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ROLE OF NEXT-GENERATION IMAGING IN PROSTATE CANCER MANAGEMENT: RESULTS FROM A CROSS-SECTIONAL SURVEY EXPLORING CLINICAL PRACTICE OF URO-ONCOLOGISTS IN NORTH-EASTERN ITALY; ON BEHALF OF GUONE (GRUPPO URO-ONCOLOGICO DEL NORD-EST)

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Background/Aim: Next-generation imaging (NGI) technologies such as multiparametric magnetic resonance imaging (MRI) and total-body NGI modalities with prostate cancer (PCa)-dedicated positron-emission tomography (PET) radiotracers (including ^{18}F/^{11}C-choline, ^{18}F-fluciclovine and ^{68}Ga/^{18}F-prostate-specific membrane antigen ligands), whole-body MRI and hybrid imaging techniques such as PET/computed tomography and PET/MRI, are becoming increasingly available for the management of patients with PCa. Due to the lack of univocal recommendations derived from clinical data comparing NGI with conventional imaging modalities, to date, their use in different PCa settings is debated (1). The present survey was developed by the Gruppo Uro-Oncologico del Nord-Est (GUONE) to describe the current clinical practice in the North-Eastern Italy. *Materials and Methods*: A cross-sectional survey was conducted by administering an anonymous online questionnaire to uro-oncologists (medical oncologists, radiation oncologists, urologists) practicing in North-Eastern Italy, using Google Forms® platform. Use of NGI was investigated in: Primary staging of PCa; management of biochemical and local recurrence; restaging in metastatic hormone-sensitive PCa, metastatic castration-resistant PCa, non-metastatic CRPC and oligometastatic-PCa. *Results*: One hundred uro-oncologists accessed and completed the survey with a 100% response rate for each item (Table I). In primary NM staging of PCa, the use of whole-body NGI increased in accordance with National Comprehensive Cancer Network risk groups (Fisher's exact test: $p<0.01$) (2); in this setting, medical specialty and years of

Table I. *Sociodemographic characteristics of survey participants.*

Characteristic	n	%
Region		
Veneto	49	49.0
Friuli Venezia Giulia	26	26.0
Other	25	25.0
Specialty		
Urology	41	41.0
Radiation oncology	32	32.0
Medical oncology	27	27.0
Years of employment		
≤5	29	29.0
6-10	17	17.0
11-15	10	10.0
≥15	50	50.0
Trainee	5	5.0
Facility type		
Community hospital	49	49.0
University hospital	26	26.0
Research cancer center	14	14.0
Private center	11	11.0
Time devoted to uro-oncology		
80-100%	27	27.0
50-80%	39	39.0
30-50%	24	24.0
<30%	10	10.0
NGI technologies available at your facility		
mp-MRI	88	88.0
^{18}F/^{11}C-Choline PET/CT	64	64.0
Whole-body MRI	31	31.0
^{68}Ga/^{18}F-PSMA PET/CT	28	28.0
PET/MRI	16	16.0
^{18}F-Fluciclovine PET/CT	2	2.0
Number of NGI technologies available at your facility		
0	8	8.0
1	22	22.0
2	29	29.0
3	22	22.0
4	11	11.0
5	8	8.0
6	0	0

CT: Computed tomography; mp: multiparametric; MRI: magnetic resonance imaging; PET: positron-emission tomography; PSMA: prostate-specific membrane antigen.

professional practice did not significantly affect this attitude. Restaging with whole-body NGI was the prevalent choice in cases of biochemical recurrence after radical prostatectomy. Moreover, with increasing prostate-specific antigen, there was a parallel increased use of whole-body NGI ($p<0.01$). In the case of suspected local recurrence, whole-body NGI plus multiparametric MRI was the option most selected (2), particularly among radiation oncologists ($p=0.03$). Overall, restaging with whole-body NGI was preferred in patients with metastatic hormone-sensitive PCa, metastatic castration-resistant PCa, non-metastatic castration-resistant PCa in the case of biochemical progression only, as well as for concomitant biochemical and clinical progression. Only in non-metastatic castration-resistant PCa was there a trend towards using conventional imaging modalities in the case of concomitant biochemical and clinical progression. *Discussion and Conclusion:* This survey describes an uro-oncology scenario in North-Eastern Italy characterized by an expanding role of NGI modalities in staging/restaging of PCa, in the management of advanced disease and in the assessment of treatment response. Several controversial issues have emerged which need to be addressed in prospective studies in order to develop a standardized and cost-effective NGI utilization.

