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THE INHIBITION OF AUTOPHAGY INCREASES SUNITINIB RESPONSE IN KIDNEY CANCER CELLS

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Background/Aim: Renal cell carcinoma (RCC) represents about 3% of all diagnosed cancers and in advanced stage is a lethal pathology. Approximately 30% of patients with RCC show metastatic disease at diagnosis and disease recurrence occurs in about 30% of subjects after radical or partial nephrectomy (1). Metastatic RCC (mRCC) is very hard to treat; in fact, subjects with mRCC at 5 years from diagnosis show an overall survival lower than 10% (1). Drug resistance was observed in most patients with mRCC, limiting the efficacy of adjuvant therapy (2). Resistance to targeted drugs is classified into two categories: intrinsic or primary and acquired or secondary resistance (3). Different mechanisms of therapy resistance including the activation of autophagy were identified (2, 3). This biological process may supply energy in case of nutrient deprivation and might trap and destroy therapeutic agents by autophagy vesicles. The aim of the study was to determine whether the inhibition of autophagy can increase the efficacy of conventional chemotherapy. *Materials and Methods:* Caki-2 and KJ29 clear cell renal cell carcinoma (ccRCC) lines were cultured and treated with desmethylclomipramine (DCMI), an autophagy inhibitor, alone or in combination with the tyrosine kinase inhibitor (TKI) Sunitinib for 48 h. Protein expression was evaluated by western blotting in cells cultured in basal condition and treated with DMCI or Sunitinib alone or in combination. Cell migration was performed after seeding 50,000 KJ29 and Caki-2 cells in 24-well plates and culturing in DMEM/F12 medium supplemented with 10% FBS up to confluence. Next, a groove between the cells was generated using a sterile tip and cells were then grown for 48 h in DMEM/F12 1% FBS in the presence of DCMI (5 μM) and Sunitinib (5 μM) individually or in combination. Cell migration (groove filling) was detected by comparing images acquired at T0 (empty groove) with those acquired after 48 h of culture by a phase contrast microscope equipped with a CCD camera. Apoptosis was evaluated by detecting apoptotic nuclei using Hoechst staining in cells cultured in basal condition or in the presence of DCMI and Sunitinib as described above. After treatment, cells were fixed, permeabilized, and stained with Hoechst 33258 (10 mg/ml) in the dark. Images were acquired at 40× magnification using a Zeiss Axiovert 200 fluorescence microscope equipped with a back-illuminated CCD camera. Statistical analysis was performed using GraphPad Prism software and Anova test. *p*-Values <0.05 were considered statistically significant. *Results:* Western blot analysis carried out by using an antibody against the autophagy marker p62 showed that the expression of this protein was significantly increased in both Caki2 and KJ29 cells treated with DMCI compared with untreated cells (Figure 1A). Moreover, the double treatment further enhanced p62 protein content. Notably, when autophagy was activated, p62/SQSTM1 expression was inversely correlated with the levels of autophagy. Interestingly, the inhibition of autophagy by treatment with DMCI reduced the expression of the mesenchymal marker Vimentin in both cell lines (Figure 1A). The combined application of DCMI and Sunitinib seemed to decrease even more Vimentin protein levels. Consistently, the analysis of cell migration by scratch-wound assay showed that the single treatment with DCMI or Sunitinib partially inhibited cell migration, but the combined treatment strongly blocked cell migration in both cell lines (Figure 1B). Finally, the mixed treatment with DCMI and Sunitinib promoted apoptosis in Caki-2 and KJ29 ccRCC cells as compared to untreated cells. In the presence of both compounds, nuclei appeared more condensed, disrupted, and irregular, whereas in control cells, they were rounded (Figure 1C). *Conclusion:* Drug resistance is a big obstacle for the treatment of advanced tumors including kidney carcinoma. Autophagy activation might be one of the mechanisms responsible for chemotherapy resistance; therefore, this process could be associated with tumor progression and the death of patients. Here, we observed that treatment with the TKI Sunitinib after autophagy inhibition by DMCI reduced more efficiently cell migration compared with Sunitinib alone. Consistently, in ccRCC cells treated with both compounds, a greater reduction of the mesenchymal marked Vimentin was observed. These data indicate that the inhibition of autophagy can increase the efficacy of conventional chemotherapy. Interestingly, the combination of DMCI and Sunitinib also caused the activation of apoptosis; therefore, inhibition of autophagy may increase cell death leading to cancer regression. Taken together, autophagy could be used by cancer cells to remove anticancer drugs, promoting chemotherapy resistance in ccRCC cells. In conclusion, the inhibition of autophagy may represent a new pharmacological strategy for the treatment of metastatic kidney cancer.

1 Dell'Atti L, Bianchi N, Aguiari G: New therapeutic interventions for kidney carcinoma: looking to the future.

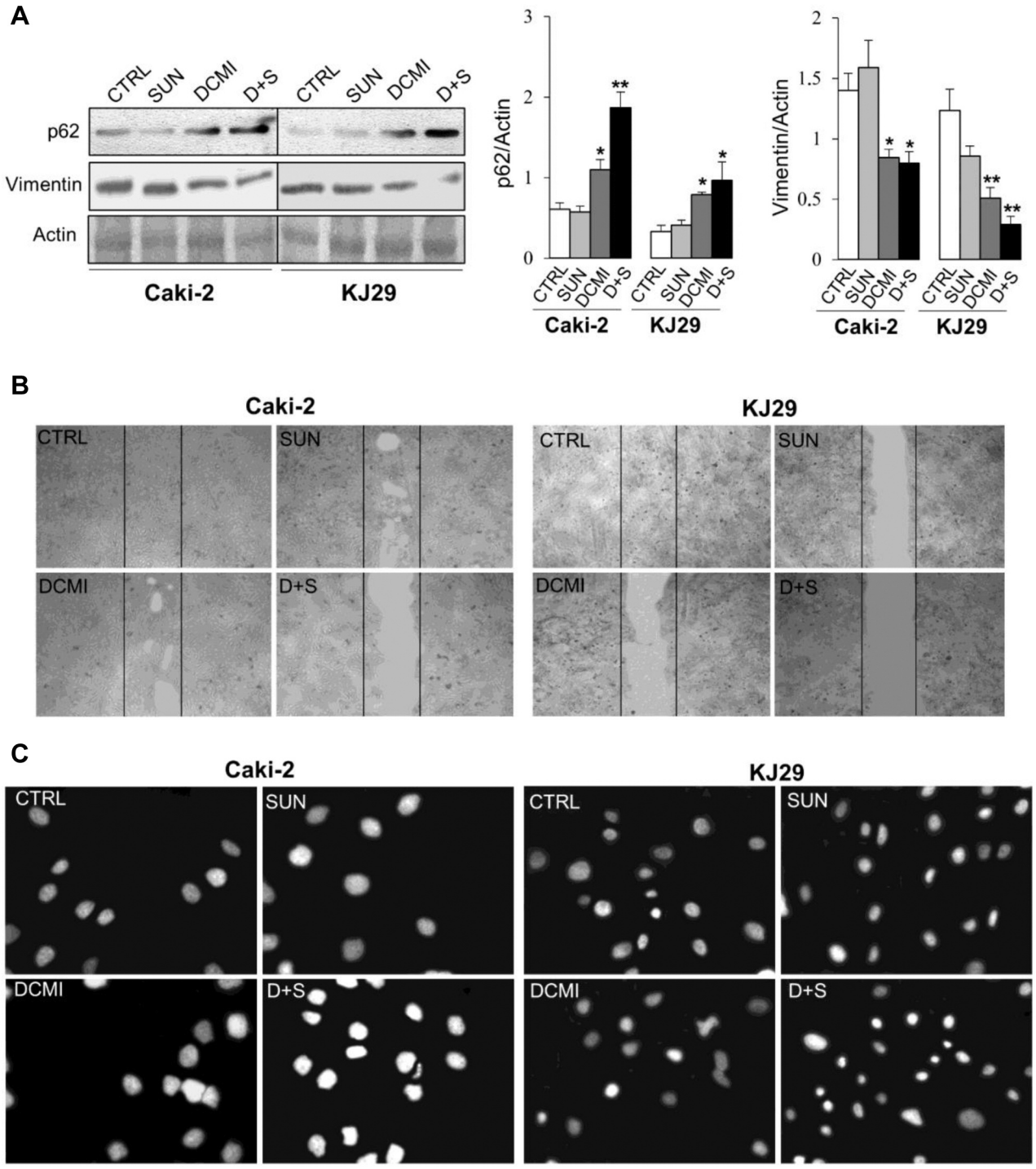

Figure 1. *The double treatment with desmethylclomipramine (DCMI) and Sunitinib (SUN) decreases Vimentin levels and cell migration, and increases apoptosis in clear cell renal cell carcinoma (ccRCC) cells. (A) Western blot analysis was performed using anti-p62 and anti-vimentin antibodies in Caki-2 and KJ29 ccRCC cells treated with SUN and DCMI alone or in combination. The application of DCMI individually or with SUN increases p62 levels and reduces Vimentin expression in ccRCC cells (for p62: *p<0.05 in Caki2 DCMI and **p<0.01 in Caki2 D+S, *p<0.05 in KJ29 DCMI and D+S; for Vimentin: *p<0.05 in Caki2 DCMI and D+S, **p<0.01 in KJ29 DCMI and D+S). Cell migration was evaluated by scratch-wound assay (B), whereas apoptosis was analyzed by Hoechst 33258 staining (C) in ccRCC cells treated for 48 h in the presence/absence of DCMI and SUN alone or in combination. The combined administration of DCMI and SUN more strongly inhibits cell migration and enhances apoptosis compared with single treatment or control (CTRL) in both cell lines. Values are expressed as mean±standard deviation and the statistical significance was calculated from at least two independent experiments in duplicate. D+S: DCMI+Sunitinib.*

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RECTAL PERFORATION BY RECTAL ENEMA, DETECTED BY DAILY CONE-BEAM COMPUTED TOMOGRAPHY IN A PELVIC RADIATION COURSE: A CASE REPORT

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Background/Aim: In radiotherapy (RT) centers, the use of rectal enema is commonly required as a preparation for patients who are scheduled to undergo prostate treatment to improve its efficiency. A daily rectal enema before each RT fraction has been evaluated as a tolerable and feasible method to reduce intra-fraction prostate movement during RT (1). We present a rare case of acute rectal perforation following rectal enema as preparation for prostate RT, detected by daily cone-beam computed tomography (CBCT), performed for image-guided RT before starting the treatment. *Case Report*: On January 17, 2023, a 77-year-old patient with high risk prostate cancer (initial prostate-specific antigen of 37 ng/ml, Gleason Score 4+4=8) underwent planning computed tomography (CT) for planned pelvic treatment at our center. The CT exam was repeated after rectal enema due to inadequate rectal condition. On January 31, 2023, the patient presented in good health, without any symptoms, to start pelvic RT. Pelvic CBCT pre-treatment showed bubbles of free air in the mesorectal space (Figure 1). Radiation treatment was not started. The patient reported that his wife had helped him to perform a rectal enema before the RT session. *Results*: A diagnostic abdominal CT confirmed the suspicion of rectal perforation. The patient

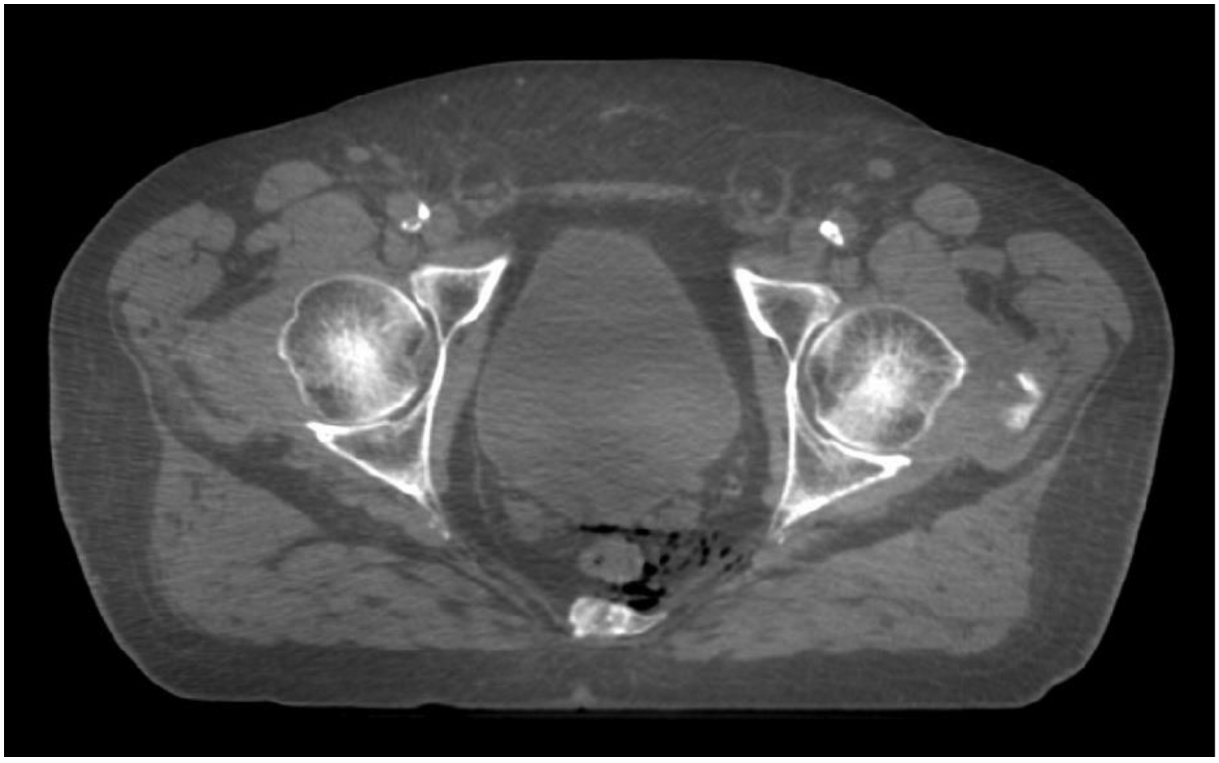

Figure 1. *Axial image of cone-beam computed tomography showing bubbles of free air in the mesorectal space.*

was hospitalized and treated conservatively with antibiotic prophylaxis. He remained asymptomatic until outpatient clinical check one month after discharge. A written informed consent for patient information and images to be published was provided by the patient. *Conclusion:* The use of rectal enema is a common practice in prostate RT, but it can become a risky procedure if not performed by healthcare or non-expert personnel. The daily pelvic CBCT imaging is able to detect a rectal perforation in an asymptomatic patient; it must be carefully evaluated.

