS

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Background/Aim: In the last decade, immune checkpoint inhibitors (ICIs) have reshaped the therapeutic scenario of many solid tumors, bladder cancer (BCa) included. However, predictive factors are still lacking. Our meta-analysis ought to investigate whether PD-L1 expression confers an advantage in terms of overall response rate (ORR) and overall survival (OS). *Patients and Methods*: We

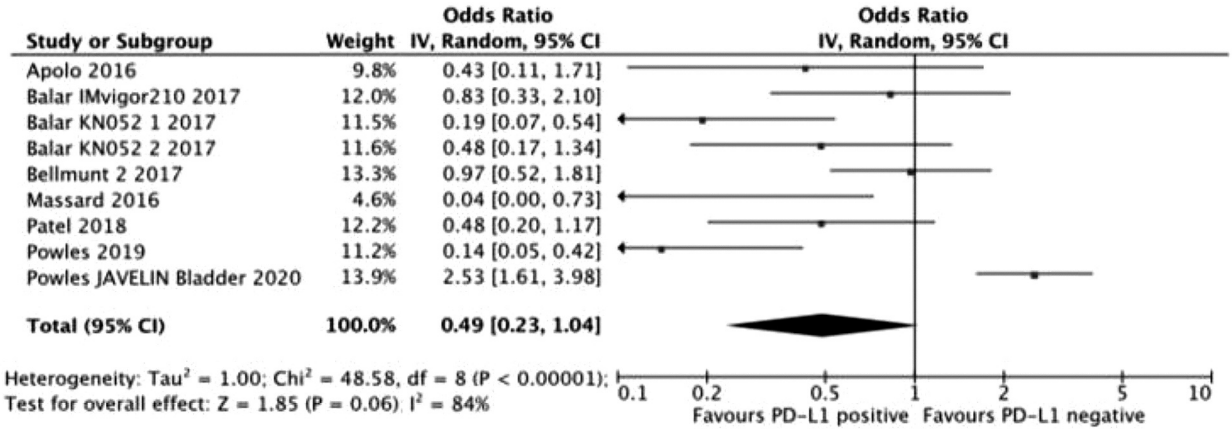

Figure 1. *Programmed death-ligand 1 (PD-L1)+ vs. PD-L1- patients: overall response rate.*

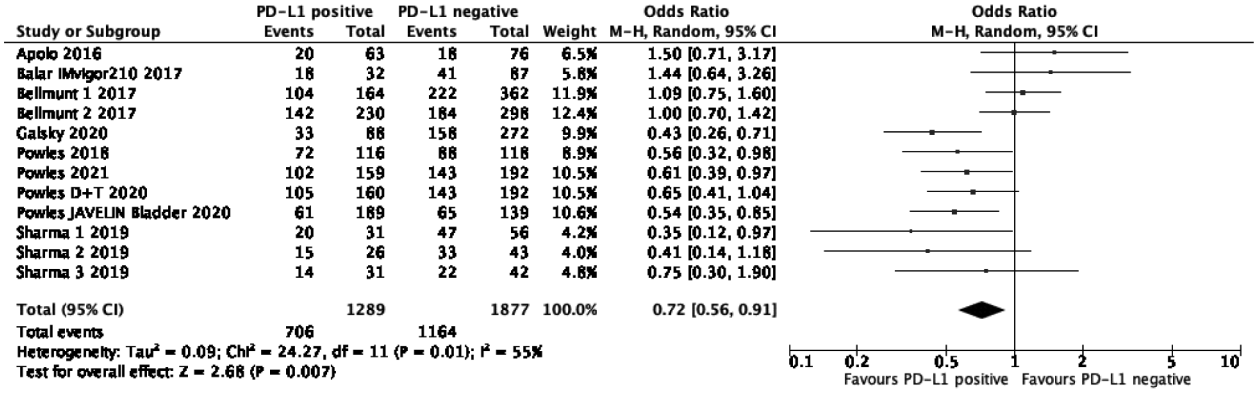

Figure 2. *Programmed death-ligand 1 (PD-L1)+ vs. PD-L1- patients: Overall survival.*

systematically searched the PubMed, EMBASE, and Cochrane databases for phase I-IV clinical trials regarding ICIs in BCa. We determined odds ratios (OR) for ORR and OS comparing PD-L1 positive with PD-L1 negative patients. *Results:* Thirteen studies were selected. Eight studies were eligible for ORR analysis, 8 for OS analysis. 1,535 patients were PD-L1 positive, 1,894 PD-L1 negative. Patients were treated with ICIs in the first or second-line or maintenance after first-line chemotherapy. PD-L1 positive patients had no clear advantage in regard to ORR compared to PD-L1 negative patients (HR=0.49; 95%CI=0.23-1.04; p=0.06) (Figure 1). PD-L1 positivity was associated with longer survival compared to PD-L1 negativity (HR=0.72; 95%CI=0.56-0.91; p=0.007) (Figure 2). *Conclusion:* There is possibly a survival advantage for PD-L1 positive patients over PD-L1 negative ones, with a less clear advantage in terms of ORR. More data are needed to allow the best patient selection and a tailored approach.

46
ONCOLOGICAL OUTCOMES OF SYSTEMATIC URETERAL FROZEN SECTIONS DURING RADICAL CYSTECTOMY IN PURE UROTHELIAL BLADDER CANCER AND IN HISTOLOGICAL VARIANTS

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Background/Aim: In our center, distal ureteral frozen sections are routinely performed during radical cystectomy (RC) for bladder cancer (BC). In case of positive findings, frozen sections are repeated until the reach of tumor negative samples. However, there is not a global consensus on timing and management of frozen sections, and prognostic data are poor. The aim of our study was to evaluate the prognostic value of positive ureteral frozen sections at RC, even if negative at final pathological report, on recurrence and survival outcomes in pure urothelial BC or in histological variants (HV). *Patients and Methods*: We evaluated 410 consecutive non-metastatic patients diagnosed with BC and treated with RC at a single tertiary referral center between January 2009 and October 2019. Cox proportional hazards regression analysis model was used to predict cancer-specific survival (CSS), overall survival (OS), and recurrence-free survival (RFS) in overall population, in pure urothelial bladder cancer and in HV. The Kaplan-Meier method was used to assess RFS, CSS, and OS in the overall population by frozen-section status, in pure urothelial bladder cancer and HV. *Results:* Median age was 71 years. At a median follow-up of 32 months, RFS, CSS and OS were 73%, 77%, and 54%, respectively. Histological variants were found in 86 patients (21%) presenting worst pathological features at final report, compared to pure urothelial BC. Positive frozen sections were found in 18% of patients without any statistical difference between pure urothelial BC and HV and were associated with worst pathological features (carcinoma *in situ*, lymphovascular invasion, lymph node involvement and non-organ confined disease). RFS, CSS and OS at Kaplan-Meyer analyses were significantly shorter in patients with positive frozen section both in pure urothelial BC and HV, compared to those with negative frozen sections. Similarly, at multivariate Cox proportional hazards regression analyses, the presence of positive frozen sections was associated with shorter RFS, CSS and OS (all $p>0.05$) in the overall population and according to histology (pure urothelial BC and HV). *Conclusion:* Identification of positive ureteral frozen sections during RC, even if negative at final pathological report, impacts on recurrence and oncological outcomes both in pure urothelial BC and in HV. Based on its prognostic implication, ureteral frozen sections status should be considered for follow-up planning in pure urothelial BC as well as in HV.

47

FIRST-LINE COMBINATION THERAPIES FOR ADVANCED RENAL CELL CARCINOMA (ARCC): AN ITALIAN SINGLE-CENTRE REAL-WORLD CLINICAL EXPERIENCE

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Background/Aim: Pembrolizumab plus axitinib (PA) was approved by the Italian Medicines Agency (AIFA) in December 2020 as a first-line treatment for advanced renal cell carcinoma (aRCC). After one year, nivolumab plus ipilimumab (NI) was approved in the same setting, only for intermediate/poor risk patients. Both combinations have shown an improvement in OS and PFS compared to sunitinib. As observed in pivotal phase III clinical trials, careful attention must be given to overlapping toxicities. This study aimed to evaluate the real-world experience of an Italian single-centre with both combinations. *Methods*: We retrospectively evaluated 32 aRCC patients, treated with first-line combination therapy between May 2019 and February 2022 in our Institution. *Results:* Sixteen patients received NI and 16 patients received PA. Three NI and 9 PA patients are still on treatment. Patient baseline characteristics are described in Table I. In the NI group, 1 patient obtained complete response (CR), 4 patients partial response (PR) and 5 patients progression disease (PD) as best response. In the PA group, 8 patients obtained PR and 4 PD as best response. With a median follow-up of 30.8 months in the NI group and 9.4 months in PA group, median PFS was 7.0 and 5.9 months

Table I. *Patient baseline characteristics.*

	NI	PA
Age, years (median)	63	57
Sex, n (%)		
Male	12 (75)	11 (69)
Female	4 (25)	5 (31)
ECOG PS, n (%)		
0	5 (31)	4 (25)
1	11 (69)	12 (75)
Histological type, n (%)		
Clear cell	11 (69)	11 (69)
Papillary	1 (6)	0 (0)
Chromophobe	0 (0)	1 (6)
NOS	4 (25)	4 (25)
Sarcomatoid component, n (%)	1 (6)	2 (13)
Heng Risk Group, n (%)		
Favorable	0 (0)	0 (0)
Intermediate	12 (75)	16 (100)
Poor	4 (25)	0 (0)
Liver metastases, n (%)	5 (31)	6 (38)

NI: Nivolumab plus ipilimumab; PA: pembrolizumab plus axitinib; ECOG PS: Eastern Cooperative Oncology Group performance status; NOS: not otherwise specified.

respectively. Median OS was 16.3 months for NI patients, while it was not reached in the PA group (87.5% of patients are still alive). All patients (100%) experienced a toxicity of any grade in both groups. G3-4 toxicity was observed in 25.0% of NI patients and 37.5% of PA patients. The most frequent G3-4 adverse events in the NI group were anemia (12.5%), pneumonia (6.2%), and fatigue (6.5%), while in the PA group were hypertransaminasemia (18.8%), hand foot syndrome (HFS) (6.3%), oral mucositis (6.3%) and arthralgia (6.3%). *Discussion and Conclusion:* The retrospective nature of this study and the small number of patients limited our results. The observed safety profiles of both combinations were worse than expected, especially for the PA combination. mPFS was similar between treatment groups, but slightly lower than in pivotal clinical trials, suggesting the need of a longer follow up.