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A COMBINATION OF TYROSINE KINASE AND AUTOPHAGY INHIBITORS STRENGHTHENS THE INHIBITION OF ANGIOGENIC PATHWAY IN KIDNEY CARCINOMA CELL LINES

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Background/Aim: Clear-cell renal cell carcinoma (ccRCC) is the most frequent histotype of renal cancer, accounting for about 70% of all kidney carcinomas (1). This histotype is also the most aggressive being responsible for most deaths in patients with kidney cancer (1). Metastatic kidney carcinoma is a lethal pathology that currently is treated in first-line therapy with tyrosine kinase inhibitors (TKI) in combination with immune checkpoint inhibitors. This combined therapy has led to improvements in overall and progression-free survival as well as objective response rate, but this combination shows an

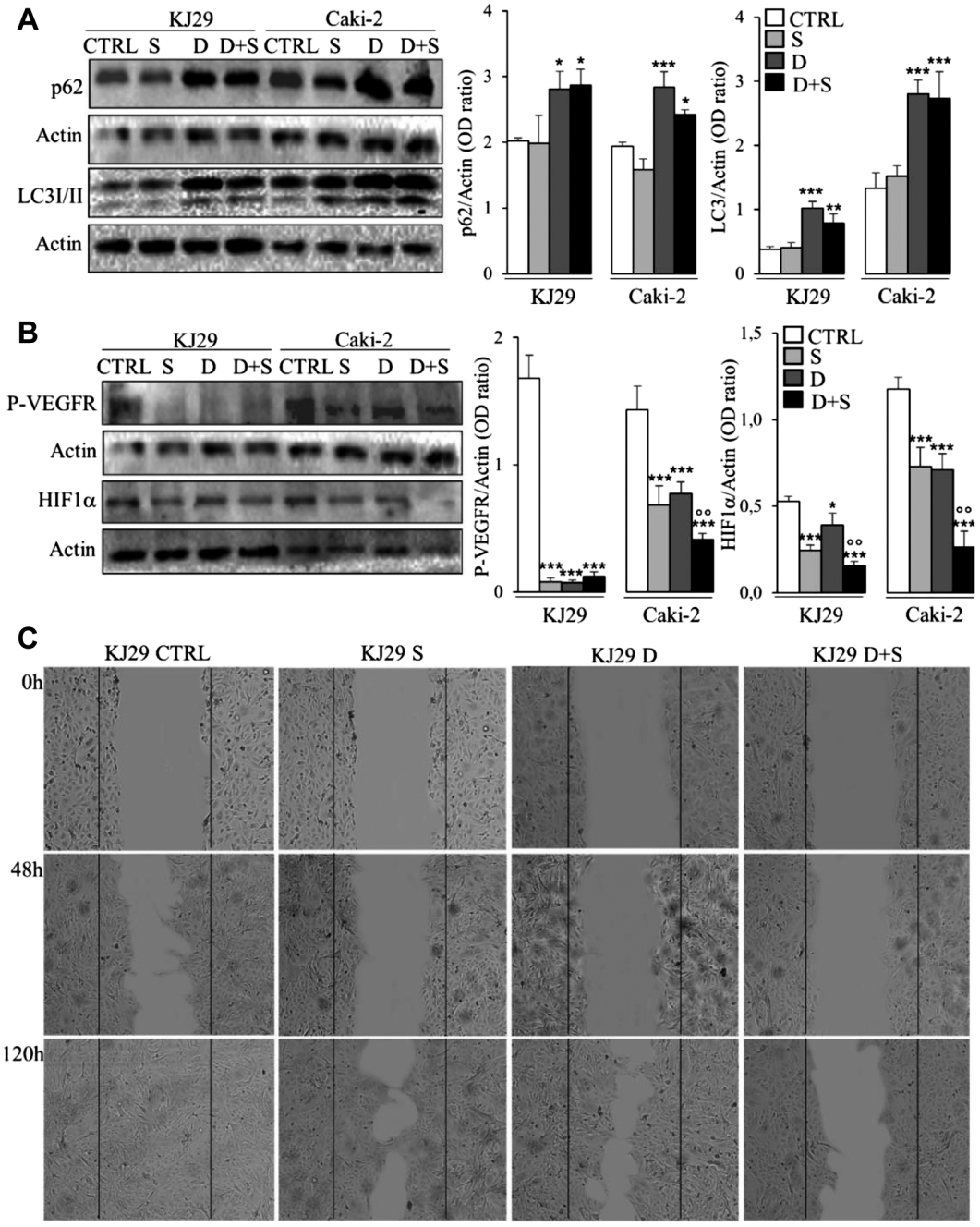

Figure 1. *The treatment of clear-cell renal cell carcinoma (ccRCC) cells with desmethylclomipramine (DCMI) and sunitinib (S) reduced activation of vascular endothelial growth factor receptor (VEGFR), hypoxia-inducible factor 1 α (HIF1α) expression and inhibited cell migration. (A) The expression of autophagy markers p62 and microtubule-associated protein 1A/1B-light chain 3 (LC3) was evaluated in Caki-2 and KJ29 ccRCC cells treated with sunitinib and DCMI alone or in combination (D+S). The application of DCMI individually or with sunitinib increased levels of both p62 and LC3 compared with untreated cells (CTRL). (B) The expression of phospho (p)-VEGFR and HIF1α was analyzed by western blotting in ccRCC cells treated as described above. The inhibition of VEGFR was studied evaluating the phosphorylation status of this receptor. All treatments caused the complete dephosphorylation of VEGFR in KJ29 cells, while this inhibition was less obvious in Caki-2 cells; the combined treatment induced greater receptor inhibition compared with single drug administration. The expression of HIF1α was reduced in both cell lines treated with sunitinib or DCMI. Importantly, the double treatment increased the down-regulation of this transcription factor. (C) Cell migration was evaluated by scratch-wound assay in KJ29 cells treated for 48 and 120 h with DCMI and sunitinib alone and in combination. The treatment with the single compound reduced cell spreading compared with untreated cells. Interestingly, the combined administration of DCMI and sunitinib inhibited cell migration more effectively and for a longer time compared with the single treatment. Values are expressed as the mean±standard deviation calculated from three independent experiments. Statistical analysis was performed by GraphPhad Prism software. Significantly different at: *p<0.05, **p<0.01 and ***p<0.001 vs. CTRL; °p<0.05 and °°p<0.01 vs. DCMI alone.*