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EVALUATION OF THE RT-PCR BASED URINARY MARKER BLADDER EPICHECK AS A DIAGNOSTIC TOOL IN UPPER URINARY TRACT TUMORS (UTUC)

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Background/Aim: Upper urinary tract urothelial carcinoma (UTUC) represents about 5-10% of all urothelial neoplasms, with increasing incidence in the last few decades. The current standard tools in the diagnosis of UTUC include cytology, computed tomography (CT) urography, and ureterorenoscopy (URS). The aim of this study was to evaluate the usefulness of Bladder Epicheck® test as a diagnostic tool in the diagnosis of UTUC. *Materials and Methods*: A total of 136 urine samples collected from the upper urinary tract (UUT) before URS for suspicion of UTUC were analyzed using cytology and Bladder Epicheck® Test. Sixteen analyses were excluded due to a non-diagnostic Bladder Epicheck® or cytology. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of both markers were calculated and compared using URS and/or histology as reference. *Results*: A tumor was detected in 40 cases (33.3%), 30 were low-grade (LG) and 10 high-grade (HG). Overall sensitivity was 65% for Bladder Epicheck® and 42.5% for cytology, increasing to 100% for Bladder Epicheck® and 90% for cytology if only HG tumors are considered. Overall specificity of Bladder Epicheck® was 81.2% and of cytology 93.7%. The PPV and NPV were 63.4% and 82.2% for Bladder Epicheck® and 77.2% and 76.5% for cytology, respectively. Considering an Episcore cut-off >75, instead of 60, the specificity of Bladder Epicheck® improved to 89% and the PPV to 74.2%. If both tests are considered, there is a slight improvement in sensitivity and NPV. *Conclusion*: Due to the high sensitivity for HG tumors, the Bladder Epicheck® Test can be used in the follow-up of patients with UTUC after conservative treatment to reduce unnecessary procedures without the risk of missing a HG recurrence or progression.

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ASSOCIATION BETWEEN MRI-DETECTED TUMOR ADC AND RISK OF 5-YEAR BIOCHEMICAL RECURRENCE AFTER RADICAL PROSTATECTOMY

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Background/Aim: Current predictive tools for estimating the risk of biochemical recurrence (BCR) after primary treatment for prostate cancer (PCa) do not take into consideration information from magnetic resonance imaging (MRI). This study aimed to demonstrate the predictive utility of tumor apparent diffusion coefficient (ADC) values in assessing the risk of a 5-year BCR after radical prostatectomy (RP). *Patients and Methods*: A retrospective analysis was conducted on a cohort of 1,207 patients with PCa who underwent MRI before RP between 2012 and 2015. The outcome of interest was 5-year BCR, defined as two consecutive PSA values of >0.2 ng/ml. ADC values were categorized into three groups using empirical cut-offs: low (<850 $\mu m^2/s$), intermediate (between 850 $\mu m^2/s$ and 1,100 $\mu m^2/s$), and high (>1,100 $\mu m^2/s$). Comparisons between groups (BCR and non-BCR) and categorical levels of ADC were performed using non-parametric statistical tests. Kaplan–Meier curves were plotted to depict survival functions, and Log-rank

tests were used to test for differences among strata of determinant variables. *Results:* The median duration of follow-up in the cohort was 59 months, with 306 (25%) patients experiencing BCR. Patients who experienced BCR had significantly lower ADC values compared to those without BCR (874 *vs*. 1,025 $\mu m^2/s$, $p<0.001$). The 5-year BCR survival rates were 87.0%, 74.4%, and 52.3% for patients with tumor high, intermediate, and low ADC values, respectively ($p<0.0001$). *Conclusion:* MRI-based tumor ADC values were found to be predictive of the risk of 5-year BCR after RP in patients with PCa and may serve as a prognostic biomarker. External validation of these findings is warranted.

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STAGING OF PATIENTS WITH NEWLY DIAGNOSED UNFAVORABLE INTERMEDIATE OR HIGH RISK PROSTATE CANCER: THE ALL-IN-ONE WHOLE BODY MRI PROTOCOL

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Background/Aim: Currently, international guidelines consider bone scintigraphy (BS) and abdominopelvic computed tomography (CT) to be the mainstay for tumor staging of unfavorable intermediate and high-risk prostate cancer (PCa) patients. The possibility of a one-step staging modality has been raised, wherein multiparametric magnetic resonance imaging (mpMRI) + whole body MRI (WB-MRI) would be used to further assess nodal and metastatic disease status in a single setting. *Patients and Methods*: This is a multicentric, prospective, interventional study comparing the accuracy of staging with All-in-One MRI *vs*. standard (CT and BS) staging pathways for unfavorable intermediate and high-risk PCa patients (EAU guidelines). All patients should undergo BS, CT, and WB-MRI within 6 weeks of each other. Radiologists will be blinded from findings of other imaging tests. Primary outcome is the per-patient sensitivity, specificity, and accuracy for detection of nodal and distant metastases with WB-MRI *vs*. BS+CT. Secondary outcomes are: 1) disease management changes; 2) the rate of equivocal findings; 3) costs, radiation exposure, patient compliance/preference, and side effects; and 4) interobserver variability. All cases will be evaluated into a multidisciplinary team meeting (MDT) that will decide for patient treatment according to WB-MRI or BS+CT. For non-metastatic patients, the accuracy of WB-MRI *vs*. BS+CT will be evaluated at final pathology and according to PSA values during follow-up. Conversely, for metastatic patients, the accuracy of WB-MRI *vs*. BS+CT will be evaluated according to changes in radiological appearance of metastases after treatment. The study started on 01/01/2022 and will recruit patients for up to 36 months. All patients will be followed for at least one year after treatment. Considering 80% an acceptable level of power, 350 patients would be evaluated. *Results:* At the time of this preliminary analysis (April 2022), 22 patients have been enrolled. Of these, two (9%) patients refused WB-MRI due to claustrophobia. Of the other 20 patients, 8 (40%) showed discordance between BS+CT *vs*. WB-MRI staging. Specifically, compared to BS+CT, 6 (75%) and 2 (25%) patients showed, respectively upstaging and downstaging after WB-MRI. Of all patients who experienced upstaging after WB-MRI, 2 (33%) switched from cN0M0 to cN1M0. Moreover, two (33%) patients switched from cN0M0 to cN0/1M1a. Last, two (33%) patients switched from cN0M0 to cN0/1M1b. Conversely, the two patients that experienced downgrading switched from cN0M1b to cN0M0. After MDT, 6 (30%) patients experienced disease management changes. Specifically 4 (66%) and 2 (33%) switched from local to hormone therapy and *vice versa*. *Conclusion:* Systemic staging with all-in-one WB MRI in patients with unfavorable intermediate and high-risk PCa results in approximately 40% of changes in disease stage and 30% of treatment changes, relative to BS+CT. These preliminary findings should be confirmed after study completion.

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ONCOLOGICAL OUTCOMES OF THULIUM–YTTRIUM–ALUMINIUM–GARNET (TM:YAG) LASER ABLATION FOR PENILE CANCER

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Background/Aim: To report oncological outcomes after Thulium–yttrium–aluminium–garnet (Tm:YAG) laser ablation for penile cancer patients. *Patients and Methods:* We retrospectively analyzed 71 patients with cT1 penile cancer (2013-2022). All patients underwent Tm:YAG ablation with a RevoLix 200 W continuous-wave laser. First, Kaplan–Meier plots and multivariable Cox regression models tested local tumor recurrence rates. Second, Kaplan–Meier plots tested progression-free survival (T3 and/or N1-3 and/or M1). *Results:* Median (IQR) follow-up time was 38 (22-58) months. Overall, 33 (50.5%) patients experienced local tumor recurrence. Specifically, 19 (29%) *vs*. 9 (14%) *vs*. 5 (7.5%) patients had 1 *vs*. 2 *vs*. 3 recurrences over time. In multivariable Cox regression models, a trend for higher recurrence rates was observed for G3 tumors (HR=6.1; *p*=0.05), relative to G1. During follow-up, 12 (18.5%) *vs*. 4 (6.0%) *vs*. 2 (3.0%) men were re-treated with 1 *vs*. 2 *vs*. 3 Tm:YAG laser ablations. Moreover, 11 (17.0%) and 3 (4.5%) patients underwent glansectomy and partial/total penile amputation. Last, 5 (7.5%) patients experienced disease progression. Specifically, TNM stage at the time of disease progression was: 1) pT3N0; 2) pT2N2; 3) pTxN3; 4) pT1N1; and 5) pT3N3, respectively. *Conclusion:* Tm:YAG laser ablation provides similar oncological results as those observed by other PSS procedures. In consequence, Tm:YAG laser ablation should be considered a valid alternative for treating selected patients with penile cancer.

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RADIO-GUIDED SURGERY WITH DROP-IN BETA PROBE FOR 68GA-PSMA, IN HIGH-RISK PROSTATE CANCER PATIENTS ELIGIBLE FOR ROBOTIC-ASSISTED RADICAL PROSTATECTOMY

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Background/Aim: The primary aim of this analysis was to evaluate the diagnostic accuracy of the combination of DROP-IN positron detector (β-Probe) and 68Ga-PSMA-11 PET/CT (PSMA-PET) in identifying lymph node metastases in high-risk prostate cancer (PCa) patients undergoing robotic radical prostatectomy (RARP) and extended pelvic lymph-node dissection (ePLND). The standard of reference was the histopathological analysis. *Materials and Methods:* This is a prospective, single-arm, single-center, non-interventional, phase II trial (NCT05596851), aimed at enrolling fifteen (n=15) PCa patients. We present an interim analysis in the first consecutive five (n=5) patients enrolled. Inclusion criteria were: a) biopsy proven, high-risk PCa; b) patients candidate to RARP + ePLND as primary therapy; c) PSMA-PET performed within 6 weeks prior to RP; d) PSMA-positive nodes in PET; e) age>18. The surgery procedure started with the intravenous injection of 1.1 MBq/Kg of 68Ga-PSMA11 directly in the surgery theatre. After injection, the surgery procedure proceeded first with ePLND followed by RP. The *in vivo* measurements of the surgery templates with β-Probe were performed with a DROP-IN system, inserting the probe into a trocar. All removed nodes were also measured *ex vivo*. The tumor-to-background-ratio (TBR) was evaluated graphically in a display showing real-time counts per time (a dedicated, operator-independent, algorithm to reliably identify pathologic *vs*. non-pathologic nodes is under development). PSMA-staining was performed in all specimens. Data derived by the PSMA-PET, β-Probe and histopathological analysis were compared in a per-region analysis. *Results:* The live β-Probe-guided ePLND was a feasible procedure, without significant changes in the surgery practice. No side effects were observed during ePLND. In total, 36 specimens were removed and analyzed. Pathology results were used to validate *in vivo* and *ex vivo* β-Probe counts interpreted based on current interpretation criteria. According to visual interpretation criteria applied during surgery, the β-Probe sensitivity was 59%, while specificity was 89%. Visual TBR interpretation (operator-dependent) revealed to be more challenging than expected. *Conclusion:* These are the first ever published data derived from a live surgery experience using a β-Probe to identify PSMA-positive lymph nodes. This new approach proved to be feasible and safe. Using current β-Probe counts' interpretation criteria, diagnostic accuracy is promising, even if still sub-optimal. The implementation of a dedicated, operator-independent, algorithm for the identification of a cut-off in TBR analysis might improve these results. The completion of this phase II trial will provide more data about the efficacy of this new generation image-guided approach.