48
TEN-YEAR FUNCTIONAL OUTCOMES OF A PROSPECTIVE RANDOMIZED CONTROLLED TRIAL COMPARING LAPAROSCOPIC *VERSUS* ROBOT-ASSISTED RADICAL PROSTATECTOMY

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Background/Aim: In the direction of minimally invasive surgery, laparoscopic radical prostatectomy (LRP) at first, and then robot-assisted radical prostatectomy (RARP) were introduced as alternatives to standard retropubic approach for prostate cancer (PCa). The main issue is still represented by the real benefit in terms of functional outcomes. Herein, we present functional and quality of life data after 10 years of follow-up. *Patients and Methods*: This is a single center prospective parallel two-arm randomized control trial (1:1 for two groups) for patients with localized PCa (T1-2-N0 M0 clinically staged according to TNM 2009). From January 2010 to January 2011, we enrolled 120 patients aged 40-75 years old. All interventions were performed with transperitoneal anterograde technique by the same experienced surgeon (F.P.). When clinically and oncologically indicated, unilateral or bilateral neurovascular bundle preservation [nerve-sparing (NS) procedure]. The objective was to compare the functional outcomes after the intervention (in terms of continence and potency recovery) during the follow-up. Continence and potency were assessed at 1, 3, 6, and 12 months, and then every 6 months until 10 years after the procedure. We considered patients with an International Index of Erectile Function (IIEF)-5 score >17 as potent and those that used no pads or one safety pad/day as continent. Multivariate data analysis approaches were used to evaluate the differences between RARP and LRP cohorts. Partial least squares-discriminant analysis (PLS-DA) was employed as supervised classification approach using R and Python software. *Results:* The two groups (RARP n=60, LRP n=60) had homogeneous distribution of the variables (demographic data and pathological results). PLS-DA modelling allowed discriminating RARP over LRP individuals. RARP approach showed significantly higher continence rates compared to LRP approach. Moreover, PLS-DA models remarked the erection rates and the potency rates (after 5-10 years) as significant for the RARP population. *Conclusion:* The 10-year follow-up findings confirmed our previously published results at 5 years (1) after the intervention. RARP provides more chances to have better functional results in terms of the recovery of continence and potency.

1 Porpiglia F, Fiori C, Bertolo R, Manfredi M, Mele F, Checcucci E, De Luca S, Passera R and Scarpa RM: Five-year outcomes for a prospective randomised controlled trial comparing laparoscopic and robot-assisted radical prostatectomy. Eur Urol Focus *4*: 80-86, 2018. PMID: 28753822. DOI: 10.1016/j.euf.2016.11.007

49
COMPARISON BETWEEN TWO HYPOFRACTIONATED TREATMENT SCHEDULES IN PROSTATE CANCER: PRELIMINARY RESULTS ON ACUTE TOXICITY

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Aim: This study compares the efficacy and toxicity of the hypofractionated schedule (70 Gy) used at our center to the hypofractionated schedule of the conventional *versus* hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer protocol (CHHiP) (60 Gy), with the aim

of reducing the waiting list and the number of accesses of patients, in the COVID-19 era. *Patients and Methods*: From June 2021 to December 2021, 20 consecutive patients were enrolled in 2 arms (mean age 65 years, range: 60-81, ECOG 0-1), affected by prostate cancer (cT1-cT3a, cN0, cM0 - GS ≤8, PSA level between 6 and 28 ng/ml), grouped according to National Comprehensive Cancer Network (NCCN) risk classes (2021) and consequently sent to short- or long-term androgen deprivation therapy (ADT). The different NCCN risk categories were equally represented in the 2 arms. Ten patients of 1st arm received a total dose of 70 Gy in 28 fractions and 10 patients of 2nd arm received a total dose of 60 Gy in 20 fractions. All patients were treated with Intensity-modulated radiotherapy-simultaneous boost integrated (IMRT-SIB) with 6 MV photons. During radiotherapy treatment, all patients were examined at least once a week. Acute genitourinary (GU) and gastrointestinal (GI) toxicity was assessed according to the CTCAE scale v.5.0 Median follow-up was 7 months (range: 6-9). *Results:* There was no significant difference in GU and GI toxicity between the two schedules. Acute GU and GI toxicity >grade 2 (G2) was not detected in either arm. In the 1st arm, 9/10 and 8/10 patients presented G0-1 GU and GI toxicities, respectively. In the 2nd arm, 8/10 patients had G0-1 GU toxicities and 8/10 had G0-1 GI. Only 1 patient (10%) of Group 1 had GU toxicity G1, at month 4 after the end of the treatment. *Discussion and Conclusion:* Acute toxicity was comparable between the two arms. These results encourage us to continue the study by enrolling more patients. Further data will be needed to evaluate late toxicities and equal treatment efficacy, to definitively adopt the CHHiP schedule.

50

CARDIOVASCULAR TOXICITY IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER PATIENTS TREATED WITH COMBINATIONS OF PARP-INHIBITOR AND ABIRATERONE: A META-ANALYSIS

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Background/Aim: Recent studies have shown that combinations of an androgen receptor signaling inhibitor (ARSi, *i.e.*, abiraterone acetate) and a poly(ADP-ribose) polymerase-inhibitor (PARPi), such as olaparib or niraparib, significantly improve clinical outcomes of metastatic castration–resistant prostate cancer (mCRPC) patients compared to ARSi monotherapy. On the other hand, these combinations have been associated with a potential increased risk of cardiovascular toxicity (CVT) and hypertension. In this meta-analysis, we aimed at investigating the incidence and the relative risk of developing CVT and hypertension in mCRPC patients treated with abiraterone and PARPi. *Materials and Methods:* Prospective studies were identified by searching the MEDLINE/PubMed, Cochrane Library and ASCO Meeting abstracts. Data extraction was conducted according to the PRISMA statement. Combined relative risks (RRs) and 95% confidence intervals (CIs) were calculated using fixed- or random-effects methods, depending on studies heterogeneity. RevMan software for meta-analysis (v.5.2.3) was used to perform statistical analyses. *Results:* Three articles were selected for this meta-analysis, including a total of 1,361 patients. The incidence of treatment-related CVT of any- and high- grade was 12.7% and 7.4%, respectively. Treatment with the combination of abiraterone and a PARPi was associated with a significant increased risk of any grade CVT (fixed-effects, RR=1.57, 95% CI=1.14-2.17; p=0.005) but not with high-grade CVT (random-effect, RR=3.39, 95% CI=0.25-46.78; p=0.36), compared to abiraterone monotherapy. The incidence of hypertension of any- and high- grade was 17.6% (compared to 17.1% in the control arms) and 7.0% (6.3% in the control arms), respectively. The combination of abiraterone and a PARPi did not increase the risk of hypertension of any-grade (RR=1.01; p=0.97) and high-grade (RR=1.11; p=0.60), compared to controls. *Conclusion:* Combination therapy of abiraterone and a PARPi has a tolerable safety profile in terms of cardiological toxicities, with a significant increase of the risk of CVT of any-grade, but not of high-grade, compared to controls. Analogously, this therapeutic strategy does not significantly increase the incidence and relative risk of hypertension of any- and high- grade

51

PATIENTS WITH CARCINOMA *IN SITU* OF THE PROSTATIC URETHRA UNDERGOING BCG INTRAVESICAL INSTILLATION: 5-YEARS FOLLOW UP

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Background/Aim: Carcinoma *in situ* (CIS) in the prostatic urethra is common in patients with high-grade superficial

bladder cancer (9%-25%). Several authors evidenced that Bacille Calmette-Guerin (BCG) has efficacy on CIS of the prostatic urethra. The aim of the study was to evaluate the use of intravesical BCG in selected patients with CIS involving prostatic urethra in 5 years follow-up. *Patients and Methods*: Between January 2010 and December 2021, 85 patients with high-risk superficial bladder cancer and CIS of the prostatic urethra were treated with intravesical BCG (once a week for 6 weeks, and once a month for 6 months). Patients with stromal invasion were excluded. Transurethral resection of the prostate was performed before the instillations in all patients. Patients' follow-up included: cystoscopy, cytology, TURP biopsy (to detect persistent or progressive disease) every 3-4 months for the first two years and then every 6 months; PET TC every year. *Results:* Data analysis and survival rate on 5-years of follow-up were studied and 37/85 patients underwent intravesical instillation BCG for prostatic mucosal, submucosal, and ductal CIS involving the prostatic urethra. During the follow-up, all patients received continuous monthly BCG treatment. Ten out of 37 patients presented complete response in the bladder and prostate since their 18-months follow-up. Sixteen out of 37 patients had periodically tumor recurrence and they are still in endoscopic controls. Eleven out of 37 patients with residual disease in the prostatic urethra were subsequently treated with radical cystectomy and are currently free from disease. Median disease-specific survival was 1.8 years. *Conclusion:* Intravesical BCG is a reasonable treatment option in selected patients with bladder CIS involving the prostatic urethra. Bladder preservation was successful in 26/37 patients during the 5-year follow-up. Nevertheless, a close follow-up and a strict indication to the radical cystectomy are necessary in case of persistent recurrence of disease in the urethra or stromal invasion.

52
SAFETY AND EFFECTIVENESS OF RADIOFREQUENCY ABLATION (RFA) FOR RENAL MASSES IN THE FRAME OF A MULTIDISCIPLINARY APPROACH

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Background/Aim: Radiofrequency ablation (RFA) is considered a therapeutic option for renal masses alternative to surgery. Particularly, in patients who are not good candidates to surgical treatment due to comorbidities or a grade of renal failure, this technique may be considered, to avoid the impact of an invasive treatment and to preserve renal function. Only patients with a mass smaller than 4 cm in size are amenable to RFA. We retrospectively evaluated the safety and the effectiveness of percutaneous CT-guided RFA in patients unfit for surgery, due to old age and/or comorbidities. *Patients and Methods*: In our retrospective study, we evaluated 136 computed tomography (CT)-guided procedures (November 2016-March 2021). The TNM stage of all patients before the procedure was T1a, N0, M0. A 4-tined expandable RFA electrode was used. As an endpoint to evaluate the effectiveness of the technique, the complete necrosis of the tumor mass (absence of contrast-enhancement on immediate as well as follow-up CT scan) was used. Patients were observed on a 5-year follow-up period. During this period, we reported also: renal function indices, such as creatinine and glomerular function rate (GFR), hemoglobin drop, the presence of postoperative pain [numeric pain rating (NRS) scale], the length of the hospital stay, and the occurrence of minor or major complications. *Results:* Of the 136 patients included, 123 had 1 treatment (with a primary effectiveness rate 91.9%), while12 required a second treatment for residual disease. Mean tumor size was 25.4 mm (SD=9.51). Recurrence was found 7 cases. No mid- to long-term complications were reported. Serum creatinine before and after the ablation were 1.08 mg/dl and 1.11 mg/dl, respectively. NRS median value was 0.8. Mean hospitalization was 1.6±1.9 days. *Discussion*: After Zlotta *et al*. described the first series of patients treated with RFA, a growing interest was raised around the technique. According to the American Association of Urology (AUA) RFA is considered a viable option for the treatment of renal masses. The European Association of Urology (EAU) reports that RFA is recommended for patients with old age and comorbidities. Although in the literature most of the publications on RFA are retrospective studies, and in some cases are limited by the small number of patients and the short follow-up, RFA has shown to be safe and effective; specifically, in some cohorts, the difference in cancer-specific survival (CSS) between RFA and the surgical approach was not statistically significant. Our data are consonant with the literature and suggest that RFA is safe and effective for the treatment of renal masses in patients who are unfit for surgery and is worth consideration in the frame of a decision-making process. *Conclusion:* Our mid-term results demonstrate that CT-guided RFA is safe and effective as a treatment for renal masses in stage T1a, N0, M0. We recommend the involvement of a multidisciplinary team, to share the decisions regarding the therapeutic approach to renal masses and to tailor the treatment according to the patient characteristics.