increased toxicity compared with TKI monotherapy, often causing treatment interruption (2). In addition, frequent therapy resistance due to different mechanisms, including the activation of autophagy, have been observed. Autophagy is a process used by cancer cells to produce energy and destroy pharmacological molecules by trapping them in autophagosomes (3). Therefore, the use of autophagy inhibitors should improve the efficacy of conventional therapy. Here, we evaluated the angiogenesis pathway and cell migration after cell treatment with the autophagy inhibitor *des*methylclomipramine (DCMI), alone and in combination with the TKI sunitinib. *Materials and Methods:* Caki-2 and KJ29 ccRCC cells were cultured in Dulbecco's modified Eagle's medium (DMEM)/F12 with 1% fetal bovine serum in the presence of DCMI, alone and in combination with the vascular endothelial growth factor receptor (VEGFR) inhibitor sunitinib for 48 and 120 h. Treated and untreated cells were used to study protein expression related to autophagy and angiogenesis as well as to evaluate cell migration. Hypoxia-inducible factor 1α (HIF1α), autophagy protein markers p62 and microtubule-associated protein 1A/1B-light chain 3 (LC3), and phospho-VEGFR protein content was analyzed by western blot and calculated as the band intensity ratio between the protein of interest and the housekeeping protein β-actin. Cell migration was performed by seeding 250,000 KJ29 cells in six-well plates and culturing them in DMEM/F12 medium supplemented with 10% fetal bovine serum (FBS) to confluence. Next, a wound between the cells was generated using a sterile tip and cells were grown for a further 48 and 120 h in DMEM/F12 with 1% FBS with 5 μM DCMI and 5 μM sunitinib alone or mixed together. Wound healing was detected by comparing images acquired at baseline with those acquired after 48 and 120 h of culture by a phase-contrast microscope equipped with a CCD camera. Statistical analysis was performed by GraphPad Prism software using analysis of variance or *t*-test as appropriate. Values of $p<0.05$ were considered statistically significant. *Results:* Treatment with DCMI significantly enhanced p62 and LC3 expression in both cell lines compared with untreated cells (Figure 1A). Conversely, the application of sunitinib did not change the levels of these proteins. As expected, treatment with sunitinib strongly reduced the phosphorylation of VEGFR in KJ29 cells, while in Caki-2 cells, this effect was milder but still significant (Figure 1B). Surprisingly, treatment with DCMI was also able to switch off the activity of VEGFR, mainly in KJ29 cells. Interestingly, a greater inhibition of VEGFR phosphorylation in Caki-2 cells treated with DCMI combined with sunitinib compared with single compounds was observed (Figure 1B). Importantly, the expression of HIF1α was reduced by the combination in KJ29 cells as well as in Caki-2 cells (Figure 1B). As observed for phospho-VEGFR, the combined treatment with these drugs caused a stronger reduction of HIF1α expression as compared to the single treatment in both cell lines (Figure 1B). The analysis of cell migration by scratch-wound assay shows that treatment with DCMI and sunitinib in cells reduced KJ29 cell migration after 48 and 120 h compared with untreated cells (Figure 1C). Moreover, the combined treatment potentiated the inhibition of cell migration not only after 48 h, but also for much longer (120 h). *Discussion:* Different mechanisms are associated with drug resistance, including the activation of autophagy in kidney cancer cells. Moreover, this process promotes cancer cell proliferation and migration (1). Therefore, the inhibition of autophagy reduces cancer progression and improves conventional therapy response. Our findings show that the application of DCMI effectively inhibited autophagy in two different kidney carcinoma cell lines. Treatment with DCMI prevented the fusion of autophagosomes with lysosomes leading to the accumulation of both p62 and LC3 autophagy proteins (Figure 1A). Interestingly, the