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PREDICTING PERI-OPERATIVE OUTCOMES IN PATIENTS TREATED WITH PERCUTANEOUS THERMAL ABLATION FOR SMALL RENAL MASSES: THE SUNS NEPHROMETRY SCORE

Chiara Vaccaro[1], Stefano Luzzago[2], Francesco Alessandro Mistretta[2], Matteo Ferro[1], Mattia Luca Piccinelli[1], Ettore Di Trapani[1], Roberto Bianchi[1], Marco Tozzi[1], Agnese Zago[1], Emanuela Santangelo[1], Stefano Caramella[1], Sara Nardini[1], Giovanni Mauri[2], Franco Orsi[3], Gennaro Musi[2] and Ottavio De Cobelli[2]

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Background/Aim: To develop a new, simple, and ablation-specific nephrometry score predicting peri-operative outcomes and to compare its predictive accuracy to PADUA and RENAL scores. *Patients and Methods:* Overall, 418 patients were treated with percutaneous thermal ablation (microwave and radiofrequency) between 2008 and 2021. The outcome of interest was trifecta status (achieved *vs*. not achieved): incomplete ablation or Clavien-Dindo 3 complications or postoperative estimated glomerular filtration rate decrease 30%. We validated the discrimination ability of PADUA and RENAL scoring systems. Furthermore, we created and internally validated a novel score (SuNS), according to multivariable logistic regression models. The predictive accuracy of the model was tested in terms of discrimination and calibration. Complexity classes were then developed. *Results*: Overall 89 (21%) patients did not achieve trifecta. PADUA and RENAL showed poor ability to predict trifecta status (c-indexes 0.60 and 0.62, respectively). We, therefore, developed the SuNS model (c-index: 0.74) based on: 1) contact surface area; 2) nearness to renal sinus or urinary collecting system; 3) tumor diameter. Three complexity classes were created: low (3-4 points; 11% of no trifecta) *vs*. moderate (5-6 points; 30% of no trifecta) *vs*. high (7-8 points; 65% of no trifecta) complexity. Results remained consistent in microwave *vs*. radiofrequency populations. *Conclusion*: We developed an immediate, simple, and reproducible ablation-specific NS (SuNS) that outperformed PADUA and RENAL NS in predicting peri-operative outcomes. External validation is required before daily practice implementation.

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PREDICTING THE RISK OF 5-YEAR BIOCHEMICAL RECURRENCE IN PATIENTS TREATED WITH RADICAL PROSTATECTOMY FOR PROSTATE CANCER: THE PIPEN RISK CATEGORIES

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Background/Aim: Currently used predictive tools to estimate the risk of biochemical recurrence (BCR) after primary treatment for prostate cancer (PCa) do not consider multiparametric magnetic resonance imaging (mpMRI) information. We developed a novel tool that considers clinical and mpMRI findings to assess the risk of 5-year BCR after radical prostatectomy (RP) for PCa. *Patients and Methods:* This is a retrospective analysis of 1,459 patients with PCa who underwent mpMRI before RP (2012-2015). The outcome of interest was 5-year BCR, defined as two consecutive PSA values of >0.2 ng/ml. Patients were randomly divided into a development (70%) and test cohort (30%) for internal validation. Kaplan–Meier plots were applied on the development cohort to estimate survival probabilities. Multivariable Cox regression models tested the relationship between BCR and different sets of exploratory variables. The accuracy (C-index) of the developed model was compared to EAU classification (partial likelihood ratio). Five novel risk categories were created and used to build and validate a nomogram based on Cox regression coefficients. *Results:* Median duration of follow-up in the whole cohort was 59 months (inter-quartile range=32-81), with 376 (26%) patients experiencing BCR. A 5-item multivariable Cox regression model (PIPEN model: PSA-D, ISUP grade group, PI-RADS category, ESUR-EPE score, Nodes) fitted to the development data yielded a C-index superior to that of EAU categories (0.74 *vs*. 0.70; p=0.004). Five PIPEN risk categories were identified and five-year BCR-free survival rates were 92%, 84%, 71%, 56%, and 26% in very low, low, intermediate, high, and very high risk patients, respectively (p<0.001). Results remained consistent in sensitivity analyses after exclusion of patients treated with adjuvant radiotherapy or with positive surgical margins. *Conclusion:* We developed and internally validated a novel 5-item (PIPEN) model for predicting the risk of 5-year BCR after RP in patients with PCa and identified five risk categories based on clinical and mpMRI findings. External validation is needed.

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A MINIATURIZED ENDOSCOPIC CAMERA TO MEASURE ENERGY SPREAD DURING BIPOLAR CAUTERIZING IN ROBOT ASSISTED RADICAL PROSTATECTOMY

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Background/Aim: Robot-assisted laparoscopy (RAL) is the gold standard for nerve-sparing prostatectomy (1). In this setting, cauterizing hemostasis is employed although its use is still debated for tissue damage (2-4). We manufactured a miniaturized endoscopic thermal camera to measure thermal spread during RAL. The aim of this proposal is to present the characteristics of this device with an Italian and European patent, highlighting the current challenges in designing thermal endoscopes to facilitate the detection of potential thermal stress for the tissues surrounding the cauterized area and fusing the data coming from the endoscopes operating in the visible range of the spectrum. *Materials and Methods:* We used sensors to measure the thermal spread. They are microbolometers operating in a region of the spectrum between 7 to 14 μm, not visible at the naked eye. For designing the thermal endoscope, we used off-the-shelf ultra-compact microbolometers cores of the FLIR Lepton® series. These devices can be integrated in printed circuit board (PCB) designed specifically for the application. In this study, we designed elongated PCBs that can fit inside a trocar with a diameter of 15 mm. We prototyped different configurations, placing the camera in front of the trocar and in one side of it. Finally, we tested the effectiveness of the various configurations using a custom phantom with 15 mm trocar entrances. *Results:* We were able to produce different prototypes of thermal endoscopes. All the endoscopes met the dimensional requirements of the standard trocars used nowadays in RAL. The testing using the phantom highlighted the importance of fusing the data coming from the thermal endoscope (consisting of video representing temperature gradients on the tissue) with the data of the standard endoscope operating in the visible range of the spectrum. *Conclusion:* The miniaturization of thermal sensors allows the construction of thermal endoscopes able to make the surgeon aware of thermal stresses caused to the tissues during RAL. The fusion of the visible and thermal data is pivotal for the correct use of the information provided by thermal endoscopes.

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IS SECOND TRANSURETHRAL BLADDER RESECTION STILL A KEYSTONE IN THE TREATMENT OF PATIENTS WITH HIGH GRADE NON-MUSCLE-INVASIVE BLADDER CANCER?

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Background/Aim: Bladder cancer is one of the most common cancers worldwide. About 75% of cases are non-muscle-invasive bladder cancer (NMIBC), which include Ta, T1, and Carcinoma *in situ* (Cis). The gold standard of treatment is transurethral resection (TURBT), which has the dual objective of histological (stage and grade of the tumor) and complete excision of the tumor. Underdiagnosis after initial TUR is common in patients with NMIBC and may be a cause of delay in accurate diagnosis and definitive treatment. Persistent disease after resection of a high-grade (HG) tumor was observed in 41% of patients and in 33-55% of patients with T1 tumors. The aim of the study was to assess the presence of residual tumor at the second resection and to examine the oncological results in terms of recurrence and progression. *Patients and Methods:* From January 2017 to April 2022, 817 patients with superficial HG bladder cancer (Ta-T1 HG) underwent TURBT. An endoscopic second look (re-TURBT) was performed 4-6 weeks after initial resection.

The scar from the previous surgery and any other suspicious lesions were always resected during re-TURBT and sent in separate samples. All patients were followed up with cystoscopy and eventual biopsy, urine cytology, abdominal ultrasound, intravesical chemotherapy according to the latest European guidelines. The oncological outcome of each patient was considered. *Results:* Of the 817 patients, 237 (29%) underwent re-TURBT. Histological findings from second TURBT were no bladder cancer in 91 (39%); Ta Low-Grade with focal areas of HG tumor in 26 (11%), Ta HG in 41 patients (17%); and T1 HG in 69 (29%). In 10 patients (4%), the histological examination at the second resection resulted in a muscle-invasive bladder tumor (T2), thus after staging and neoadjuvant therapy they underwent radical cystectomy. Considering re-TURBT performed on the scar of the previous operation, 31/69 patients (45%) with previous T1 HG presented a recurrence against 9/41 patients (22%) with Ta HG. Finally, Cis was found in 17/146 patients (11%) of which 4 with associated Ta HG, 9 with T1 HG, and 4 with T2. After at least 12 months follow-up, we observed recurrences in 87/237 (38%) and progression in 19/237 (8%). The recurrence and progression rate in T1 HG patients undergoing re-TURBT was higher than in Ta HG patients (recurrence-rate T1HG *vs*. TaHG: 43% *vs*. 21%; progression-rate T1HG *vs*. TaHG: 13% *vs*. 1%). *Conclusion:* Re-TURBT is a useful tool that allows more accurate staging for subsequent diagnostic or surgical decisions, removes residual tumor tissue, and reduces the risk of underdiagnosis. It is also essential in cases where the histological finding of the initial resection is a T1HG tumor, due to higher rates of recurrence and progression, thus ensuring therapeutic benefit and better tumor eradication.

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BEYOND THE PTV APPROACH TOWARD ROBUST OPTIMIZATION: A NOVEL STRATEGY FOR SBRT TREATMENT PLANNING. AN ANCILLARY STUDY WITHIN THE RADIOSA TRIAL (AIRC IG-22159)

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Background/Aim: Clinical target volume (CTV)-to- planning target volume (PTV) margins proposed in literature are arbitrarily defined, and classical optimization in stereotactic body radiation therapy (SBRT) considers uncertainties in patient-setup only. The aim of this retrospective study was to evaluate the dosimetric efficacy of robust optimization (RO) for lymph node lesions in oligometastatic prostate cancer (PCa). *Patients and Methods*: Twelve patients with PCa treated at IEO with a delivered plan isodose curve of 50% intersecting the bladder/rectum were selected. For each, two radiotherapy (RT) treatment plans were generated (Figure 1): (i) a PTV-based (PTVb) plan on the planning CT (pCT) using 5 mm as CTV-to-PTV margin; (ii) a robust optimized (RO) plan on the pCT using 3 mm as margin and including five additional CTs, four simulating shifts of PTV

Table I. *Median values of considered parameters on the planning scenario, worst scenario, and median percentage variations across all patients for the two considered planning approaches.*

	Planning CT		*p*-Value	Worst scenario		*p*-Value	% variation (Worst scenario - planning CT)		*p*-Value
	PTVb	RO		PTVb	RO		PTVb	RO	
PTV									
D98%	30.31	30.48	*p*>0.05	28.76	29.48	***p*<0.05**	–5.35	–3.36	***p*<0.05**
D99%	30.25	30.39	***p*<0.05**	28.26	29.28	***p*<0.05**	–6.18	–4.23	***p*<0.05**
D95%	30.55	30.58	*p*>0.05	29.39	29.87	***p*<0.05**	–3.97	–2.35	***p*<0.05**
D50%	31.08	31.00	*p*>0.05	30.91	30.90	*p*>0.05	–0.58	–0.48	***p*<0.05**
D1%	31.47	31.22	*p*>0.05	31.53	31.28	*p*>0.05	0.35	0.21	***p*<0.05**
HI	0.95	0.97	***p*<0.05**	0.82	0.88	***p*<0.05**	–14.13	–9.79	***p*<0.05**
Bladder									
D1%	12.86	14.24	*p*>0.05	15.91	17.42	*p*>0.05	22.46	20.08	*p*>0.05
Rectum									
D1%	10.93	11.38	*p*>0.05	13.21	13.62	*p*>0.05	16.23	16.03	*p*>0.05

A *p*-value (from Wilcoxon signed-rank tests) <0.05 was considered statistically significant. Significant changes are shown in bold.