53

ACCURACY OF MRI IN THE DIAGNOSIS OF PROSTATE CANCER: A RETROSPECTIVE STUDY

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Background/Aim: In the diagnostic process of a patient with suspected prostate cancer, elevated PSA values or abnormal digital rectal examination (DRE), MRI can play a key role in deciding whether to perform a prostate biopsy. The aim of the study was to evaluate the specificity and sensitivity of prostate MRI using prostate biopsies. *Patients and Methods*: We retrospectively evaluated 623 patients that underwent prostate mapping in our Institution (Urologic Department, Fondazione IRCCS Casa Sollievo della Sofferenza, Italy) from January 2019 to December 2021. Of the 623 patients, aged 37-86 years (mean age 68.3), 105 had not an MRI prior to prostate biopsy and were therefore eliminated from the study. In total, 518 patients were enrolled, who had prostate MRI showing signal alterations suspicious for neoplasia in morphological sequences and were classified into three groups according to the Prostate Imaging Reporting and Data System (PI-RADS) value: PIRADS 3, 4 and 5. The pre-operative workup included: prostate MRI, total and free prostate-specific antigen (PSA), anamnesis, objective examination with digital rectal exam, renal function tests, blood count and coagulation. There were 416 patients with PIRADS 3, 76 with PIRADS 4, and 26 with PIRADS 5. *Results:* We found biopsy positivity for neoplasia in 291 out of 416 (70%) patients with PIRADS 3, 68 out of 76 (90%) patients with PIRADS 4. and 25 out of 26 (95%) patients with PIRADS 5. We then divided the 416 patients with PIRADS 3 into three subgroups according to PSA value. In subgroup A, 66 patients had a PSA less than 4 ng/ml; in subgroup B, 199 patients had a PSA between 4 and 10 ng/ml, while, in subgroup C, 151 had a PSA greater than 10 ng/ml. In the subgroups A, B, and C, the number of patients found to have neoplasia was 17/66 (26%), 131/199 (66%), and 137/151 (91%), respectively. *Discussion and Conclusion:* Our data showed that the ability of MRI to detect prostate cancer increases as PIRADS increases, especially when combined with the PSA assay, which is an extremely useful tool, especially in cases of uncertain PIRADS. MRI remains a cornerstone of diagnostics and staging depending on the possibility of targeted MRI biopsy retrievals; however, radiological images alone may lead to false positive conclusions.

54

PET/CT IN THE DETECTION OF UNDIAGNOSED PROSTATE CANCER

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Background/Aim: Prostate cancer is the second most diagnosed cancer in males worldwide and, in Italy, the most diagnosed invasive cancer in men aged 50 to 79. Multiparametric magnetic resonance imaging (mpMRI), according to the international guidelines, is currently the most comprehensive tool for non-invasive primary tumor staging of prostate cancer (PCa). However, more than 20% of primary cancers are missed on mpMRI. The standardized uptake value (SUV) index derived from 18F-choline positron emission tomography/computed tomography (PET/CT) and 68Ga-prostate-specific membrane antigen (PSMA) PET/CT may represent a promising modality for identification of PCa in patients with persistently increased serum PSA, but equivocal or negative digital rectal examination (DRE) and mpMRI. The aim of the study was to evaluate the diagnostic accuracy of PET/TC in the decision making of PCa diagnosis. *Materials and Methods:* Between January 2019 and June 2021, 25 patients with persistently increased serum PSA suspicious for PCa, negative DRE and negative mpMRI (Prostate Imaging - Reporting and Data System version 2 ≤3) underwent to 18F-choline PET/CT and 68Ga-PSMA PET/CT (19 and 6 patients, respectively). *Results:* Mean age of total patients (n=25) was 58.6 years. Twenty-one out of 25 patients (84%) showed considerable high SUV (>5.0) and underwent cognitive prostate biopsy. Out of the 21 patients, 1 showed no pathologic findings and was subjected to strict follow-up with outpatient visits every 3 and 6 months, while 2021 showed PCa. Pathology results were multifocal Gleason score 6 (3+3) in 10, Gleason score 7 (3+4) in 8 and Gleason score 7 (4+3) in 2 patients. All 20 patients underwent a robot-assisted radical prostatectomy. *Conclusion:* 18F-choline PET/CT and 68Ga-PSMA PET/CT showed high detection accuracy of PCa in patients with elevated and increasing PSA levels and a negative or equivocal DRE and mpMRI. Thus, it should be considered as an emerging and promising staging modality, not only for recurrent, but also for primary prostate cancers.

55
CARDIOVASCULAR TOXICITY IN PATIENTS TREATED WITH IMMUNE CHECKPOINT INHIBITORS PLUS TYROSINE-KINASE INHIBITORS FOR SOLID TUMORS: A META-ANALYSIS

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Background/Aim: Combinations of an immune checkpoint inhibitor (ICI) targeting programmed death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) or cytotoxic T-lymphocyte associated protein 4 (CTLA4) and a tyrosine kinase inhibitor (TKI) have recently led to a paradigm shift in the treatment of different cancer types. However, these combinations can be associated with an increased toxicity. We performed a meta-analysis with the aim of assessing the incidence and relative risk (RR) of cardiovascular toxicity (CVT) and hypertension in patients treated with ICI+TKI combinations for solid tumors. *Material and Methods*: Prospective studies were identified by searching the MEDLINE/PubMed, Cochrane Library and ASCO Meeting abstracts. Data extraction was conducted according to the PRISMA statement. Combined RRs and 95% confidence intervals (CIs) were calculated using fixed- or random-effects methods, depending on studies heterogeneity. RevMan software for meta-analysis (v.5.2.3) was used to perform statistical analyses. *Results:* Seven studies were selected for the analysis of CVT, with a total of 4,029 patients. The incidence of any- and high-grade CVT with ICI+TKI combinations compared to the controls was 0.7% *versus* 0.2% and 0.6% *versus* 0.2%, respectively. Treatment with ICI+TKI combinations significantly increased the risk of any grade CVT compared to controls (fixed-effects, RR=2.67, 95% CI=1.09-6.54; p=0.03). However, these combinations did not significantly increase the risk of high-grade CVT (RR=2.21, 95% CI=0.88-5.56; p=0.09). Concerning hypertension, twelve studies were selected for the analysis, with a total of 5,899 patients. The incidence of hypertension of any grade and high-grade was 37.4% and 18.8%, respectively, with ICI+TKI combinations, compared to 25.8% and 12.1% in the control arms. Treatment with ICI+TKI combinations significantly increased the risk of hypertension of any grade compared to controls (random-effects, RR=1.57, 95% CI=1.02-2.40; p=0.04), but not of hypertension of high-grade (RR=1.41, 95% CI=0.86-2.34; p=0.18). *Conclusion:* Although ICI+TKI combinations are associated with an increased risk of any grade CVT, the lack of a significant risk of high-grade CVT along with the low incidence of CVT events suggests that a routine cardiovascular assessment is not required for asymptomatic patients.

56
RADIOMICS IN PI-RADS 3 MULTIPARAMETRIC MRI FOR PROSTATE CANCER IDENTIFICATION: A LITERATURE REVIEW AND PROPOSAL OF A MODEL COMBINING CLINICAL AND RADIOMIC FEATURES

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Background/Aim: Clinical management of Prostate Imaging Reporting and Data System (PI-RADS) 3 prostate lesions is still a debate topic, with high variability in different center protocols. Indicators able to identify clinically significant prostate tumors among PI-RADS 3 lesions are needed. Radiomics applied to multiparametric magnetic resonance imaging (MRI) seems a promising option. The first aim of this work was to review the literature describing the application of radiomics in cases of PIRADS 3. The second aim was to re-implement literature models on 80 PI-RADS 3 lesions dataset. The third aim was to propose a novel model combining PSA-density and radiomics features. *Patients and Methods*: We retrospectively retrieved medical and radiological data from our Institution Electronic Medical Records. The final cohort included 80 patients who underwent prostate MRI (June 2016-March 2021) for suspected malignancy or active surveillance. The standard MRI protocol included: i) axial, coronal, and sagittal fast-relaxation fast spin-echo (FRFSE) T2-weighted sequences, with 3 mm thickness; ii) axial single-shot fast spin-echo (SSFSE) T2-weighted sequence, with 4 mm thickness (pelvis); iii) axial fast spin-echo (SSFSE) T1-weighted sequence, with 4 mm thickness (pelvis); iv) axial gradient recalled-echo (GRE) T1-weighted sequence, with 3 mm thickness (prostate lodge

and seminal vesicles), before and after intravenous administration of paramagnetic contrast medium (perfusion study); v) axial diffusion-weighted imaging (DWI) sequences with b values of 50 and 2000 s/mm^2 and 3 mm thickness (prostate lodge); DWI sequences then went through post-processing to obtain apparent diffusion coefficient (ADC) maps. Each patient underwent a targeted biopsy of the PI-RADS 3 lesions at our Institution, performed by trans-perineal rectal access and fusion technique with the reference MRI. Literature and the proposed model were trained and assessed through 100 5-fold cross-validation repetitions. *Results:* Among the five works found in the literature, two were considered re-implementable on an independent dataset. Eighty patients with at least one PI-RADS 3 lesion (according to PI-RADS v2.1) detected on prostate MRI on a 3T MRI scanner were retrospectively included. Final pathological analysis utilizing MRI-targeted biopsy was used as a reference standard. The first literature model (for GS >7 identification) obtained a sensitivity of 40% and a specificity of 71% on our dataset. The second one (for GS>6 identification) had a sensitivity of 47% and a specificity of 65%. PSA-density predicted clinically significant tumors with 66% sensitivity and 71% specificity. The proposed model, which combines PSA-density, a T2 radiomic feature of texture regularity, and a radiomic texture feature computed on the ADC maps, obtained a sensitivity of 80% and a specificity of 76%. *Conclusion:* T2 and ADC radiomic features, combined with PSA-density, might help to improve the identification of clinically significant prostate tumors in PI-RADS 3 lesions. However, validation on independent and larger datasets is needed to understand whether radiomics models can work with multi-center data.