inhibition of autophagy enhanced the reduction of angiogenesis, analyzed as VEGFR dephosphorylation, suggesting that autophagy is a mechanism involved in the activation of angiogenesis. Consistent with this, the reduction of autophagy by DCMI administration strengthened the down-regulation of HIF1α induced by sunitinb (Figure 1B). HIF1α is an upstream effector of angiogenesis that is constitutively activated in both Caki-2 and KJ29 ccRCC cells and promotes the activation of VEGFR. Importantly, the inhibition of autophagy combined with the administration of sunitinib caused a greater reduction of HIF1α expression and in turn the inactivation of VEGFR, leading to the inhibition of the angiogenesis pathway. Furthermore, the combined treatment with DCMI and sunitinib induced a stronger reduction of cell migration compared with the single treatment and for a longer time (Figure 1C). *Conclusion*: Our findings indicate that autophagy is involved in processes linked to angiogenesis, cell migration and therapy resistance. Therefore, the inhibition of autophagy combined with current chemotherapy may represent an intriguing option for improving drug response in advanced kidney carcinoma.

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TESTIS-SPARING SURGERY FOR GERM CELL TUMORS: OUTCOMES OF A SINGLE-INSTITUTION EXPERIENCE

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Background/Aim: We present the oncological and functional results of a series of 23 germinal testicular tumors treated with testis-sparing surgery (TSS), with special regard to the safety of this procedure (1-5). *Patients and Methods:* Overall, 23 TSSs were performed in 20 patients at the Urology Department of Bolzano. Seven patients were monorchid and two had bilateral cancer. The other patients had a normal contralateral testis. The age ranged from 15 to 61 years (mean=34 years). All patients had tumor marker assessment, inguinal access, and frozen section evaluation, associated with biopsies of the surrounding tissue. *Results and Discussion*: Tumor markers were negative in all except five patients, in whom they were mildly elevated. Frozen sections showed a germ-cell tumor in all cases, confirmed by definitive histology. Tumor size ranged from 5 to 30 mm (mean=14.5 mm). Out of the 10 TSSs performed for solitary testis or synchronous bilateral tumor, nine also had germ-cell neoplasia *in situ* (GCNIS): six patients underwent active surveillance while four cases received radiotherapy. Out of the 13 TSSs performed in patients with normal contralateral testis, a seminoma was found in five cases, an embryonal carcinoma in two, a postpubertal-type teratoma in three, and a prepubertal-type teratoma in the last three cases. GCNIS was found in six cases, seminoma in four and embryonal carcinomas in two; two of these underwent immediate orchiectomy while the other four underwent active surveillance. During follow-up (mean=54.4 months, range=5-204 months), two patients under active surveillance for GCNIS experienced a relapse after 14 and 20 months. One occurred in a patient with normal contralateral testis which was treated with radical orchiectomy without compromising his oncological outcome. The other occurred in a patient with previous bilateral tumor and a TSS was repeated with subsequent radiotherapy with the intent to preserve his hormonal production. In the remaining patients, 10 of whom had a normal contralateral testis, no further local recurrences or metastases were found. Seven out of nine patients who underwent imperative TSS needed hormonal replacement therapy: one of these under active surveillance for GCNIS underwent orchiectomy for endocrine insufficiency after 98 months, without finding relapse. All other patients had a normal level of testosterone after surgery. *Conclusion*: TSS appears to be safe and feasible without compromising oncological safety and should be proposed in selected cases, including patients with normal contralateral testis, to preserve endocrine function, fertility, and the male body image (6).