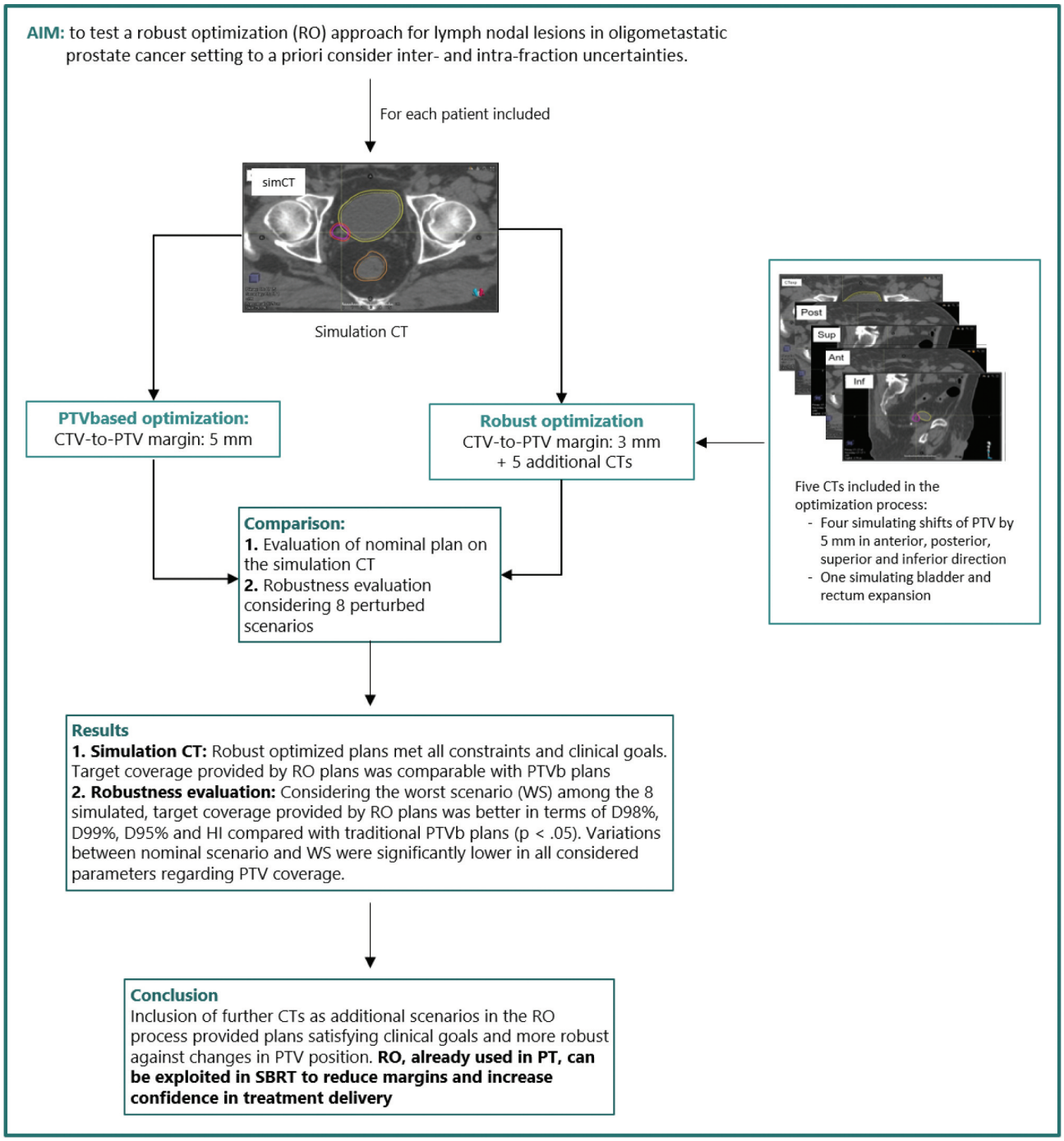

Figure 1. *Schematic workflow of methods.*

by 5 mm, and one simulating a bladder/rectum expansion. Both plans simulated 30 Gy/3 fractions Volumetric Modulated Arc Therapy (VMAT). The two strategies were compared (i) regarding the pCT in terms of PTV-coverage and constraints compliance; (ii) in terms of robustness, simulating eight error scenarios. *Results*: RO plans met all constraints and clinical goals, and provided target coverage comparable with PTVb plans, except for D99% which was significantly better (p<0.05, Table I). Regarding robustness evaluation, considering the worst scenario (WS), PTV

coverage was significantly higher ($p<0.05$, Table I) compared with PTVb plans, and variations between nominal and WS were significantly lower ($p<0.05$, Table I) in all considered parameters. *Conclusion:* Inclusion of CTs as additional scenarios in the optimization process provided more robust plans against changes in PTV position. RO, already used in Proton Therapy (PT), can be exploited in SBRT to reduce margins, and increase confidence in treatment delivery.

Key Words: SBRT, robust optimization, inter-fractional anatomical variations, lymph node metastases, oligometastatic prostate cancer.

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DEFINING PLANNING TARGET VOLUME IN PROSTATE CONE-BEAM COMPUTED TOMOGRAPHY IMAGE GUIDED RADIOTHERAPY WITH OR WITHOUT IMPLANTED FIDUCIAL MARKERS

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Background/Aim: Radical radiation treatment of prostate cancer, due to the intra- and inter-fractions movements of the target, is today always associated with image systems for positioning control before treatment delivery. The cone-beam computed tomography (CBCT) is one of the most commonly used systems. In this study, we investigated the possible advantage in clinical target volume (CTV) to planning target volume (PTV) margins reduction using intraprostatic fiducial markers (FMs) by comparing the results of daily CBCT between different operators, and between the same operators, over the time. *Patients and Methods*: In our center, the patients treated with radical radiotherapy for prostate cancer undergo daily CBCT before treatment delivery to verify target position. From January to May 2022, thirteen consecutive patients were identified, seven patients (54%) had intraprostatic gold FMs and six patients (46%) did not. Seven Radiation Oncologists in June 2022 retrospectively reviewed three CBCT exams for each treatment course, concerning the first, last, and the median one; they carried out a second review in September. They recorded the movements of the treatment table required for the target correct position with respect to the planning CT. Analysis of variance was carried out for comparison of different groups to assess inter-intra-observer variation in both sets of data (first set in June and second set in September); *t*-test for unpaired data was used to test differences in mean values of different parameters related to movements. Mean couch shifts in left-right (X), anterior-posterior (Y), and superior-inferior (Z) directions, and mean values of couch rotations (X° - Y° and Z° respectively for Roll, Rot, and Pitch) were tested. We also compared CTV-PTV margins derived with the formulation described by van Herk *et al*. (1). *p*-Values <0.05 were considered significant; we used Microsoft Excel 2013 for analysis. *Results:* With analysis of variance, we found no statistically significant difference between operators in both sets of measures, nor in the analysis of image with fiducial markers, neither in images without them. The mean couch shifts in X, Y, and Z directions as well as mean values for couch rotations for CBCT with or without FMs are summarized in Table I. We found a statistically significant difference between the two groups of patients in the mean values of angle correction for Y° and Z°, lower in the non-fiducials group (Y° - $p=0.04$ and Z° - $p=0.01$). We also derived CTV-PTV margins in the three directions using the formulation suggested by van Herk, obtaining (as a mean between the two sets) 8 mm (X), 5 mm (Y), and 13 mm (Z) for CBCT without FMs and 5 mm (X), 3 mm (Y), and 9 mm (Z) for CBCT with FMs (with a significant difference for Z direction - $p=0.03$). *Conclusion:* There is no difference between operators in the analysis of images. The mean couch shifts in all directions are smaller for CBCT with FMs but not statistically significant. For this reason, CTV-PTV margins in FMs group, calculated with the van Herk formula (1), are smaller and statistically significant in the Z direction. This is very important to allow dose escalation to the target and reduction of dose and toxicity to surrounding healthy organs. In rotation analysis, as previously reported in a single review set (2), the use of intraprostatic FMs, added to daily CBCT, seems useful to better detect some errors, especially for Rot (Y°=0.7 and Y°=1.3 for CBCT without and with FMs respectively – $p=0.04$) and Pitch (Z°=0.9 and Z°=1.9 for CBCT without and with FMs respectively - $p=0.01$) allowing for complete correction; as

Table I. *The mean couch shifts in X, Y, and Z directions and mean values for couch rotations for cone-beam computed tomography (CBCT) with or without fiducial markers (FMs).*

Axes	Without FMs	With FMs	*t*-test *p*-Value
X	4.3±2.7	3.0±2.1	$p>0.05$
Y	4.0±1.6	2.6±1.3	$p>0.05$
Z	5.2±4.5	4.0±3.0	$p>0.05$
X°	2.3±0.8	1.5±0.4	$p>0.05$
Y°	0.7±0.3	1.3±0.3	**$p=0.03$**
Z°	0.9±0.5	1.9±0.1	**$p=0.01$**

Significant values are shown in bold.

rotational errors play an important role in correct positioning, they cannot be ignored.

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CORRELATION BETWEEN SERUM ALBUMIN LEVEL AND BLADDER CANCER: A MONOCENTRIC RETROSPECTIVE STUDY

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Background: Non-muscle-invasive bladder cancer (NMIBC) is the most common histological pattern of bladder tumor with high recurrence and progression rate, which requires close follow-up over years. Several inflammatory biomarkers may predict treatment efficacy and prognosis in bladder cancer. Among them, the relationship between serum albumin level and urothelial cancer is still controversial (1). Nowadays, several studies are evaluating the prognostic value of pretreatment serum albumin (ALB) level in patients with bladder cancer without clear results (2). The aim of our study was to analyze the correlation of preoperative ALB with worse clinical outcomes and histological staging in urothelial cancer. *Patients and Methods*: A retrospective analysis of patients who underwent transurethral resection of the bladder cancer (TURB) at our institution from December 2020 to December 2021 was conducted. Serum albumin was obtained from a venous blood sample in pre-hospitalization, about 30 days before admission; we analyzed its correlation with the histological type of bladder cancer obtained during TURB and with outcomes of recurrence and mortality at middle and long term (3-12 months). Statistical analysis was performed using T test, and univariate and multivariate logistic regression analyses were conducted assuming p-value<0.05 to be statistically significant. *Results:* A total of 262 patients were included in the study (79% male, 21% female), with a mean age of 72.15±11.64 years; patients with systemic disease that could influence ALB levels were excluded. After statistical analysis, a correlation between ALB and carcinoma *in situ* (Cis), both synchronous and metachronous, was found: the preoperative peripheral blood level of ALB was significantly lower in patients with Cis NMIBC compared with patients affected by Ta NMIBC or T1 NMIBC (p<0.05). The results of univariate and multivariate logistic regression analyses showed that tumor size, urinary cytology, differentiation grade, Cis, and serum ALB were independent prognostic factors for NMIBC recurrence and response to treatment (BCG-therapy) (p<0.05). Furthermore, our results suggested that pretreatment serum ALB levels was related to a worse cancer-specific overall survival (p<0.05). The cutoff value of ALB in order to predict NMIBC recurrence and Cis correlation was 32.75 g/l, with a 76.0% sensitivity and 8% specificity. *Conclusion:* Lower serum albumin level is an independent negative prognostic factor related to malignant flat lesion of urothelial tissue (Cis), both synchronous and metachronous, in patients with bladder cancer, and correlates with worse middle and long term prognosis. Further data are required to consider serum ALB as a diagnostic and prognostic biomarker in bladder tumors.

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MULTIDISCIPLINARY TREATMENT OF RENAL CELL CARCINOMA WITH THROMBUS IN THE INFERIOR VENA CAVA AND RIGHT ATRIUM, A CASE REPORT

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Background: Renal cell carcinoma accounts for about 3% of all cancers, with the highest incidence occurring in the western world. This neoplasm in a small percentage of cases, about 10%, and especially in an advanced stage, can cause the formation of an intravascular thrombus involving the renal vein or vena cava. The case we present is a patient with a renal neoformation and thrombus in the inferior vena cava involving the right atrium. *Case Report:* The patient, a 79-

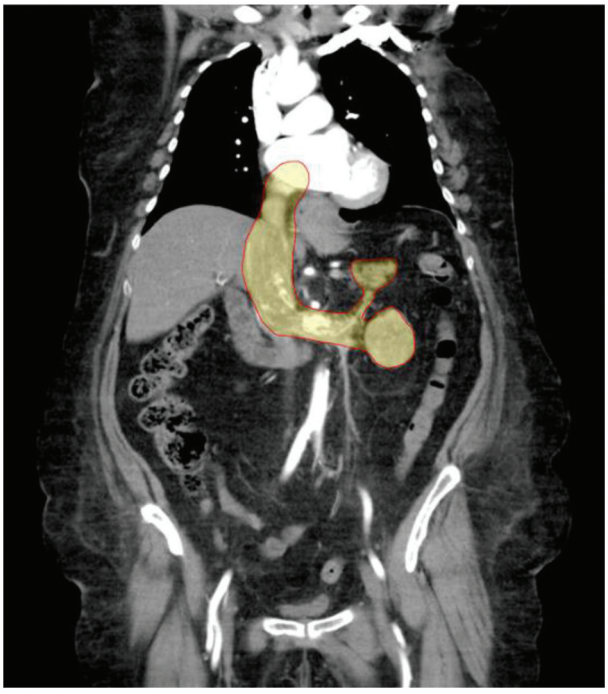

Figure 1. *Thrombus*.

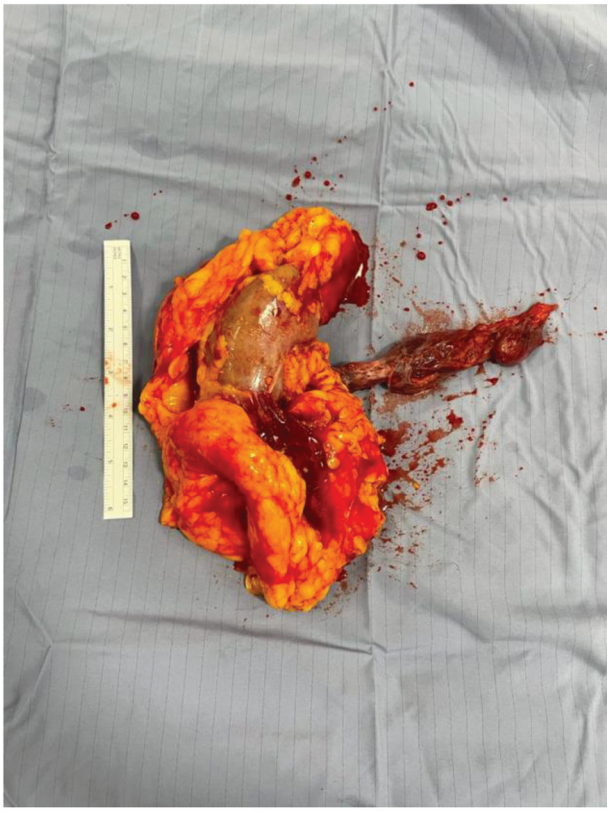

Figure 2. *Left kidney specimen*.

year-old woman, was admitted to the Cardiac Surgery Department for precordial pain, dyspnea, and blood pressure fluctuations for about a month. After the initial hematological and instrumental checks, the patient underwent a computed tomography scan that revealed a 45 × 41-millimeter left mesorenal lesion infiltrating the perirenal fat and vascular hilum. The renal vein was found to be completely occupied by gross thrombus involving the inter course of the inferior vena cava to the right atrium (Figure 1). A surgical indication of left atrial nephrectomy and removal of the right atrial thrombus and vena cava in circulatory arrest was provided. The American Society of Anesthesiologists (ASA) grading of the patient was Level III. The operation was performed in a hybrid operating room by a multidisciplinary team of surgeons (urologists, cardiac surgeons, vascular surgeons, abdominal surgeons) who simultaneously treated the thrombus in the atrium and inferior vena cava in circulatory arrest. The left radical nephrectomy was then performed (Figure 2). Histological examination of both renal neoformation and thrombus was clear cell renal carcinoma grade III according to WHO/ISUP 2013. pT3b pNx. The resection margins were free of neoplasia. *Conclusion:* At oncological follow-up 6 months after surgery, the patient was in good general clinical condition, blood exams were normal, and there was no neoplastic recurrence at the level of the left renal lodge.