57
BCG FAILURE IN NMIBC: A SINGLE CENTER EXPERIENCE OF HYPERTHERMIC INTRAVESICAL CHEMOTHERAPY (HIVEC)

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Background/Aim: Intravesical bacillus Calmette-Guérin (BCG) therapy following trans-urethral resection of the bladder (TURB) is the standard treatment for reducing recurrences in patients affected by intermediate and high-risk non-muscle invasive bladder cancer (HR-NMIBC). According to the literature, this cancer is characterized by high rates of recurrence (60-80% at 5 years) and progression (20-40%). Unfortunately, BCG may be unavailable and treatment failure may occur. Literature provides data on the efficacy of the hyperthermic intravesical chemotherapy (HIVEC) with mitomycin C (MMC) as first treatment in HR-NMIBC following TURB. The aim of this study was to evaluate the efficacy of MMC HIVEC in the setting of BCG failure. *Materials and Methods:* From December 2017 to May 2021, we collected data from patients with HR-NMIBC not responding to BCG (refractory/relapsing/unresponsive/intolerant) submitted to MMC HIVEC at 43˚C with COMBAT® system. The schedule included induction (weekly session for 6 weeks) and maintenance (monthly session for 6 months) courses. All patients were followed with fluorescence cystoscopy with hexaminolevulinate and bladder mapping at the end of the induction, with cystoscopy every 3 months in the first 2 years of follow-up and CT-scan every 6 months for 2 years. Eighteen-month progression-free survival (PFS)

Table I. *Demographic and baseline pathological features.*

Characteristics	n (%)
Patients	53
Sex	
Male	46 (86.8%)
Female	7 (13.2%)
Age*, years	69±11
Smoking history	
Non smoker	9 (17.0%)
Former smoker	40 (75.5%)
Current smoker	4 (7.5%)
Pathological stage	
Ta	29 (54.7%)
T1	7 (13.2%)
T*is*	8 (15.1%)
Ta + C*is*	6 (11.3%)
T1 + C*is*	3 (5.7%)
Pathological grade (according to WHO 1973)	
Grade 1	5 (9.4%)
Grade 2	20 (37.7%)
Grade 3	28 (52.9%)
BCG failure	
BCG unresponsive	23 (43.4%)
BCG relapsing tumor	13 (24.5%)
BCG refractory tumor	5 (9.4%)
BCG intolerance	12 (22.7%)

SD: Standard deviation; BCG: bacillus Calmette-Guerin; WHO: World Health Organization. *Data presented as mean±SD.

and recurrence-free survival (RFS) were evaluated. *Results:* A total of 53 patients were enrolled. Demographics and baseline pathological data are summarized in Table I. After a median follow-up of 18 months (interquartile range: 12-23), 29 (54.7%) patients were disease-free; 11 (20.7%) experienced NMIBC recurrence, managed in 3 cases (5.66%) with BCG or HIVEC re-induction and in 8 (15.1%) patients with radical cystectomy; 2 (3.7%) patients died due to BC progression (T2 and metastatic disease) and 3 patients experienced upper tract urothelial carcinoma treated with radical nephroureterectomy. Twelve-month PFS was 100% whilst RFS was 91.4%. All complications related to HIVEC treatment were Clavien grade I-II and 9 (16.9%) patients discontinued treatment for spasms and/or intolerance. *Conclusion:* In our experience, HIVEC with MMC was an effective and safe treatment for patients with BCG failure.

59

ORTHOTOPIC URINARY DIVERSION IN OCTOGENARIAN PATIENTS: A NARRATIVE REVIEW

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Background/Aim: The incidence of bladder cancer (BC) increases with age, thus worsening treatment outcomes and increasing tumor stage. Radical cystectomy (RC) and urinary diversion is the gold standard therapy for muscle invasive bladder cancer; however, this surgery remains a morbid operation and the identification of modifiable risk factors is important to potentially decrease complication rates following surgery. Unfortunately, age is a factor that negatively affects surgical and oncological outcomes and is associated with a greater number of complications following radical cystectomy. The type of urinary derivation (UD) has been at the center of numerous debates, a non-continent urinary derivation such as ileal conduit (IC) or ureterocutaneostomy (UCS) seems to be the best choice in elderly patients (>75 years old), while orthotopic neobladder (ON) derivation is the least practiced. The aim of our narrative review was to examine whether age greater than 75 years is an exclusion factor for all bladder cancer patients who are candidates for radical cystectomy and orthotopic UD. *Materials and Methods:* We reviewed the literature to identify studies reporting outcomes, complications, patient-selection criteria, and quality-of-life data on elderly patients, who underwent orthotopic neobladder following radical cystectomy. A comprehensive literature review was performed within the Pubmed and Cochrane database, using the keyword search phrases "cystectomy", "frailty", "elderly" for bladder cancer, focusing on a timeline since 2015. About 70 studies were identified and after careful selection about 30 studies were analyzed. *Results:* Age factor was the main parameter of interest. In six studies, patients >70 years old underwent RC, ON was performed in about 20% of cases (patients >75 years old, with no comorbidities, with localized disease and normal performance status). In different studies patients >80 years old with multiple comorbidities (CCI >4, and ASA score >III), but considered "fit for surgery", underwent RC with external UD. In two studies, patients >80 years with high CCI (>6), who had already undergone abdominal surgery were not treated with RC. In the literature there is no evidence for a specific age used as an exclusion criterion; however, elderly patients with multiple comorbidities and an unfavorable American Society of Anesthesiologists score (ASA) and Charlson comorbidity index (CCI) are not considered fit for this type of UD, preferring external UD such as ileal conduit or ureterocutaneostomy or by preferring therapeutic strategies other than surgery. *Conclusion:* An accurate preoperative selection of elderly patients could ensure good clinical, surgical, and oncological outcomes, giving the possibility even to the octogenarians to receive an orthotopic derivation with ON.

60

CORRELATION BETWEEN MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING OF THE PROSTATE AND DEFINITIVE HISTOLOGICAL EXAMINATION AFTER RADICAL PROSTATECTOMY: HOW ACCURATE IS THE IMAGING?

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Aim: To evaluate the accuracy of multiparametric (mp)-MRI in detecting all clinically significant prostate cancer (csPCa) (grade group ≥2) outbreaks, using radical prostatectomy specimens as the gold standard. We also evaluated the presence of csPCa outside the lesion detected by the mp-MRI. Finally, we compared the mpMRI accuracy to target plus systematic biopsy. *Patients and Methods*: The study

prospectively evaluated 57 patients who underwent robot-assisted radical prostatectomy from December 2019 to February 2021. All patients had positive mpMRI (PIRADS ≥3) and underwent standard and fusion biopsies. Cross sections of the surgical specimens were performed. The lesions identified on mp-MRI and presented in the same axial quadrant and segment of the operative specimen were considered concordant. Histologically confirmed tumor foci not identified on mp-MRI were considered false negatives, while lesions with no histopathological match were considered false positives. The index lesion was the area containing the tumor with the highest GG. When multiple lesions had the same GG, the lesion with the highest percentage of the highest Gleason pattern was considered the index lesion. mp-MRI findings and definitive histology both with an evaluation "per lesion" and "per patient" were compared. *Results:* Results "per lesion" are shown in Table I. The sensitivity of the mp-MRI was 37% (67/180) and for PCa was 48% (66/138). However, combination with biopsies allowed detection of 142/180 lesions (79%) and of 102/138 (74%) csPCa. Concerning the results "per patient", presence of histologically-confirmed csPCa only in the mp-MRI target was observed in 31.6% of patients, while presence of histologically-confirmed csPCa only in the same lobe of mp-MRI target in 47.7% of patients. The negative predictive value of mp-MRI for csPCa outside the PIRADS area was only 32%. Prostate biopsies detected PCa outside the mp-MRI lesion in 39 patients; 27 of those harboring csPCa, and 15 being on the contralateral lobe. *Conclusion:* mp-MRI misses a higher percentage of csPCa foci, and shows a low negative predictive value compared to final histology. However, prostate biopsy may improve the accuracy compared to final histology, with the risk of missing 25% of csPCa foci. These results must be taken into account when planning PCa treatment based on mp-MRI, especially in the case of focal treatment.

Table I. *Results "per lesion".*

Identification of lesions at histology	N=180
Missed lesions by mp-MRI	113/180 (62.8%)
Missed lesions by mp-MRI with csPCa	71/113 (62.8%)
Identification of lesions by mp-MRI	N=69
csPCa lesions identified	66/69 (95.7%)
False positive	2/69 (2.9%)
True positive	1/69 (1.4%)
Index lesion and final histology in patients	
Correctly identified by mp-MRI	48/57 patients (84%)
Missed by mp-MRI	9/57 patients (16%)

mp-MRI: Multiparametric MRI; csPCa: clinical significant prostate cancer.

61
ACCURACY OF A NEW ELECTRONIC NOSE (ENOSE) FOR PROSTATE CANCER DIAGNOSIS IN URINE SAMPLES

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Background/Aim: The definitive diagnosis of prostate cancer (PCa) depends on histopathological verification in prostate biopsy cores. However, prostate biopsy is not free of risk and urologists still perform a high number of unnecessary procedures. Many blood and urine biomarkers have been proposed and validated for this purpose, but none has managed to effectively improve diagnostic effectiveness. Recent advances demonstrated that PCa produces specific urinary volatile organic compounds (VOCs). We have already proven that trained dogs can recognize specific VOCs. Unfortunately, dogs cannot be approved in clinical practice, therefore is important to develop a device able to mimic the olfactory system of dogs. The current study aimed to evaluate the accuracy of a new eNose, in order to recognize prostate cancer (PCa) in urine samples. *Materials and Methods:* We prospectively enrolled, in a blind cohort study, 174 patients referred to our center between March 2020 and March 2021. They were divided into PCa group (A) with a histological confirmation of PCa, and control group (B) which included:

females and males between 18-25 years, with no familiarity for PCa, and prostate-specific antigen (PSA) <1 ng/ml, and men >45 years with no familiarity for PCa, negative digital rectal examination, and PSA <2.5 ng/ml. A urine sample was collected for each one after hospital admission and stored at -20˚C until the analysis. The eNose was developed and produced at Politecnico di Milano and the training was performed exactly like dog training. All statistical tests were two-sided and statistical significance was set at $p<0.05$. Statistical analyses were performed with STATA 16.1 (StataCorp LLC 2019, College Station, TX, USA). *Results:* Eighty-eight of 174 patients (50.6%) belonged to group A and 86 (49.4%) to group B. The eNose sensitivity reached 85.2% (95% CI=76.1-91.9) and specificity 79.1% (95% CI=69.0-87.1). Considering only men >45 years, the eNose had sensitivity 85.2% (95% CI=76.1-91.9) and specificity 72.7% (95% CI=57.2-85.0). The diagnostic accuracy was reported as the area under the receiver operating characteristic curve (0.821, 95% CI=0.764-0.879). *Conclusion:* The eNose appears to be a promising, accurate, reproducible, and low-cost device to introduce in a clinical setting for PCa diagnosis. Further studies are necessary to investigate the eNose on a large-scale setting in order to validate its application in diagnostic PCa nomograms.

63
URINE LYOPHILIZATION DOES NOT ALTER THE DIAGNOSTIC ACCURACY OF PROSTATE CANCER BY CANINE OLFACTION

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Background/Aim: Researchers have been interested in identifying new PCa diagnostic pathways, to reduce the number of prostate biopsies. Many biomarkers have been developed but none appeared able to effectively improve diagnostic accuracy. It has also been demonstrated that trained dogs can detect various neoplastic and non-neoplastic diseases by sniffing body fluids. We have demonstrated that trained dogs can detect specific PCa Volatile Olfactory Compounds (VOCs) in urine. Herein, we aimed to investigate whether the lyophilization of urine samples, a freeze-drying process, affects the diagnostic accuracy of PCa by canine olfaction. *Patients and Methods*: We enrolled 60 patients referred to our center from January 2016 to January 2017. Overall, 30 patients were affected by PCa (A), others belonged to the control group (B) which included females, males with non-neoplastic diseases (negative family history for PCa, PSA <2 ng/ml) and males with neoplastic disease different from PCa. For each patient a urine sample was collected after hospital admission and stored at –20˚C until the analysis. Two female German Shepherd Explosive detection dogs were used for this study. Dogs were trained using the clicker training method to detect and signal VOCs. They were taught to sit in front of the urine sample recognized as cancerous. To investigate whether the lyophilization can alters the VOCs levels in urines, leading the loss of PCa detection by canine olfaction, three different samples collected were used: i) 2 ml of thawed urine from PCa and control groups; ii) 4 ml of freeze-dried urine from PCa and control groups; iii) 4 ml of freeze-dried urine from PCa group and 4 ml of thawed urine from control group. Urine samples were randomly selected and positioned in the experimental setting; all urine samples from group A and B were analyzed in double blind. Each dog tested all 60 samples after random positioning. *Results:* In the first test, dogs achieved a sensibility (SN) and specificity (SP) of 100% (95% CI=99.0-100.0). In the second and third tests, both dogs achieved SN and SP of 100% (95% CI=98.0-100.0). *Conclusion:* Lyophilization is mainly used to preserve perishable materials, to extend shelf life or make the material more convenient for transport. We demonstrated that urine lyophilization does not lead to the failure of detection of PCa samples by trained dogs, thus the process does not eliminate specific PCa VOCs.