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THE ROLE OF PROSTATE-SPECIFIC MEMBRANE ANTIGEN POSITRON-EMISSION TOMOGRAPHY IN THE PREOPERATIVE STAGING OF HIGH-/INTERMEDIATE-RISK PROSTATE CANCER

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Background: Prostate cancer is the second most common cancer in men and accurate staging of patients with primary prostate cancer is essential for optimal treatment decisions. According to the latest guidelines, computed tomography with contrast (CT) and bone scintigraphy (BS) are the gold standard examinations for staging patients at intermediate/high risk of prostate cancer. The aim of this study was to compare conventional imaging modalities with newer and potentially more accurate imaging modalities. *Patients and*

Methods: A total of 62 patients diagnosed with intermediate-/high-risk prostate cancer according to European Association of Urology risk groups for biochemical recurrence of localized and locally advanced prostate cancer were considered. Forty patients underwent conventional imaging modalities (CT and BS) for preoperative staging while the remaining 22 patients underwent prostate-specific membrane antigen positron emission tomography (PSMA PET)-CT after negativity or uncertain results of conventional imaging modalities despite the intermediate/high risk. The radiological examinations were reviewed by the same radiologist and nuclear physician. All patients underwent pelvic lymphadenectomy following assessment of lymph node involvement using a validated nomogram [Briganti score (1)]. *Results:* The median interval between radiological examination and surgery was 28 days (interquartile range=35-23 days). The mean age was 71 years (standard deviation=5 years) and the median prostate-specific antigen level was 14.5 (interquartile range=9-24) ng/ml. Metastatic pathology with bone involvement was found in 7/62 (11%) patients while 25/62 (40%) patients showed lymph node involvement on histological examination. PSMA PET-CT had superior sensitivity in detecting metastatic disease in 12/22 (54%) patients who had negative standard imaging, and influenced clinical decision-making in 7/12 patients (58%). All patients with positive PSMA PET-CT for lymph node involvement or bone metastases were found to have high-grade prostate cancer on histopathological examination. *Conclusion:* PSMA PET-CT shows high diagnostic accuracy for detecting prostate cancer metastases and lymph node involvement, and can be considered a suitable preoperative diagnostic examination in patients with high-risk prostate cancer.

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STEREOTACTIC BODY RADIATION THERAPY AND ABIRATERONE ACETATE FOR PATIENTS AFFECTED BY OLIGOMETASTATIC CASTRATE-RESISTANT PROSTATE CANCER: A RANDOMIZED PHASE II TRIAL (ARTO–NCT03449719)

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Background: The presence of a limited number of metastatic lesions may indicate an intermediate status of disease, characterized by a lower tumor burden, and defined as 'oligometastatic disease' (1). There is level I evidence that metastasis-directed therapy improves outcomes in patients with distinct histology (*e.g.*, melanoma, lung, colorectal and prostate cancer) (2). Stereotactic body radiation therapy (SBRT) represents a non-invasive therapeutic strategy for the treatment of oligometastatic disease; however, despite several retrospective reports about its use in metastatic castrate-resistant prostate cancer (CRPC) (3), currently no prospective evidence exists on a combined approach of SBRT with androgen receptor-targeted agents in patients with metastatic CRPC. ARTO (NCT03449719) is a multicenter, phase II randomized clinical trial testing the benefit of adding SBRT to abiraterone acetate (AA) in patients with oligometastatic CRPC. *Patients and Methods*: All patients were affected by oligometastatic CRPC, defined as ≤3 non-visceral metastatic lesions. Patients were randomized 1:1 to receive either AA alone (control arm) or AA with concomitant SBRT to all sites of disease (experimental arm). The primary endpoint was the rate of biochemical response, defined as a prostate-specific antigen

Table I. *Main adverse events in treatment and control arms.*

	Abiraterone alone, n (%)		Abiraterone+SBRT, n (%)	
Type of adverse event	Grade 1/2	Grade >2	Grade 1/2	Grade >2
Blood count abnormality	4 (4.9)	1 (1.2)	6 (8)	1 (1.3)
Other blood test abnormality	13 (15.8)	4 (4.9)	10 (13.3)	1 (1.3)
Osteoporosis/fracture	5 (6)	0 (0)	2 (2.7)	0 (0)
Fatigue	8 (9.7)	1 (1.2)	9 (12)	0 (0)
Hot flashes	2 (2.4)	0 (0)	2 (2.7)	0 (0)
Hyperglycemia/diabetes	3 (3.6)	0 (0)	3 (4)	0 (0)
Lower urinary tract symptoms	4 (4.9)	3 (3.6)	2 (2.7)	1 (1.3)
Hematuria	3 (3.6)	1 (1.2)	2 (2.7)	2 (2.7)
Gastrointestinal disorders	1 (1.2)	0 (0)	2 (2.7)	0 (0)
Cardiovascular disorders	11 (13.4)	3 (3.6)	7 (9.3)	3 (4)
Limb edema	0 (0)	0 (0)	3 (4)	0 (0)
Total	54 (65.8)	13 (15.8)	48 (64)	8 (10.6)

SBRT: Stereotactic body radiotherapy.

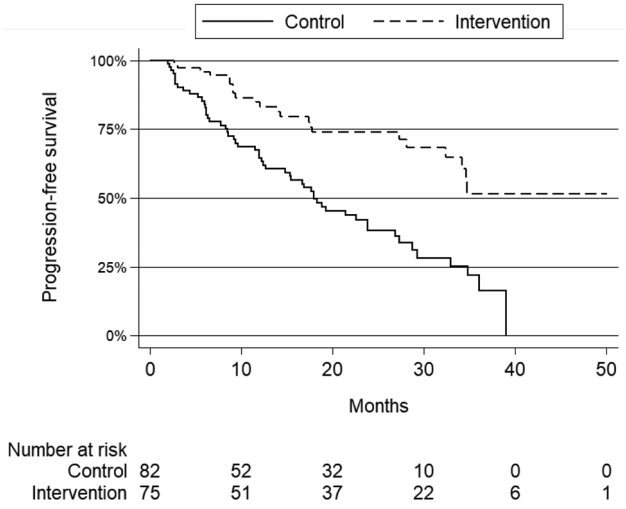

Figure 1. *Cox regression analysis of progression-free survival.*

decrease ≥50% from baseline measured at 6 months from treatment start. Complete biochemical response, defined as prostate-specific antigen level of <0.2 ng/ml at 6 months from treatment, and progression-free survival (PFS) were secondary endpoints. *Results:* One hundred and fifty-seven patients were enrolled between January 2019 and September 2022. Biochemical response was detected in 79.6% of patients (90.6% *vs*. 68.2% in the experimental *vs*. the control arm, respectively), with an odds ratio of 4.50 [95% confidence interval (CI)=1.70-11.95; p=0.003] in favor of the experimental arm. Complete biochemical response was detected in 38.8% of patients (56% *vs*. 23.2% in the experimental *vs*. control arm, respectively), with an odds ratio of 3.64 (95% CI=1.80-7.38; p<0.001). SBRT yielded a significant PFS improvement, with a hazard ratio for progression of 0.35 (95% CI=0.21-0.57; p<0.001) in the experimental *vs*. control arm, respectively (Figure 1). Main adverse events are reported in Table I. *Conclusion:* The trial reached its primary endpoint of biochemical control and PFS, suggesting a clinical advantage for SBRT in addition to first line AA treatment in patients with metastatic CRPC. Phase III trials are warranted to test survival endpoints in larger cohorts.

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LONG-TERM ANALYSIS OF ACTIVE SURVEILLANCE PROTOCOLS IN LOW-RISK PROSTATE CANCER: REAL-LIFE DATA MAY CHANGE FOLLOW-UP SCHEDULES

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Background/Aim: Active surveillance (AS) programs are widespread to combat overdiagnosis and overtreatment of low-risk prostate cancer. The strategy aims to avoid or delay radical treatment and its consequences in men with no disease progression. We analyzed the available data in our real-world practice in order to assess the time to progression or reclassification, the proportion of men with progression or reclassification in relation to time, according to prostate-specific antigen (PSA) determination and its trend, and re-biopsy findings. The final goal was to optimize follow-up scheduling by reducing the burden of follow-up examinations while maintaining diagnostic discrimination. *Patients and Methods*: We retrospectively analyzed data from a prospective cohort of patients with low-risk prostate cancer enrolled in three AS protocols INT 95/11 (SAINT), INT 46/07 (PRIAS), and INT 113/16 (SPRINT), from March 2005 to May 2019. The three protocols had very similar inclusion criteria, comprising patients with clinical stage ≤T2a, initial PSA ≤10 ng/ml and Gleason Score ≤3+3/Gleason Grade Group (GG) 1. Differences concerning entry criteria are shown in Table I. Per-protocol exit criteria included: Increase in grade from GG1 to higher (upgrading), increase in number of positive cores allowed in each protocol, patient's decision, age >80 years, life-expectancy <10 years. We considered three categories for the PSA doubling time (DT): Very unfavorable: PSA-DT <3 years, unfavorable PSA-DT: 3-10 years, and favorable: PSA-DT >10 years or PSA DT <0 years (whenever the PSA has a downward trend, the DT becomes a negative number). The determination index R2 was introduced to measure the fit of the estimated PSA-DT to the real PSA trend resulting from multiple PSA tests of each individual patient. Chi-square test was performed to detect the association between PSA-DT categories and upgrading. *Results:*

Table I. *Inclusion criteria of the three active surveillance protocols at our institution: INT 95/11 (SAINT), INT 46/07 (PRIAS) and INT 113/16 SPRINT.*

	INT 95/11 (SAINT)	INT 46/07 (PRIAS)	INT 113/16 (SPRINT)
Clinical stage	<cT2a	<cT2a	<cT2a
Initial PSA	≤10 ng/ml	≤10 ng/ml	≤10 ng/ml
Gleason grade group	1	1	1
PSA density		<0.2 ng/ml/cm^3	<0.25 ng/ml/cm^3
Positive cores at biopsy	≤25%, Core length containing cancer ≤50%	Until 2016, a maximum of 2, or 15% of positive cores for saturation biopsies*	No limit
mpMRI required	No	From 2016, for >2 positive cores	Yes

mpMRI: Multiparametric magnetic resonance imaging. *In 2016, PRIAS was amended and removed limits on positive core numbers among patients undergoing mpMRI and targeted biopsy of Prostate Imaging Reporting & Data System (PI-RADS) >2 lesions.

Table II. *Maximum grade in surveillance biopsy over a 7-year period.*

	Per year, n (%)						
Gleason grade group	1	2	3	4	5	6	7
No tumor	385 (40.48)	109 (43.95)	54 (42.86)	132 (42.44)	22 (45.83)	24 (50)	46 (55.42)
1	419 (44.06)	102 (41.13)	50 (39.68)	137 (44.05)	18 (37.5)	19 (39.58)	26 (31.33)
2	93 (9.78)	20 (8.06)	13 (10.32)	23 (7.4)	5 (10.42)	2 (4.17)	6 (7.23)
3	33 (3.47)	9 (3.63)	5 (3.97)	13 (4.18)	3 (6.25)	1 (2.08)	4 (4.82)
4	18 (1.89)	7 (2.82)	4 (3.17)	6 (1.93)	0 (0)	2 (4.17)	1 (1.2)
5	3 (0.32)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Overall, 13,985 PSA tests and 1,823 biopsies from 1,114 patients were evaluated. At the median follow-up time of 31 months (range=0-174 months), 591 patients (53%) had discontinued AS, including 289 (26%) who experienced upgrading. Although most upgrading events occurred at the first surveillance biopsy, the subsequent yearly upgrading rate did not significantly change over time, ranging from 14.2-15.6%. Upgrading occurred more frequently in patients with very unfavorable PSA-DT (38.1%) and unfavorable PSA-DT (18%), than in patients with favorable PSA-DT (9.2%) ($p<0.0001$). Of note, most progressions were from GG1 to GG2, while up to 40% of re-biopsies did not show the presence of cancer (Table II). R2 addition improved the ability of upgrading prediction among patients with unfavorable PSA-DT of 3-10 years. Moreover, in the favorable category, most patients (>90%) did not experience upgrading. However, in one-third of patients with very unfavorable PSA-DT or with unfavorable PSA DT and R2>0.7 at the time of surveillance biopsy, there was upgrading. *Discussion and Conclusion:* In a series of patients undergoing AS without MRI support, a stable rate (15%) of reclassification/progression was recorded for each year of follow-up. Finally, a relevant proportion of men left AS over time, but in most of them, the surveillance biopsies did not show a grade reclassification to a true adverse pathology (GG>2). Although the PSA-DT may vary for each individual over time, it would seem to be a very informative parameter, showing that the risk of upgrading in men with favorable PSA-DT is less than 10%. Patients with a very unfavorable PSA-DT, as well as a subgroup of those with unfavorable PSA-DT, displayed a risk of upgrading exceeding 30%. Our findings may help in redesigning AS follow-up protocols in order to reduce the burden of repeated tests in a significant proportion of men with persistently favorable features.

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THERAGNOSTIC PSMA BEYOND PROSTATE CANCER: A MONOCENTRIC, PROSPECTIVE OBSERVATIONAL STUDY ON THE DIAGNOSTIC PERFORMANCE OF PSMA PET/CT IN PATIENTS WITH METASTATIC CLEAR-CELL RENAL CELL CARCINOMA

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Background/Aim: Prostate-specific membrane antigen positron-emission tomography (PSMA PET/CT) is almost a certainty for staging and restaging of prostate cancer. However, it is well known that expression of PSMA it is not restricted to prostate cancer. Other malignant tumor entities overexpress this protein and clear-cell renal cell carcinoma (ccRCC) has been found to be one of these. The aim of this study was to evaluate the diagnostic performance of PSMA PET/CT in patients at first evaluation of suspected metastatic ccRCC, and to assess its potential use with a theragnostic intent. *Patients and Methods*: This monocentric prospective observational study included patients with metastatic ccRCC who underwent PSMA PET/CT for restaging purposes within 1 month of the restaging contrast-enhanced CT, used as a reference standard. A positive PSMA scan was defined when at least one lesion had a mean standardized uptake value (SUV_{mean}) above the SUV_{mean} of the liver. The active tumor volume and the total lesion activity were calculated with a semiquantitative method. *Results:* PSMA PET/CT was positive in all four patients, showing a total of 54 multiple pathological foci overall [median number of lesions=11, interquartile range (IQR)=8.8-15.8]; in contrast-enhanced CT, the total number of pathological foci was 39 (median=8.5, IQR=7.8-10.5). In one patient, PSMA PET/CT detected additional soft-tissue uptakes which were not detected on contrast-enhanced CT; however, another patient showed less localization than with contrast-enhanced CT (lung). In all patients, PSMA expression was highly positive at metastases, with a median SUV_{mean} of 17.7 g/ml (IQR=16.1-19.3 g/ml) at the most avid metastases. The median active tumor volume was 59.7 cm^3 (IQR=35.9-64.7 cm^3) and the total lesion activity was 567.4 g/ml/cm^3 (IQR=830.1-306.8 g/ml/cm^3). The median SUV_{mean} of the parotid gland was 16.1 g/ml (IQR=14.3-16.9 g/ml) and the median SUV_{mean} of liver parenchyma was 8.1 g/ml (IQR=6.3-9.2 g/ml). All four patients were eligible for therapeutic treatment with PSMA targeting considering the VISION criteria (1). *Conclusion:* Our initial experience showed that PSMA PET/CT has a high diagnostic performance in detecting metastatic ccRCC and that this pathology may benefit from a theragnostic approach for PSMA-targeted therapy. Further studies are needed to confirm these findings and to assess the potential use of PSMA theragnostic in other urological cancer types besides prostate cancer.

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RETROSPECTIVE ANALYSIS OF RADIOTHERAPY PLANS FOR PROSTATE CANCER AFTER REVISION OF MRI TARGETED LESIONS DETECTED BY QUANTIB

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Background/Aim: The aim of this retrospective analysis was the evaluation of coverage of radiotherapy plans after magnetic resonance imaging (MRI) revision of intraprostatic lesions detected by the Quantib® system (Quantib B.V. Rotterdam, the Netherlands), a Food and Drug Administration- and Council of Europe-approved artificial intelligence-powered, MRI viewing and reporting platform based on deep learning. Quantib® is able to help the radiologist in identification of intraprostatic target lesions suspected as disease (1, 2). *Patients and Methods*: We evaluated five patients treated with hypofractionated radiotherapy (70 Gy in 28 fractions) affected by intermediate-to-high risk prostate cancer (Table I). All patients were staged using pre-radiotherapy MRI. The following lesions were identified: Patient 1: one Prostate Imaging Reporting and Data System (Pi-RADS) 4 lesion; patient 2: one Pi-RADS 5 lesion, patient 3: one Pi-RADS 5 lesion, patient 4: one Pi-RADS 4 lesion and one Pi-RADS 3 lesion; patient 5: two Pi-RADS 4 lesions. The Quantib® system was not available at our hospital at the time of diagnosis. It was decided to review these MRIs with the Quantib® system and, through image fusion, to evaluate the coverage of these lesions on the previous treatment plan and the subsequent prostate-specific antigen trend in the follow-up. Contouring of the patients was performed without MR fusion. Regarding the radiological review, the analysis was carried out using Quantib® without considering the previous report to avoid bias. *Results:* A total of five lesions were identified in five patients. In one case, Quantib® failed to detect the lesions previously identified: these lesions had been identified as Pi-RADS 3 and Pi-RADS 4 and were located in the transitional zone, where Quantib® has the greatest difficulty in detecting. The remaining lesions detected by Quantib® were anatomically related to those previously identified on MRI. As regards the review of radiotherapy plans, the coverage of intraprostatic lesions was optimal (dose delivered to *95%* of the volume was between 67.9 Gy and 70.7 Gy, and that to 98% was between 65.4 Gy and 70.7 Gy). Moreover, evaluating the prostate-specific antigen value in the follow-up (between 3 and 9 months), a response to radiation treatment was detected with a drop of this value. *Conclusion:* The analysis shows how the Quantib® system can help the identification of intraprostatic target lesions, but the evaluation of the images must always be carried out in parallel, as demonstrated by case 4 here. Regarding treatment plan evaluation, the review after identification of the target images on MRI confirmed optimal radiotherapy coverage of the target volume and a subsequent biochemical response at minimum follow-up. These are preliminary results and a more detailed analysis is needed.

Table I. *Patient characteristics*.

				Median PSA value, ng/ml			
Patient	ISUP grade	Lesion Pi-RADS, n	HT	At diagnosis	At RT start post HT start	Post RT	Lesion coverage
1	4	Pi-RADS 4: 1	Yes	5.25	5.62	0.05	D95% 68.3 Gy D98% 68 Gy
2	4	Pi-RADS 5: 1	No	12.77		1.07	D95% 67.9 Gy D98% 65.4 Gy
3	5	Pi-RADS 5: 1	Yes	8.58	1.44	0.41	D95% 69.5 Gy D98% 67.8 Gy
4*	2	Pi-RADS 4: 1 Pi-RADS 3: 1	No	28.37			
5	3	Pi-RADS 4: 1 Pi-RADS 4: 1	No	16.59		2.58	D95% 70.7 Gy D98% 70.7 Gy D95% 68.6 Gy D98% 69 Gy

D95%: Dose delivered to 95% of the volume; D98%: dose delivered to 98% of the volume; HT: hormonal therapy; ISUP: International Society of Urological Pathology; Pi-RADS: Prostate Imaging Reporting and Data System; RT: radiation therapy. *Not detected by Quantib® (located in the transition zone).

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GEOGRAPHICAL DIFFERENCES IN THE MANAGEMENT OF METASTATIC *DE NOVO* RENAL CELL CARCINOMA IN THE ERA OF IMMUNE COMBINATIONS WITH A FOCUS ON THE ROLE OF CYTOREDUCTIVE NEPHRECTOMY

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Background: The upfront treatment of metastatic renal cell carcinoma (mRCC) has been revolutionized by the introduction of immune-based combinations. The role of cytoreductive nephrectomy (CN) in these patients is still debated. The ARON-1 study (NCT05287464) was designed to globally analyze real-world data of patients with mRCC receiving first-line immuno-oncology combinations. This sub-analysis was focused on the role of upfront or delayed partial or radical CN in three geographical areas (Western Europe, Eastern Europe, America/Asia). *Patients and Methods:* We conducted a multicenter retrospective observational study in patients with mRCC treated with first-line immune-based combinations from 55 centers in 19 countries. From 1,152 patients in the ARON-1 dataset, we selected 651 patients with *de novo* mRCC; 255 patients (39%) had undergone CN, partial in 14% and radical in 86% of cases; 396 patients (61%) received first-line immune-based combinations without previous nephrectomy. The primary endpoint was overall survival (OS) while progression-free survival (PFS) and the tumor response rate were secondary endpoints. *Results:* Median OS from the diagnosis of *de novo* mRCC was 41.6 months and not reached (NR) for the CN subgroup and 24.0 months for the no CN subgroup, (p<0.001). Median OS from the start of first-line therapy was NR in patients who underwent CN and 22.4 months in the no CN subgroup (p<0.001). Median OS was longer for patients who underwent CN compared to those who did not in all three geographical areas (Western Europe: NR *vs*. 23.7 months, p<0.001; Eastern Europe: NR *vs*. 29.8 months, p=0.005; America/Asia: 57.3 months *vs*. 25.5 months, p<0.001, respectively). *Conclusion:* No significant differences in terms of patients' outcomes seem to clearly emerge from our analysis, even though the CN rate and the choice of the type of first-line immune-based

combination varied across the different Cancer Centers participating in the ARON-1 project.

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STEREOTACTIC BODY RADIATION THERAPY WITH MRI-DEFINED FOCAL SIMULTANEOUS INTEGRATED BOOST FOR PATIENTS WITH LOCALIZED PROSTATE CANCER: ACUTE TOXICITY AND DOSIMETRY RESULTS FROM A PROSPECTIVE STUDY

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Background: After prostate stereotactic body radiotherapy (SBRT), local recurrence typically occurs in the pre-treatment multiparametric magnetic resonance imaging (mpMRI) region of a Prostate Imaging Reporting and Data System (PI-RADS) 4 or 5 dominant intra-prostatic lesion (DIL) (1). The addition of a focal boost to the DIL is an emerging strategy to potentially improve tumor control in patients with organ-confined prostate cancer (2, 3). This study aimed to report the early acute toxicity and dosimetry results of a prospective observational study of prostate SBRT with a simultaneous integrated boost (SIB) to the mpMRI/targeted biopsy-defined focal lesions. *Patients and Methods*: Patients with newly diagnosed organ-confined prostate cancer with clinical stage T1-T2c adenocarcinoma, Gleason score ≤8, prostate-specific antigen (PSA) level <20 ng/ml, and prostate volume ≤90 cc were included in the study. The presence of DIL on mpMRI, confirmed on targeted ultrasound-fusion biopsy, was mandatory for inclusion in the study and up to two separate nodules were allowed. Intra-prostatic fiducial markers and recto-prostatic hydrogel spacer were placed under transrectal ultrasound guide. MRI-based SBRT-simulation was performed in all patients. SBRT was delivered with volumetric modulated arc radiotherapy, administering 36.25 Gy to the prostate with a SIB of 40 Gy (dose gradient range=100-120%) to the DIL (Figure 1). Genitourinary (GU) and gastrointestinal (GI) toxicity was reported using the Common Terminology Criteria for Adverse Events. The objective of the study was to evaluate the dosimetric parameters and the rate of acute toxicity of the SBRT-SIB approach. Results, in terms of toxicity and dosimetry, were compared with a group of patients treated with prostate SBRT without boost in the same period. *Results:* From January to December 2022, a total of 42 men underwent prostate SBRT at our Institution. Among these, 18 patients (43%) with mpMRI-defined DIL, confirmed by targeted biopsy, received prostate SBRT with SIB to the focal lesions. The median patient age was 75 years (range=56-80 years). Fifteen patients (83%) had cT2 disease, median initial PSA was 7 ng/ml (range=3.6-19.2 ng/ml), and the baseline International Prostate Symptom Score was mild and moderate in 61% and 39%, respectively. The majority of DILs were in the peripheral zone (89%). Most patients had either Gleason score 3+4 (39%) or 4+3 (33%). In seven (39%) patients, androgen-deprivation therapy was administered in accordance with current clinical practice. All the SBRT-SIB plans met the predetermined target coverage objectives. Table I reports the results of the SBRT-SIB treatment plan analysis for critical organs at risk. At a median follow-up of 6 months (range=3-14 months), no acute GU or GI toxicity of grade 3 or more was observed. Furthermore, 90 days after SBRT-SIB, the cumulative acute grade 1-2 GU and GI toxicity rates were 44.4% and 16.7%, respectively. In comparison with the non-boost SBRT group (24 patients), the rectal $V_{40\ Gy}$, $V_{36\ Gy}$ and $V_{24\ Gy}$, and the bladder $V_{40\ Gy}$, $V_{37\ Gy}$ and $V_{18.1\ Gy}$ did not differ significantly (all $p>0.05$). Moreover, no differences were found between groups in terms of acute grade 2 GU (16.7% boost *vs*. 20.8% no boost; $p=0.74$) and GI toxicity (5.6% boost vs 4.2% no boost; $p=0.83$). *Conclusion:* Our preliminary results show that approaching prostate cancer with 5-fraction SBRT delivering a whole dose of 36.25 Gy and a focal dose of 40 Gy SIB to mpMRI/targeted biopsy-defined DILs is safe and effective, with excellent adherence to the planning protocol. Data collected on a 6-month follow-up suggest that this treatment is not associated with increased acute morbidity. Longer follow-up is needed to evaluate tumor control and late toxicity. In this respect, further enrollment of patients is ongoing.