64
LOCALLY ADVANCED RENAL CELL CARCINOMA: THE VALUE OF A MULTIDISCIPLINARY TEAM

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Background/Aim: Despite an increasing interest in novel perioperative systemic therapies, surgery remains the gold standard treatment for locally advanced non-metastatic renal cell carcinoma (RCC). Surgical strategies are often challenging for these complex patients, thus it is essential to accurately plan the intervention, optimizing the collaboration between multiple specialists. In this study, we report surgical outcomes for a contemporary series of patients with locally advanced non-metastatic RCC treated at a referral Academic Center. *Patients and Methods*: We included cT3-T4 N0-N1 M0 RCC patients treated between January 2017 and December 2020. All cases of RCC with level III-IV Inferior Vena Cava (IVC) thrombosis were managed by a multidisciplinary surgical team, employing liver transplant techniques to expose IVC and perform thrombectomy without the need of sternotomy and extracorporeal circulation (ECC). Intraoperative complications were reported according to the Intraoperative Adverse Incident Classification (EAUiaiC), while postoperative complications according to the modified Clavien- Dindo classification. *Results:* Thirty-two patients were included in the analytic cohort: 20 (62.5%) were cT3a, 5 (15.6%) cT3b, and 7 (21.9%) cT4; 26 (81.3%) patients were cN1. Nine patients (28.1%) underwent partial nephrectomy, while 23 (71.9%) radical nephrectomy. A template-based lymphadenectomy was performed in 12 cases (37.5%); 25% were pN1. Surgical approach was open in 13 (40.6%) cases, laparoscopic in 3 (9.4%), and robotic in 16 (50%). In 4/5 cases of RCC level IV IVC thrombosis, liver transplant techniques allowed surgeons to successfully complete IVC thrombectomy with no need of ECC. Intraoperative complications were recorded in 3 (9.4%) patients, who were all grade I. Overall complication rate was 37%, while no major postoperative complications (Clavien-Dindo grade 3-5) were recorded. At a median follow-up of 24 months, cancer-specific mortality was 8%. Five patients experienced local recurrence and 2 distant metastases (overall recurrence rate 21%). *Conclusion:* Locally advanced RCC is a complex, challenging, and heterogeneous disease. Patient selection and hospital team experience are key to optimize patient outcomes. Multidisciplinary collaboration between surgeons of different specialties can optimize the outcomes of these patients.

65
THE VALUE OF EAU INTRAOPERATIVE ADVERSE INCIDENT CLASSIFICATION IN SMALL RENAL MASSES SURGERY

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Background/Aim: Intraoperative adverse events (ioAEs) that occur during partial (PN) or radical nephrectomy (RN) are often overlooked or underestimated; therefore, they are likely to be underreported in the urologic literature. Recently, the European Association of Urology (EAU) proposed a new set of quality criteria for reporting and grading ioAEs, the EAU Intraoperative Adverse Incident classification (EAUiaiC). There is lack of evidence on the prevalence of ioAE and its impact during renal cancer surgery. The objective of this study was to explore the intraoperative morbidity of PN/RN in a contemporary cohort of patients with organ-confined renal masses at a referral Academic Center. *Patients and Methods*: We prospectively collected data from patients undergoing PN or RN for cT1-T2N0M0 renal masses between January 2017 and December 2020. ioAEs were reported according to the EAUiaiC. Univariable logistic regression analysis was performed to assess the potential predictors of ioAEs. *Results:* Overall, 493 patients were included [418 (84.8%) PN; 75 (15.2%) RN]. Median age at diagnosis was 66 years [interquartile range (IQR)=56.0-74.0], median body mass index (BMI) 26.1 kg/m^2 (IQR=23.4-28.7), median American Society of Anesthesiologists (ASA) physical status score 2 and median tumor diameter 4.0 cm (IQR=3.0-5.2). ioAEs were recorded in 18 (3.6%) patients, all grade 1 events according to the EAUiaiC. The most frequent events were represented by pleural lesions and intraoperative bleeding. At univariable analysis, the occurrence of ioAEs was significantly associated with prolonged anesthesia time, prolonged operative time, longer hospitalization, BMI, history of abdominal surgery, treatment with antiplatelet drugs, cT stage, tumor complexity, number of renal vessels, surgical approach, and type of treatment (PN *vs*. RN). *Conclusion:* In experienced hands, a low proportion of patients undergoing PN or RN for organ-confined renal masses experienced ioAEs, which were all managed without long-term side effects. The EAUiaiC allowed standardized reporting of such events, providing a foundation for the assessment of their ultimate drivers among patient-, tumor- and provider-related factors.

66
KEYNOTE-564 TRIAL TO CLINICAL PRACTICE: POTENTIAL USE OF ADJUVANT PEMBROLIZUMAB IN NON METASTATIC CCRCC

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Background/Aim: The renal cell carcinoma (RCC) EAU Guidelines do not recommend adjuvant systemic therapy in patients with clear-cell RCC (ccRCC) at higher risk of recurrence after surgery with radical intent. The recent KEYNOTE-564 trial results provided new perspectives, suggesting positive impact of adjuvant immunotherapy with pembrolizumab on disease-free survival in patients with adverse RCC features. The aim of this study was to explore the differences in clinical characteristics and oncological outcomes between patients with intermediate-to-high risk ccRCC and patients with lower-risk ccRCC. *Patients and Methods*: We collected data from patients with ccRCC who underwent partial (PN) or radical nephrectomy from January 2017 to December 2020. Patients were classified as low- or intermediate-to-high-risk of recurrence according to the KEYNOTE- 564 protocol-defined criteria. *Results:* A total of 284 patients were included. Of these, 206 (70.7%) were classified as low-risk and 78 (29.3%) as intermediate-to-high-risk. Comparing the two groups, patients with low-risk ccRCC were younger than those with intermediate-to-high-risk ccRCC (median age 66 *vs*. 71 years, p=0.004), had higher proportion of organ-confined disease (97.1% *vs*. 67.1%, p<0.001) and had tumors of lower complexity (median PADUA score 8 *vs*. 10, p<0.001). PN was performed more often in these patients (93.7% *vs*. 30.8%, p<0.001). A higher incidence of intraoperative complications (classified according to the EAUiaiC) was recorded in intermediate-to-high-risk patients compared to the low-risk (14.1% *vs*. 2.9%, p=0.006; all complications were grade 1), while no difference was found between the two groups in terms of postoperative complications (32.1% *vs*. 20.9%, p=0.06) and hospital stay. At a median follow-up of 26 months [interquartile range (IQR)=14-35], 14 (5.3%) patients developed recurrence (0.5% *vs*. 17.3% in the low-risk and intermediate-to-high risk groups, respectively, p<0.001). *Conclusion:* Almost one out of three patients with ccRCC was classified as intermediate-to-high risk of recurrence. These patients were different from those with lower risk disease from a clinical standpoint and had a non-negligible risk of recurrence at a mid-term follow-up. While waiting for definitive data from KEYNOTE-564 trial, our preliminary findings support consideration of adjuvant therapy in real-life clinical practice for patients with intermediate-to-high risk ccRCC.

67
APPLICATION OF 99MTC-SESTAMIBI SPECT/CT FOR IDENTIFICATION OF POTENTIALLY ELIGIBLE PATIENTS FOR ACTIVE SURVEILLANCE

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Background/Aim: Diagnosis of small renal masses (SRMs) are increasing; however, it has not been accompanied with an improved cancer-specific-survival, suggesting that many SRMs are benign or have low malignant potential and thereby do not require treatment. Several novel imaging techniques are emerging as methods to define histology prior to surgery. SPECT/CT with 99mTc-sestamibi (TcS) seems able to identify oncocytic neoplasm as oncocytomas and chromophobe tumors (chRCC), with high sensitivity (87.5%) and even higher specificity (95.2%). The aim of this study was to analyze the oncological outcomes of patients who underwent surgery for localized renal masses, simulating a scenario in which TcS would have classified renal masses as positive or negative, in order to evaluate the proportion of patients who could have safely undergone a protocol of active surveillance. *Patients and Methods*: We collected data from patients undergoing partial (PN) or radical (RN) nephrectomy for cT1N0M0 renal masses from January 2017 to December 2021. Based on postoperative histological results, patients were classified as potentially TcSP and potentially TcS-negative (TcSN). *Results:* Overall, 584 patients were included [442 (75.7%) TcSN; 142 (24.3%) TcSP]. Among the TcSN patients, 393 (89.7%) underwent PN, 49 (10.3%) underwent RN; 37 lesions (8.4%) were benign and 405 (91.6%) were malignant. In the TcSP group, 131 (92.3%) patients underwent PN and 11 (7.7%) RN; 94 lesions (66.2%) were benign (oncocytomas) and 48 (33.8%) were malignant (chRCC). At a median follow-up of 28 months [interquartile range (IQR)=44-16], 106 (99.1%) patients were alive without evidence of disease, while 1 (0.9%) died for non-tumor-related causes, in the TcSP group. Among TcSN patients, 358 (96%) were alive without evidence of disease, 4 (1.1%) died for tumor-related causes,

11 (2.9%) died for other causes. Out of 373 TcSN patients, 20 (5.4%) experienced recurrence [14 (3.8%) local, 6 (1.6%) systemic]. Out of 107 TcSP patients, 1 (0.9%) underwent surgery for chRCC local recurrence after 36 months from previous PN (p=0.048). *Conclusion:* cT1N0M0 oncocytic tumors have favorable oncological outcomes compared to all the other histotypes. Therefore, preoperative use of 99mTcS SPECT/CT, potentially coupled with a confirmatory percutaneous renal mass biopsy, may help to select patients with localized renal masses who are more likely to harbor an oncocytic neoplasm and, consequently, more likely to benefit from active surveillance.

68
EVOLUTION OF ACTIVE SURVEILLANCE FOR PROSTATE CANCER: A SINGLE INSTITUTE EXPERIENCE LASTING 17 YEARS

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Background/Aim: Active surveillance (AS) for prostate cancer has been offered as an alternative to radical treatment in our multidisciplinary clinic. According to evolving knowledge and technology improvement, three AS protocols opened to recruitment: the mono-institutional SAINT (2004), the Prostate Cancer Research International Active Surveillance (PRIAS; 2007), and the mono-institutional SPRINT (2016). We aimed to evaluate outcomes of this long and complex experience. *Patients and Methods*: Selection criteria are presented in Table I. In 2016, multiparametric magnetic resonance imaging (MRI)/target biopsy allowed inclusion with >2 positive cores (PRIAS, SPRINT). In 2020, PRIAS study included favorable intermediate-risk patients, selected through MRI/target biopsy (1). Monitoring was scheduled as shown in Table II. Additional biopsies were recommended by PSA doubling time <10 years and treatment advised by protocol reasons: i) increase in Grade Group (GG); ii) increase in the number of positive cores accepted by protocols. The switch from AS to watchful waiting (WW) was recommended due to comorbidities or age >80 years. Kaplan-Meier analysis estimated survival end-points. *Results:* From December 2004 to March 2022, 1,324 patients were enrolled: 206 in SAINT, 756 in PRIAS,

Table I. *Inclusion criteria according to protocol.*

Protocol	DRE	PSA (ng\ml)	PSA density (ng\ml\cc)	Grade group	Positive cores/tot	Tumor extent per core
SA-INT	≤T2a	≤10	/	≤1	≤25%	≤50%
PRIAS (no MRI)	≤T2	≤10	<0.2	≤1	≤2	/
PRIAS (MRI)	≤T2	≤20	<0.25	≤2	≤50% if GG2	/
SPRINT	≤T2a	≤10	/	≤1	/	/

PSA: Prostate-specific antigen; PRIAS: Prostate Cancer Research International Active Surveillance; MRI: magnetic resonance imaging.