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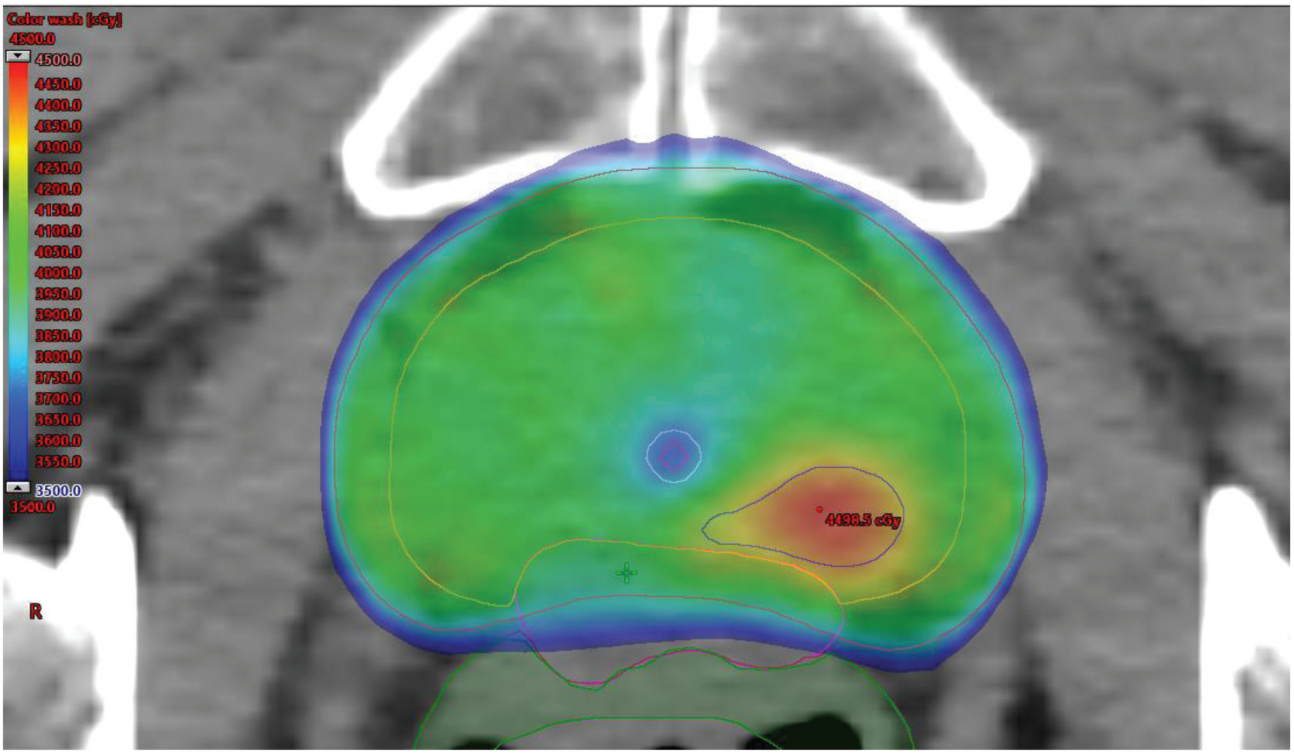

Figure 1. *Typical dose distribution (color wash) for prostate stereotactic body radiotherapy plan with simultaneous integrated boost to the dominant intra-prostatic lesion. The prescribed dose was 36.25 Gy in 5 fractions to the whole gland [prostate planning target volume ($PTV_{prostate}$) (red)] with a 40 Gy focal boost to the dominant lesion [PTV_{boost} (blue), maximum dose 45 Gy]. Hot spots to the urethra (pink) were avoided (maximum dose ≤36.25 Gy). The recto-prostatic hydrogel spacer (magenta) allowed for dose reduction to the anterior rectal wall (green).*

Table I. *Treatment plan analysis for organs at risk.*

	Dosimetric parameter	Objective	Result (mean±standard deviation)
Bladder	$V_{40\ Gy}$	<2 cc	0.64 cc ± 0.97 cc
	$V_{37\ Gy}$	<10 cc (optimal 5 cc)	6.15 cc ± 3.82 cc 1
	$V_{18.1\ Gy}$	<40%	7.94% ± 8.49%
Rectum	$V_{40\ Gy}$	<1 cc	0.03 cc ± 0.10 cc
	$V_{36\ Gy}$	<2 cc (optimal 1 cc)	0.35 cc ± 0.68 cc
	$V_{24\ Gy}$	<50%	11.09% ± 10.17%

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PERITUMORAL INFLAMMATION IN PROSTATE BIOPSY CORE: DECIPHERING THE IMMUNE INFILTRATE

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Background/Aim: We recently developed the prostate inflammation score (PIS) as a readily available parameter that can be assessed by pathologists during microscopic evaluation of the prostate. This study aimed to evaluate the immune infiltrate in prostate biopsy cores using immune histochemistry (IHC) and decipher the type and number of immune cells of each PIS class. *Materials and Methods:* The PIS was used to categorize patients into three groups: PIS 1: No inflammatory cells or scattered inflammatory cell infiltrate without nodules; PIS 2: interstitial Inflammatory cell infiltrate organized in lymphoid nodules but no glandular disruption; PIS 3: interstitial infiltrate with glandular disruption. For the present study, we randomly selected 21 patients with PIS 2 and 18 patients with PIS 3. CD8, CD20 and CD4 antibodies were used for IHC. Each slide was digitally scanned, manual segmentation of the areas of interest (cancer foci and glandular tissue) was performed by the pathologist and an artificial intelligence algorithm determined the connectivity of membranes stained for each marker by automated image analysis. We compared clinical and quantitative IHC features in patients with PIS 2 *versus* those with PIS 3. As a sensitivity analysis, all calculation were repeated in patients with a negative biopsy and patients with a positive biopsy. Finally, we compared quantitative IHC features in patients with no cancer or low-grade prostate cancer v*ersu*s patients with clinically significant prostate cancer. *Results:* CD4 connectivity values were consistently increased in negative biopsies and those with low-grade cancer as compared to samples with high-grade cancer (p=0.021). Significantly higher CD8 connectivity values were seen in PIS 3 *versus* PIS 2 group (p=0.024). Finally, increased CD8 expression levels were detected in the extratumoral region of positive PIS 3 biopsies as compared to PIS 2 (p=0.017). *Conclusion:* Peritumoral inflammation assessed by the PIS in prostate biopsy cores is associated with different patterns of immune cell infiltration in prostate biopsy cores. Subsets of $CD8^+$ T cytotoxic and $CD4^+$ T helper lymphocytes, which have opposite roles in the immune response, are represented in greater numbers in neoplastic and benign prostate tissue, respectively. The more inflamed the prostate, the higher the number of $CD8^+$ cells. The immune microenvironment of prostate cancer deserves to be further explored as a source of promising prognostic and immunotherapy biomarkers.

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PERITUMORAL INFLAMMATION IN PROSTATE BIOPSY CORE PREDICTS BIOCHEMICAL RECURRENCE AFTER ACTIVE TREATMENT FOR PROSTATE CANCER

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Background/Aim: The relationship between prostate inflammation and prostate cancer is still unclear. In order to evaluate the prognostic role of prostatic hyperplasia and prostate cancer outcomes, we recently developed the prostate inflammation score (PIS) as a readily available parameter that can be assessed by pathologists during microscopic evaluation of the prostate. This study aimed to assess the association of PIS with biochemical recurrence (BCR) after radical prostatectomy. *Patientss and Methods:* Since 2013, we have prospectively enrolled all patients undergoing prostate biopsy at our Institution in this observational study. Grade and aggressiveness of prostatic inflammation were prospectively assessed by a dedicated uropathologist. The PIS was used to categorize patients into three groups, based on the dual classification of grade and aggressiveness of prostatic inflammation described by Irani *et al*. (1): PIS 1: No inflammatory cells or scattered inflammatory cell infiltrate without nodules; PIS 2: interstitial Inflammatory cell infiltrate organized in lymphoid nodules but no glandular disruption; PIS 3: interstitial infiltrate with glandular disruption. For the present study, we included all those patients with a positive prostate biopsy who consequently underwent radical prostatectomy and were followed-up with repeated prostate-specific antigen (PSA) measurements. Patients with detectable PSA after surgery were excluded. Biochemical recurrence was defined as PSA≥0.2 ng/ml in two consecutive measurements as our primary outcome. Competing risk regression was used to evaluate predictors of BCR, and Kaplan–Meier method to estimate BCR-free survival (BCRFS). *Results:* A total of 4,065 patients were screened; 595 patients were ultimately included and stratified by the PIS into three groups. The average follow-up time was 32 months. Patients with PIS 1 (n=439) were younger and with lower prostatic volumes compared to those with PIS 2 (n=101) and PIS 3 (n=52). No difference was found in Gleason score, clinical stage, or prostate-specific antigen at diagnosis. The 5-year BCRFS was 80%, 90% and 95% for patients with PIS 1, PIS 2 and PIS 3, respectively (p=0.0025). At multivariable Cox regression analysis adjusting for age, Gleason score, clinical stage and prostate-specific antigen at diagnosis, hazard ratios for BCRFS were 0.40 (95% confidence interval=0.18-0.87) and 0.20 (95% confidence interval=0.05-0.83) for patients with PIS 2 and 3,

respectively, compared to those with PIS 1. *Conclusion:* Peritumoral inflammation assessed by the PIS in prostate biopsy cores is associated with BCR after radical prostatectomy and may represent a readily available parameter for improving prediction of aggressiveness of prostate cancer and its clinical evolution.

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IMPACT OF MAGNETIC RESONANCE IMAGING SCAN AND IMAGE ACQUISITION PROTOCOL IN DETECTING CLINICALLY SIGNIFICANT PROSTATE CANCER AT BIOPSY: RESULTS FROM THE PROMOD WORKING GROUP

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Background/Aim: The Prostate Imaging Reporting and Data System (PI-RADS) Steering Committee does not provide uniform consensus regarding the optimal magnet strength for use in magnetic resonance imaging (MRI) of the prostate, although low-level evidence suggests a higher diagnostic performance of 3-T *versus* 1.5-T instruments for diagnosis of clinically significant prostate cancer (csPCa). Moreover, while biparametric MRI (bpMRI) results in an elimination of adverse events, shortened examination time and reduced costs, the comparability of its accuracy when compared to multiparametric MRI (mpMRI) is still debated. Our study aimed to assess the impact of magnet strength and protocol acquisition (bpMRI *vs*. mpMRI) used in prostate MRI in detecting csPCa. *Patients and Methods*: The PROMOD working group included a retrospective multicentric cohort of patients who underwent prostate MRI and subsequent MRI-targeted systematic prostate biopsy in the case of positive findings at MRI, defined as PI-RADS≥3 lesion. The endpoint of our analysis was the csPCa detection rate, defined as International Society of Urological Pathology grade group ≥2. MRI accuracy for diagnosis of csPCa was compared by sensitivity, specificity, and negative (NPV) and positive (PPV) predictive values, according to the magnet strength (3 T *vs*. 1.5 T) and acquisition protocol (bpMRI *vs*. mpMRI). Multivariable logistic regression was performed to evaluate predictors of csPCa. *Results:* A total of 9,294 patients were included; 4,348/9,294 (47%) of them underwent prostate MRI with a 3-T magnet, while the remaining 4,946 (53%) with 1.5-T. bpMRI and mpMRI acquisition were performed in 1,298 (14%) and 7,996 (86%) patients, respectively. Notably, centers which performed bpMRI used only 3-T scanners. Overall, the csPCa detection rate was 41% (3,807/9,294). PI-RADS≥3 lesions were found in 87% of 3-T assessed patients *versus* 91% of those with 1.5 T, and in 91% of the mpMRI group *versus* 73% of the bpMRI group (all $p<0.001$). The csPCa detection rate was 3,153/7,996 (39%) in mpMRI *versus* 654/1298 (50%) in bpMRI groups, 44% (1917/4348) in the 3-T group and 38% (1883/4946) in the 1.5-T group (all $p<0.001$). Sensitivity,

specificity, NPV and PPV of MRI PI-RADS≥3 were: 98%, 14%, 40% and 93% for 1.5-T MRI compared with 96%, 19%, 87% and 84% for the 3-T group; and 94%, 48%, 64% and 89% for the bpMRI group compared with 97%,12%, 40% and 88% for the mpMRI group. For MRI PI-RADS≥4, these values were: 87%, 48%, 49% and 93% for 1.5-T MRI compared with 84%, 55%, 58% and 81% for the 3-T group; 88%, 72%, 76% and 86% for the bpMRI group compared with 84%, 48%, 50% and 83% for the mpMRI group. At multivariable analysis adjusted for age, prostate-specific antigen density, PI-RADS score and previous biopsy history (naïve *vs*. previous negative), and type of acquisition (bpMRI *vs*. mpMRI), performing MRI with a 3-T scanner was independently associated with a higher likelihood of csPCa. *Conclusion:* While 3-T MRI showed higher accuracy in detecting csPCa at subsequent MRI-targeted biopsy when compared with 1.5-T MRI, the diagnostic performance of bpMRI was comparable with that of mpMRI. Our findings suggest how bpMRI use can be implemented in daily clinical practice in order to reduce the waiting time for MRI prior to biopsy.