Table II. *Monitoring schedule according to protocol.*

Protocol	PSA frequency (months)	DRE	mpMRI (years from diagnosis)	Biopsy (years from diagnosis)
SA-INT	3	6	Not stated	1, 2, and subsequently every 2
PRIAS (no MRI)	3	6	Not stated	1, 4, 7, 10, and subsequently every 5
PRIAS (MRI)	3	6	Inclusion and before biopsy	1, 4, 7, 10, and subsequently every 5
SPRINT	3	6	Inclusion; 1, 2, 4, 7	1, 2, 4, 10

PSA: Prostate-specific antigen; DRE: digital rectal examination; mpMRI: multiparametric magnetic resonance imaging; PRIAS: Prostate Cancer Research International Active Surveillance.

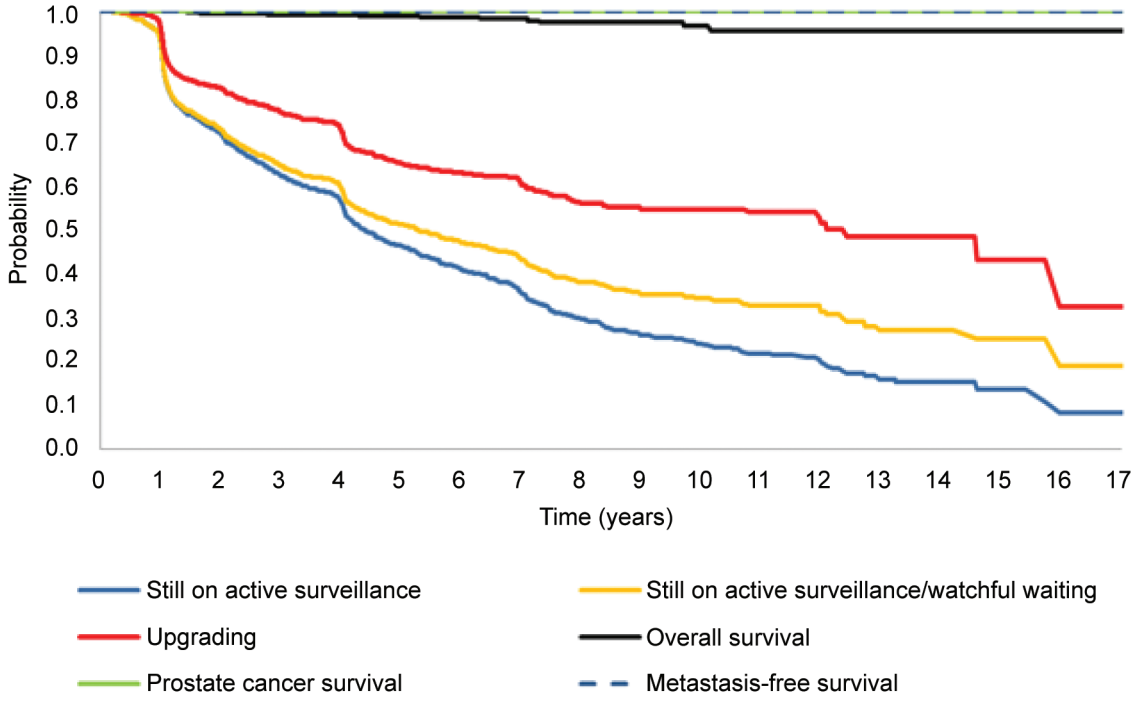

Figure 1. *Kaplan-Meier survival analyses for each study end-points: on active surveillance (blue line); on monitoring (yellow line); upgrading-free survival (red line); overall survival (black line); prostate cancer-specific survival (green line); metastasis-free survival (hatching blue line).*

240 in SPRINT; a further 122 patients have been followed off-protocol. Median age was 66 years (range=41-79), median iPSA was 5.6 ng/ml (range=0.3-24). Out of 1,324 patients, 1,252 (94.6%) were NCCN very low or low risk, 72 (5.4%) favorable intermediate-risk (2); 494 (37%) patients are still on AS, at median time of 57 months (range=5-210). A total of 810 patients dropped out: 490/810 (60.5%) per protocol, 10 (1.2%) due to anxiety, 187 (23%) due to personal choice, 15 (1.8%) due to non-PCa deaths. Furthermore, 108 (13.5%) patients switched to WW, definitively avoiding radical treatments. At 5 and 10 years, probability of being still on monitoring (AS or WW) was 51.4% and 34.4%, respectively; upgrading-free survival was 65% and 55%, respectively. Neither prostate cancer deaths nor metastases occurred during AS. The estimated overall survival was 99% and 97% at 5 and 10 years, respectively (Figure 1). *Discussion and Conclusion:* For 17 years, we proposed AS according to evolving criteria and tools. So far, widening criteria has allowed more patients to avoid or delay treatment, while did not alter overall survival. No cases of metastatic disease or cancer-related death occurred during AS. Most patients dropped out due to GG reclassification. Nonetheless, many withdrew with no reclassification and may have kept the risk of overtreatment. Systematic adoption of MRI and newer predictive markers may improve the selection and exclusion criteria for AS.

1 Prostate Cancer Research International Active Surveillance - PRIAS Project. Available at: https://www.prias-project.org/ [Last accessed on April 29, 2022]

2 Mohler JL, Armstrong AJ, Bahnson RR, D'Amico AV, Davis BJ, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, Hurwitz M, Kane CJ, Kawachi MH, Kuettel M, Lee RJ, Meeks JJ, Penson DF, Plimack ER, Pow-Sang JM, Raben D, Richey S, Roach 3rd M, Rosenfeld S, Schaeffer E, Skolarus TA, Small EJ, Sonpavde G, Srinivas S, Strope SA, Tward J, Shead DA, and Freedman-Cass DA: Prostate Cancer, Version 1.2016. J Natl Compr Canc Netw *14(1)*: 19-30, 2016. PMID: 26733552. DOI: 10.6004/jnccn.2016.0004

69
RESPONSE ASSESSMENT TO SECOND-LINE SYSTEMIC THERAPIES IN ADVANCED PROSTATE CANCER USING 68GA-PSMA-11 PET/CT

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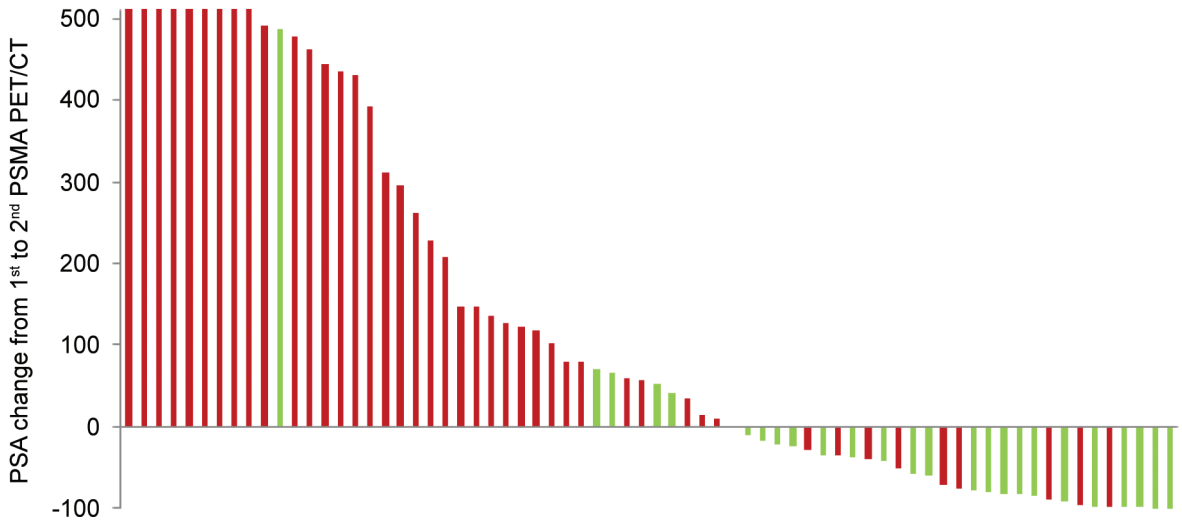

Figure 1. *Distribution of prostate-specific antigen (PSA) change (%) in responder (green) and non-responder group (red). Values higher than 500% were truncated. Analysis was performed in 70 patients who underwent 2nd prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT).*

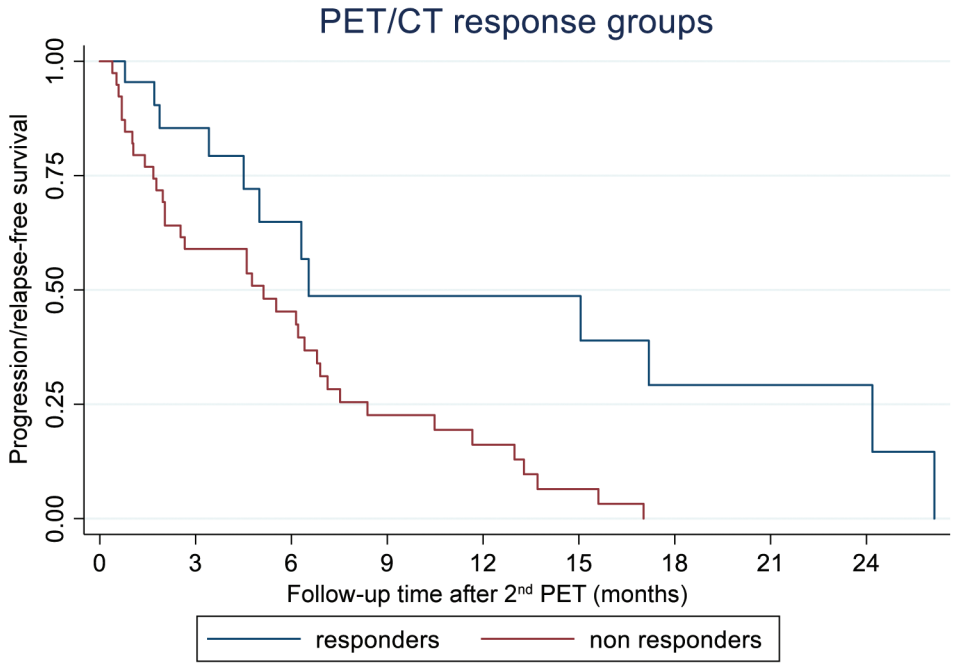

Figure 2. *Progression-free survival after 2nd positron emission tomography/computed tomography (PET/CT), according to PET/CT response groups (p-Value=0.005).*