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ONCOLOGICAL OUTCOMES AND PROGNOSTIC IMPLICATIONS OF T1 SUBSTAGING IN OVERALL MANAGEMENT OF HG NMIBC: RESULTS FROM A LARGE SINGLE-CENTRE SERIES

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Background/Aim: A wide variation of recurrence and progression are observed among patients with high-grade (HG) T1 non-muscle-invasive bladder cancer (NMIBC). Despite the efforts of the European Association of Urology (EAU) NMIBC Committee, current risk calculators struggle to accurately predict prognosis among this heterogeneous group. Our study evaluated how T1 substaging may improve the overall management of these patients. *Patients and Methods*: Our cohort enlisted 444 patients with a diagnosis of primary T1G3 BC at our Institution. Data from diagnosis to subsequent repeated transurethral resection of bladder tumor (RE-TURBT), eventual bacillus Calmette-Guérin (BCG) treatment and follow-up were collected. Cystoscopy and urine cytology were performed following EAU NMIBC guidelines recommendation, while computed tomography was performed yearly. All specimens were analyzed by two dedicated uropathologists. The population was stratified into T1a (focal infiltration of the *lamina propria*) and T1b (extensive) for statistical analyses, whenever possible. Differences in medians and proportions were assessed using Wilcoxon–Mann–Whitney and Person chi-square test. Kaplan–Meier and multivariate Cox regression analyses regarding recurrence-free, progression-free (PFS) and cancer-specific survival were performed. We included clinicopathological characteristics at first TURBT and BCG treatment as variables. *Results:* The median age of patients at diagnosis was 75 years (interquartile range=66-81 years); 388 patients were male (87.4%) At first TURBT, patients with T1b disease had larger tumors (>3 cm: 55.4% *vs*. 36.6%, p=0.003) when compared with those with T1a. At RE-TURBT, residual HG BC was found in 23% of T1a and 14.5% of T1b (p=0.1), while pathological upstaging (≥T2) was shown in 1.3% with T1a *vs*. 6.6% with T1b (p=0.04). At a median follow-up of 40 months (interquartile range=17-72 months), recurrence-free survival was 39.7% for the T1a group and 38.8% for the T1b group. Progression was observed in 27 (11.2%) and 21 (18.1%) patients with T1a and T1b disease (p=0.07). Cancer-specific survival was 83% and 75%, while cystectomy was performed in 16.5% *versus* 19%, respectively. Overall, patients with T1b disease had worse survival curves when compared to those with T1a, albeit this reached statistical significance only for PFS (p=0.01). At multivariable analyses, an adequate BCG course was an independent predictor for all outcomes evaluated (all p<0.01), while T1 substaging did not independently predict any endpoints evaluated. *Conclusion:* Extensive invasion of the *lamina propria* in primary T1 NMIBC was associated with poorer overall PFS and higher risk of upstaging to MIBC at RE-TURBT. Even if T1 substaging alone is suboptimal for predicting oncological outcomes of HG T1 NMIBC, its combination with other factors (lymphovascular invasion, multifocality, associated carcinoma *in situ*, no prior BCG treatment, >3 cm tumor size, and older age) may improve risk stratification and guide overall management disease.

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ADDITIONAL VALUE OF MAGNETIC RESONANCE IMAGING OF THE PROSTATE IN PATIENTS WITH PROSTATE-SPECIFIC ANTIGEN >10 NG/ML WITH/WITHOUT POSITIVE DIGITAL RECTAL EXAMINATION: A RETROSPECTIVE MULTICENTER STUDY

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Background/Aim: European Association of Urology guidelines for prostate cancer (PCa) strongly recommend the use of magnetic resonance imaging (MRI) as a screening tool for asymptomatic men with a prostate-specific antigen (PSA) level between 3 and 10 ng/ml and a normal digital rectal examination (DRE). No consensus regarding the use of this screening tool outside this clinical setting has been assessed. This study aimed to evaluate the additional value of prostate MRI as a first-line diagnostic tool in patients with PSA >10 ng/ml with/without positive DRE who underwent prostate biopsy. *Patients and Methods:* This was a retrospective, multicentric analysis of patients who underwent prostate MRI and subsequent systematic biopsy plus targeted biopsy in the case of positive findings at MRI, (Prostate Imaging Reporting and Data System ≥3). The PROMOD study database was used. When PCa was found, data regarding the overall Gleason grade (GG) was collected, as well as maximum GG found both for systematic and targeted cores. The endpoint of our analysis was the clinically significant (cs)PCa detection rate, defined as GG≥2. The PCa and csPCa detection rate using systematic and targeted cores were assessed and compared by chi-square test. Patients were primarily stratified according to DRE (suspicious *versus* negative), then classified into three categories according to the serum PSA level at biopsy: PSA<10 ng/ml, between 10-20 ng/ml and >20 ng/ml. *Results:* A total of 6,614 men were included. Suspicious DRE was found in 2,412/6,614 (36.5%). PSA <10 ng/ml was found in 5,108 patients (77.2%) while 1,190 (18%) had a serum level of 10-20 ng/ml and 316 (4.8%) >20 ng/ml. Overall, the PCa and csPCa detection rates were 71% (4,671/6,614) and 51% (3,340) respectively. Rates of positive MRI (PI-RADS≥3) and csPCa were higher in patients with suspicious DRE or PSA >10 ng/ml (all $p<0.001$). Considering patients with negative systematic biopsy, csPCa was found in targeted cores of 191/729 (26%) of those with a positive DRE, 126/470 (27%) of those with PSA between 10-20 ng/ml and 39/92 (42%) for those with PSA >20 ng/ml. When the GG was 1, PCa was found in systematic cores, csPCa was detected in 9% (37/405) of patients with a positive DRE, in 15% (25/168) of those with PSA 10-20 ng/ml and in 13% (3/24) of those with PSA>20 ng/ml. When compared to systematic biopsy, an overall upgrade to higher GG PCa in targeted cores were recorded in 7% of patients with a positive DRE, 9% of those with PSA 10-20 ng/ml and in 9% of those with PSA >20 ng/ml. The retrospective and multicentric nature of our cohort, including centers with different biopsy techniques and MRI acquisition protocols, represents the major limit of this study. *Conclusion:* MRI and subsequent MRI-guided biopsy increase the rate of csPCa detection and improve the accuracy of PCa staging at biopsy in cases with positive DRE and PSA >10 ng/ml.

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STEREOTACTIC BODY RADIOTHERAPY FOR PROSTATE CANCER IN A 72-YEAR-OLD PATIENT PREVIOUSLY TREATED WITH OPEN TRANSVESICAL ADENOMECTOMY FOR BENIGN PROSTATIC HYPERPLASIA: OUTCOME AND SAFETY DATA AT 14 MONTHS

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Background/Aim: SBRT represents a treatment option in the setting of low/intermediate-grade prostate cancer (1). Data on clinical outcomes and toxicity do not differ significantly from those of normo-fractionated radiotherapy (2). However, there is concern as to the role of SBRT in patients who previously underwent open surgery for benign prostatic hyperplasia, as it may lead to unacceptable genitourinary toxicity burden. *Case Report*: In January 2022, a 72-year-old patient diagnosed with Gleason score 6 (3+3) adenocarcinoma of the prostate and a previous history of benign prostatic hyperplasia with lower urinary tract symptoms was referred to our Department. The original diagnosis had been made in 2019 after he underwent open transvesical adenomectomy for symptom relief. From that time, the prostate-specific antigen level had risen progressively and reached a value of 12 ng/ml in December 2021. Multiparametric magnetic resonance imaging and prostate-specific membrane antigen–positron-emission tomography were performed for restaging purposes, and both confirmed intraprostatic disease only. SBRT to the prostate was therefore delivered with curative intent in March 2022; a total dose of 36.5 Gy was prescribed and administered in five daily fractions (every other day). Acute and late genitourinary and gastrointestinal adverse events were recorded according to the Common Terminology Criteria for Adverse Events (version 5.0). All dosimetric criteria were respected and the patient underwent SBRT as scheduled (Table I). Acute grade 1 dysuria was referred at the end of the treatment; no late genitourinary effects were documented during a follow-up of 14 months. No acute or late gastrointestinal toxicity was reported. After a follow-up of 14 months, complete biochemical response was documented with a prostate-specific antigen nadir of 1. ng/ml. *Discussion and Conclusion:* There is growing evidence on the role of SBRT in the setting of localized prostate cancer, as it has been proven to be non-inferior to conventional radiotherapy for the treatment of organ-confined disease. We described the case of a patient who was diagnosed with prostate cancer after having undergone open transvesical adenomectomy for benign prostatic hyperplasia, which generally contraindicates a subsequent extremely hypofractionated radiotherapy course. SBRT was perfectly tolerated, except for mild acute genitourinary toxicity, and the patient currently shows no evidence of disease after a follow-up of more than 1 year. If confirmed in larger population-based case series, this result may suggest an even wider applicability of this important treatment modality for prostate cancer.

Table I. *Dose prescription and organs at risk (OAR) constraints.*

Target/OAR	Dose constraints	Result
PTV 36.25 Gy	Dmax <45.8 Gy	39.67 Gy
	D2% <41.68 Gy	38.42 Gy
	D98% >34.44 Gy	34.71 Gy
PRV urethra	V36.25 Gy <3 cm^3	0.148 cm^3
Bladder	V36.25 Gy <1 cm^3	0.036 cm^3
	Mean dose	6.94 Gy
Rectum	V36.25 Gy <1 cm^3	0.021 cm^3
	Mean dose	15.75 Gy

D: Dose; PRV: planning organ at risk volume; PTV: planning target volume; V: volume.

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BLADDER-PRESERVING 'TRIMODALITY' THERAPY FOR MUSCLE-INVASIVE BLADDER CANCER: TEN-YEAR RETROSPECTIVE MONO-INSTITUTIONAL EXPERIENCE

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Background: Bladder cancer is a common neoplasm worldwide, particularly frequent in those of older age and in Western countries (1). More than two-thirds of bladder cancer diagnoses are of the non muscle-invasive type, while almost 30% are muscle invasive (2). Two different therapeutic options are proposed for muscle-invasive bladder cancer: radical surgery (cystectomy) with or without neoadjuvant/adjuvant systemic therapy or 'trimodality' approach, *i.e.* maximal endoscopic transurethral resection of macroscopic lesions followed by concomitant chemo-radiotherapy. Surgery followed by adjuvant radiotherapy can also be considered as an alternative option in selected patients, such as the frail or older ones. Similarly, consolidative immunotherapy after chemo-immunotherapy has been under investigation in recent years to increase efficacy outcomes (3). The aim of our study was to retrospectively evaluate our 10-year experience in treating patients affected by invasive bladder cancer (cT2-cT3 cN0-N1 M0) using a conservative, multimodal, bladder-sparing approach characterized by radical concomitant chemo-radiotherapy after maximal transurethral resection of bladder tumor. *Patients and Methods:* Between August 2012 and December 2022, 20 patients were submitted to cystoscopy with histological diagnosis of muscle-invasive bladder cancer. Their median age was 74 years (range=56-86 years). Eighteen patients were male. All patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. All patients had a diagnosis of urothelial cancer: 18 with papillary, two with non-papillary and one with sarcomatoid variant. Sixteen patients had unifocal disease, while four had multifocal. All patients were submitted to complete restaging with post-surgery cystoscopy and chest abdominal computed tomography, while seven patients were also submitted to ^{18}fluorodeoxyglucose positron-emission tomography–computed tomography. Twelve patients were submitted to single transurethral resection of bladder cancer (TURB) before chemoradiotherapy while seven were submitted to reTURB and only one to double reTURB. Despite this, eight patients still had macroscopic residual tumor before chemoradiotherapy. All patients were submitted to radiotherapy with radical intent, receiving doses ranging from 54 Gy (locoregional nodes) and 66 Gy (bladder and/or tumor/tumoral bed): eight patients with 60 Gy and 12 patients up to 66 Gy. Eighteen patients were submitted to concomitant chemoradiotherapy (eight with 5-fluorouracil plus mitomycin C, four with gemcitabine, three with cisplatin and three with another agent), while two patients received neoadjuvant chemotherapy before radical radiotherapy. *Results:* At a mean follow-up of 2 years (range=4-41 months), 12 patients were still alive while eight had died. Eleven patients showed a complete or partial response, while two patients had stable disease, for an overall response rate of 65%. Three patients had local recurrence (one of whom underwent salvage cystectomy and one had simultaneous nodal and systemic progression), one other showed locoregional lymph node relapse and finally three had metastatic spread. The mean (± standard error) OS rates at 1 and 2 years were both 67±13.2% SE. Two year progression-free and cancer-specific survival were 79.7±9.1% and 85±8.0%, respectively. Non-papillary histology seemed to influence progression-free and cancer-specific survival, even if not reaching statistical significance. All patients completed the radiotherapy course without any treatment delay and no grade 3 or more toxicity (Common Terminology Criteria for Adverse Events v4.0) was reported. *Conclusion:* In our 10-year experience, a conservative bladder-sparing approach appeared to be safe and effective in the middle-term management of muscle-invasive bladder cancer. However, due to the lack of robust data, prospective or randomized clinical trials are urgently needed to compare this conservative approach to the surgical one, even in the era of immunotherapy.

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