Background/Aim: Prostate-specific membrane antigen (PSMA) is overexpressed in patients with metastatic castration-resistant prostate cancer (mCRPC), and gallium-68-(68Ga-) PSMA-11 positron emission tomography/computed tomography (PSMA-PET/CT) is emerging as standard of care for guiding treatment decisions. Understanding how PSMA expression is impacted during treatment could provide information on its utility to guide clinical decision making. We evaluated PSMA expression on PET/CT in patients before and after treatment with life-prolonging therapies, including abiraterone and enzalutamide, taxanes, 223-radium and 225Ac/177Lu-PSMA. *Patients and Methods*: CRPC patients were enrolled in this observational, retrospective, single-center cohort study. PSMA pathological uptake was assessed on baseline PSMA-PET/CT. PSMA-

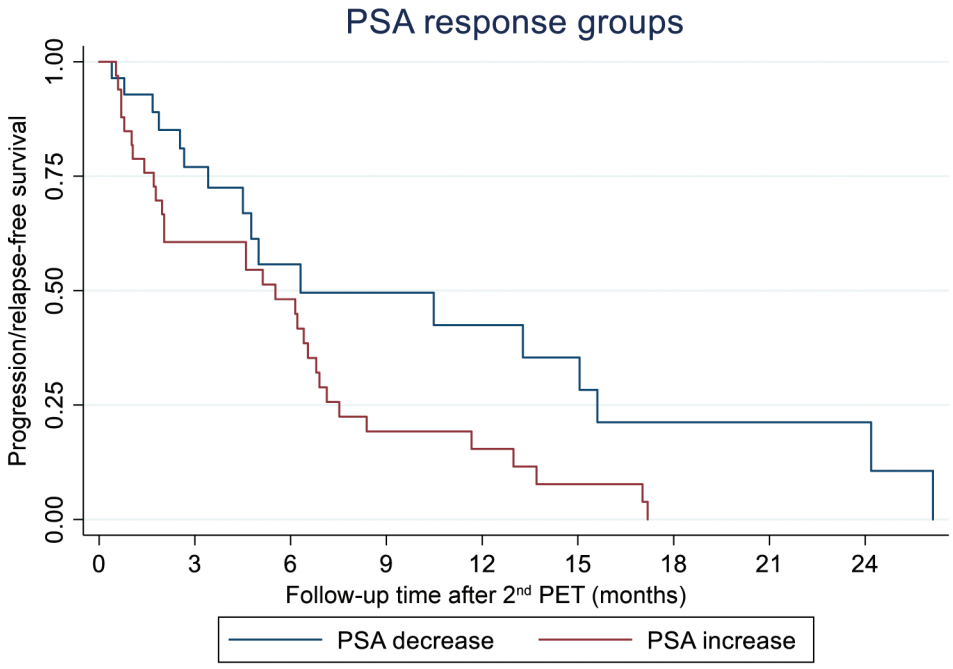

Figure 3. *Progression-free survival after 2nd positron emission tomography/computed tomography (PET/CT) according to prostate-specific antigen (PSA) change groups (p-Value=0.031).*

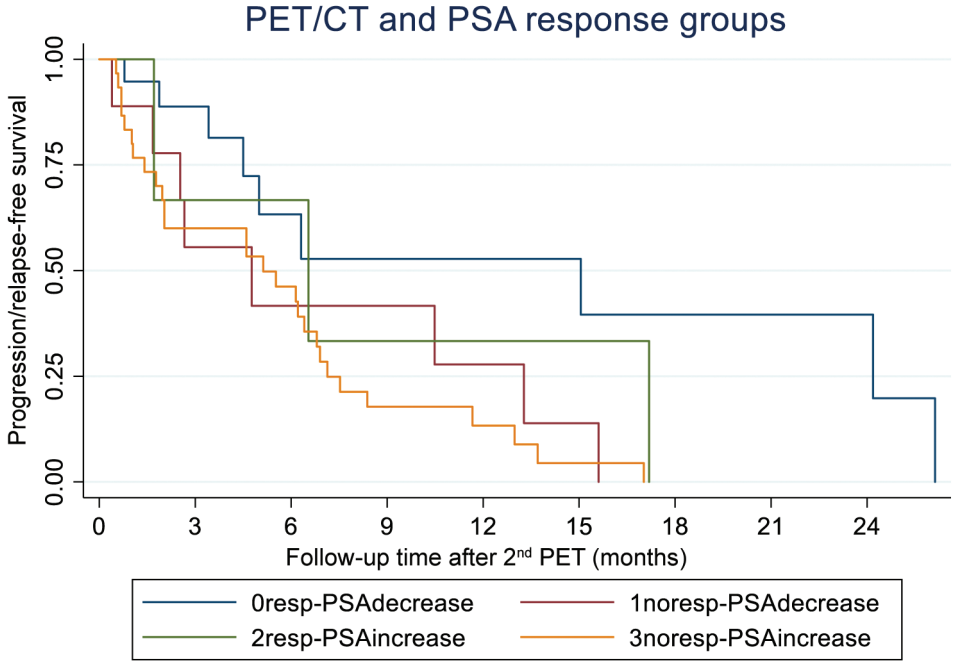

Figure 4. *Progression-free survival after 2nd positron emission tomography/computed tomography (PET/CT) according to four groups combining PET/CT response and prostate-specific antigen (PSA) change.*

PET/CT response (using PCWG3 response assessment criteria) was assessed by second PSMA-PET/CT, according to which patients were classified as responders or non-responders. Biochemical treatment response was assessed as prostate-specific antigen (PSA) increase/decrease from baseline. Progression-free survival (PFS) was defined as time to PSA recurrence or evidence of radiological progression. *Results:* The study comprised 160 patients with CRPC (152 with mCRPC).

At first PSMA-PET/CT, 95% of patients had positive PSMA on PET/CT, regardless of prior systemic therapy. Maximized standardized uptake value (SUVmax) was positively associated with PSA level and PSA velocity at baseline (both $p<0.001$). In patients with a second PSMA-PET/CT (n=70), non-responders (64.3%) had non-significantly lower median SUVmax on first PSMA-PET/CT than responders (17.5 *vs*. 20.4, respectively; $p=0.127$). SUVmax between response groups did not show any statistical difference related to either type or switch of treatment. Patients with a PSA increase between first and second PSMA-PET/CT had significantly lower SUVmax on first PSMA-PET/CT *versus* those with a decrease (15.8 *vs*. 30.4, respectively; $p=0.018$). PSA change between first/second PSMA-PET/CT was +146% in non-responders and -57% in responders ($p<0.001$), with a 79% agreement between PET/CT and PSA response (Cohen's k=0.553, $p<0.001$) (Figure 1). PFS was significantly shorter in PET/CT non-responders *versus* responders ($p=0.005$) (Figure 2), with PSA increase *versus* decrease ($p=0.031$) (Figure 3), and in non-responders with a PSA increase or decrease *versus* responders with a PSA decrease ($p=0.006$ and $p=0.050$, respectively) (Figure 4). There was a non-significant difference in overall survival at 24 months between PET/CT responders *versus* non-responders ($p=0.180$); no difference was observed between PSA response groups ($p=0.932$). *Conclusion:* PSMA expression on 68Ga-PSMA-11 PET/CT may be more predictive of PFS than PSA parameters and could be a useful tool for guiding clinical treatment decisions in patients with mCRPC. Further studies evaluating the role of PSMA expression on survival are warranted.

70

MASSIVE METASTATIC TESTICULAR YOLK SAC TUMOR - TREATMENT AND LONG TERM OUTCOME

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Background/Aim: Pure yolk sac tumors represent a small portion of adult gonadal and retroperitoneal germ cell tumors (GCT). We present the case of a young male patient who presented to our hospital with a massive metastatic gonadal yolk sac tumor. *Case report*: A 31-year-old male presented to the emergency room of our hospital in March 2014 complaining of an extremely enlarged and presumably infected scrotum. Physical examination revealed a malnourished, pale, Caucasian male with a massively enlarged scrotum with numerous necrotic, secreting, foul smelling areas which involved the skin and subcutaneous tissues. There were obviously enlarged lymph nodes in the inguinal areas bilaterally (Figure 1). CT scan showed a suspicious 11-mm lesion of the right lung base, bulky retroperitoneal paraaortic lymph nodes extending for 11 cm, causing dislocation of the aorta and kidney with mild left hydronephrosis, and grossly enlarged bilateral inguinal lymph nodes. CT also demonstrated vast areas of emphysematous necrosis within the scrotal tissue but was not able to identify a healthy testicle. Blood chemistry showed elevated serum tumor markers (human chorionic gonadotropin 32,918 ng/ml, alpha fetoprotein 4,703 ng/ml, lactate dehydrogenase 3,582 U/l) and severe anemia (hemoglobin 6.1 g/dl). The patient was admitted to our division where he was transfused, hydrated, given intravenous antibiotics and stabilized. The next day he was brought to the operating suite. Given the presence of para-aortic lymph nodes, it was assumed that the neoplasm originated from the left testis. Therefore, after extensive irrigation and disinfection of the necrotic areas, the surgical team performed a right inguinal incision and confirmed the presence of a normal looking testicle which was mobilized with its spermatic cord. The left testicular mass which had infiltrated the scrotum was then identified, dissected, and removed with a portion of its spermatic cord. This specimen weighed 1,500 g (Figure 2). All of the infiltrated and necrotic scrotal tissue was then removed leaving only macroscopically healthy scrotal and inguinal tissue. The weight of the tissue removed was 920 g (Figure 3). The right testicle was intentionally left enclosed in its tunica vaginalis and fixed in an extra Dartos pouch in the right scrotum, and the remaining scrotal tissue was modeled and sutured. The patient was brought from the operating room to the intensive care unit and then transferred to the Urology ward on postoperative day 3 (Figure 4). There were no postoperative complications, and the patient was moved to Medical Oncology where he began treatment with bleomycin, etoposide and platinum on postoperative day 17. He received 4 cycles of chemotherapy with bleomycin, etoposide and cisplatinum. Tumor markers gradually decreased reaching normal levels 71 days after surgery. Serial CT scans showed complete regression of the visceral metastases and residual scarring of the retroperitoneal lymph node tissue. The left kidney underwent gradual atrophy. After more than 8 years of follow-up, the patient is healthy and has fathered a baby boy. *Conclusion:* In this case report we describe a rarely observed, extremely advanced testicular tumor which was the end result of a long period of neglect and denial by the patient. This phenomenon has been described in the literature. It is more frequently observed for head and neck tumors but also for breast and testicular tumors. Many psychosocial, physiological, and demographic factors have been found to be associated with patients who display maladaptive and unhealthy denial. For example, poor medical knowledge, socioeconomic stresses, and tumors that grow slowly are factors strongly linked to these patients. Delay in medical care may be correlated with patients' mistrust in medicine that arises from their prior experiences of cancer diagnosis and treatment. Our patient presented with an

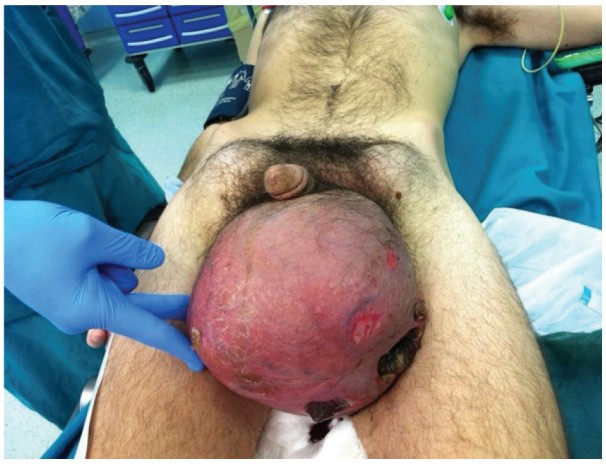

Figure 1. *Initial presentation of the testicular yolk sac tumor.*

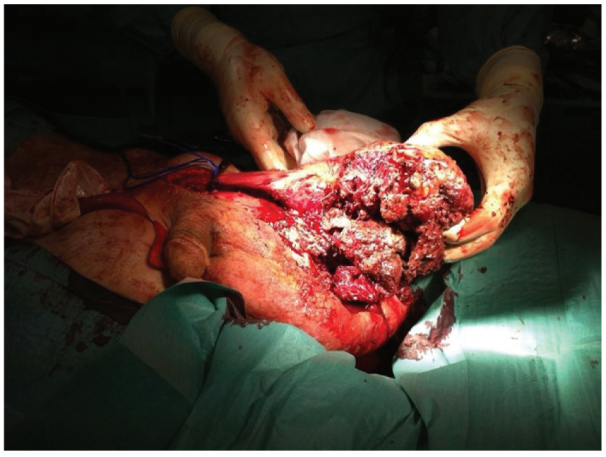

Figure 2. *Testicular mass.*

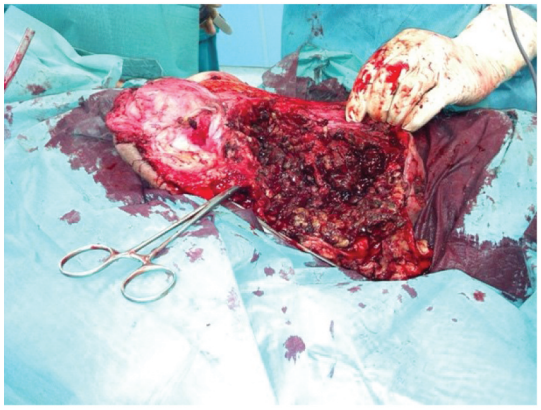

Figure 3. *Necrotic scrotal tissue with infiltrating residual tumor. Figure 3. Necrotic scrotal tissue with infiltrating residual tumor.*

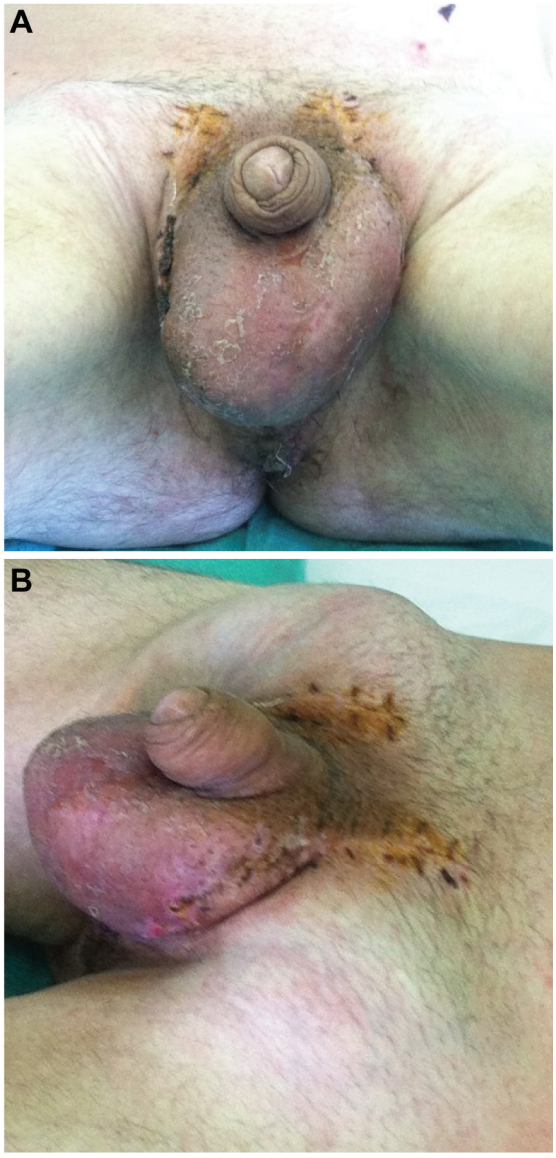

Figure 4. *Early postoperative result.*

extremely advanced testicular yolk sac tumor (pT4, N3, M1a, S2, UICC Stage IIIC). Surgical treatment of this case resulted in excellent cosmetic results and maintenance of fertility and chemotherapy has allowed long term cancer-free survival.

71
DIAGNOSIS AND TREATMENT OF NON–MUSCLE-INVASIVE BLADDER CANCER. LITERATURE REVIEW AND 10-YEAR SINGLE-CENTER EXPERIENCE

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Background/Aim: Non-muscle-invasive bladder cancer is characterized by recurrence and, in some cases, by progression and invasion of the bladder muscular layer. The aim of this study was to review the current literature evidence focusing on emerging strategies for diagnosis and treatment of bladder cancer, as well as presenting data based on a 10-year experience. *Materials and Methods:* Pacific Northwest Evidence-based Practice Center (PNEPC) selected studies using predefined criteria of non-muscle-invasive bladder cancer (NMIBC) with electronic databases, reference lists, and clinical trials registries. Literature data were extrapolated, and the outcomes were synthesized qualitatively and using meta-analysis. Data from our experience over the last 10 years with non-muscle invasive bladder tumors were compared to meta-analysis data. *Results:* In the literature, urinary biomarkers have sensitivity for bladder cancer ranging from 0.57 to 0.82 and specificity from 0.74 to 0.88. Most studies have found fluorescence cystoscopy to be associated with a lower risk of subsequent bladder recurrence than white light cystoscopy, but no difference in the risk of progression or mortality. Intravesical therapy was shown as more effective than no intravesical therapy in reducing the risk of bladder cancer recurrence [bacillus Calmette-Guèrin (BCG), relative risk (RR)=0.56; 95% confidence interval (CI)=0.43-0.71 for mitomycin C (MMC); 0.66-0.72 for doxorubicin and epirubicin]. Intravesical therapy appeared effective in all subgroups defined by stage, grade, multiplicity, recurrence status and tumor size. Compared to no intravesical therapy, BCG was associated with a higher rate of local and systemic adverse events. In our Urology Department, 5,047 patients underwent trans-urethral resections of bladder cancer (TURBT) in the last 10 years. Our data plotted with the international data were absolutely in line with the current results in terms of urinary cystoscopy and intravesical therapy. *Conclusion:* Urinary biomarkers are lacking for a substantial portion of bladder cancer patients. Further research is needed to investigate the advantages of fluorescence cystoscopy over white light cystoscopy. Intravesical therapy reduces the risk of bladder cancer recurrence compared to no intravesical therapy. BCG is the only intravesical therapy that has been associated with a reduced risk of bladder cancer progression; however, it is associated with a high rate of adverse events.

72

NOVEL ENDOSCOPIC APPROACH FOR TREATMENT OF URETERAL ORIFICE STENOSIS AFTER TRANSURETHRAL RESECTION OF BLADDER TUMOR

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Background/Aim: Transurethral resection of ureteral orifice (UO) is required in up to 35% of transurethral resections of bladder tumor (TURBT), resulting in 6 to 16% of cases of UO stenosis. Flank pain and impaired renal function are the two major concerns of this complication. Ureteroneo-cystostomy represents classic management of this complication. Transurethral resection of stenotic UO followed by ureteral stent positioning gained popularity in recent years. However, this approach can be challenging in cases of totally obliterated ureteral lumen. The aim of this study was to describe a new technique employing transrectal ultrasound-guided direct injection of methylene blue in the ureter to visualize ureteral lumen during endoscopic resection of UO stenosis. *Patients and Methods*: We retrospectively evaluated seven patients with UO stenosis following TURB-T between January 2018 and November 2021. All patients had monolateral obstruction with hydronephrosis and worsening renal function. All patients had UO severe scarring, hampering clear visualization of meatus location. Success of procedure was defined as ureteral stent placement after meatus resection. Urethrocistoscopy was performed to evaluate presumed location of obliterated UO. End-fire ultrasound probe was then inserted transrectally and target ureter was identified. A 21 G needle with 5 ml of methylene blue and 5 ml of contrast medium was then inserted through a transrectal route and ureter puncture was performed under ultrasound guidance. Inoculation of methylene blue was done keeping ureteral orifice area under direct vision, with water outflowing open. If methylene blue leak was identified, a deep incision with standard loop was performed. Then, a ureteral JJ stent was placed. *Results:* Overall success rate was 85.7% (6/7 patients). Procedures had a median duration of 24 min (range=20-35 min). We did not record any perioperative complication. Median hospital stay was 2 days. Ureteral stent was removed in all patients 4 weeks postoperatively. Median follow-up was 9 months (range=3-20). All patients successfully treated had improvement in renal function, while no one had recurrence during follow-up. *Conclusion:* This new technique could be a viable option in patients with severe UO orifice scarring and/or contraindications of intravenous injection of methylene blue.

73

NEUTROPHIL TO LYMPHOCYTE RATIO AS A PREDICTIVE MARKER FOR CLEAR CELL RENAL CARCINOMA AGGRESSIVENESS

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Background/Aim: This analysis aimed to evaluate if variations in preoperative neutrophil-lymphocyte ratio (NLR) in patients with clear cells renal carcinoma (metastatic and not metastatic) are predictive of tumor size and nuclear grade and therefore if this parameter could be used to evaluate patient prognosis. *Patients and Methods:* We retrospectively investigated the records of 133 patients affected by metastatic and not metastatic clear cell renal carcinoma (ccRCC) who underwent radical or partial nephrectomy from 2016 to 2021 in our Center and collected preoperative NLR count data one month before surgery. Histopathological analysis (T staging) was performed according to 2017 TNM classification system (ISUP grade). Moreover, NLR was investigated in relation with tumor size and nucleolar grade. *Results:* Patients were classified in three groups according to tumor size (<4 cm, >4 and ≤7 cm, >7 cm) and four groups according to nucleolar grade (G1, G2, G3, G4) (all classifications were according to the ISUP 2013 guidelines). Overall median absolute neutrophil count was 3.18±1.32/μl, lymphocyte count was 2.1±0.5/μl and NLR was 2.64±1.24. Specifically, in patients with ccRCC, an incremental increase in tumor size (<4 cm: 1.2, >4 and ≤7 cm: 2.1 and >7 cm: 3.1) and nucleolar grade (G1: 2.1, G2: 2.6, G3: 3.4 and G4: 4.1) was associated with a greater NLR (p<0.001). *Conclusion:* An elevated NLR was associated with greater RCC tumor size and higher nucleolar grade. NLR appears to be a valuable tool in predicting biological aggressiveness of suspicious renal tumors. Further studies are required to validate NLR integration into current daily-used predictive models of prognosis for patients with ccRCC.

Authors Index*

(Figures indicate abstract number. *Missing abstracts were withdrawn.)