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IMAGING SHAPES THE LONG-TERM ONCOLOGICAL OUTCOME OF PATIENTS WITH OLIGO-RECURRENT PROSTATE CANCER SUBMITTED TO METASTASIS-DIRECTED THERAPY (THE PRECISE-MDT STUDY)

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Table I. *Clinical, imaging, treatment and follow-up characteristics of patients submitted to ^{18}F-fluorocholine or prostate-specific membrane antigen (PSMA)- positron-emission tomography/computed tomography (CT)-guided metastasis-directed therapy (MDT) after propensity score matching.*

		MDT		
	Overall (n=240)	^{18}F-Fluorocholine-guided (n=120)	PSMA-guided (n=120)	*p*-Value
Pre-imaging clinical characteristics				
Age (years)	72.07±6.55	71.71±6.87	72.43±6.23	0.397
Initial AJCC stage				
I	10 (4.17%)	5 (4.17%)	5 (4.17%)	>0.999
II	59 (24.58%)	26 (21.67%)	33 (27.50%)	0.295
III	142 (59.17%)	72 (60.00%)	70 (58.33%)	0.792
IV	29 (12.08%)	17 (14.17%)	12 (10.00%)	0.322
ISUP grade				
1	31 (12.92%)	17 (14.17%)	14 (11.67%)	0.565
2	65 (27.08%)	32 (26.67%)	33 (27.50%)	0.885
3	55 (22.92%)	25 (20.83%)	30 (25.00%)	0.443
4	39 (16.25%)	18 (15.00%)	21 (17.5%)	0.600
5	50 (20.83%)	28 (23.33%)	22 (18.33%)	0.341
Primary treatment				
Surgery	200 (83.33%)	95 (79.00%)	105 (87.50%)	0.079
Radiotherapy (±ADT)	36 (15.01%)	22 (18.50%)	14 (11.67%)	0.140
Medical therapy	4 (1.66%)	3 (2.50%)	1 (0.83%)	0.313
CRPC at MDT, n (%)	40 (16.67%)	17 (14.17%)	23 (19.17%)	0.254
PSA at MDT (ng/ml)	2.66±3.56	2.93±2.44	2.39±1.99	0.243
Imaging findings				
Number of metastases, n (%)				
1	183 (76.25%)	91 (75.83%)	92 (76.67%)	0.879
2	38 (15.83%)	17 (14.17%)	21 (17.50%)	0.481
3-5	19 (7.92%)	12 (10.00%)	7 (5.83%)	0.232
Site of metastases, n (%)				
Lymph node	169 (70.42%)	90 (75.00%)	79 (65.83%)	0.120
Bone	70 (29.17%)	30 (25.00%)	40 (33.33%)	0.157
Visceral	1 (0.42%)	0 (0.00%)	1 (0.84%)	0.315
MDT parameters and clinical follow-up				
MDT total dose, Gy (per lesion)	33.42±4.68	33.35±4.17	33.49±5.17	0.824
MDT BED, Gy (per lesion)	119.90±26.48	124.60±33.53	116.62±19.97	0.207
Concurrent systemic treatment in addition to MDT, n (%)	100 (40.83%)	43 (35.80%)	57 (47.50%)	0.067
PSA nadir after MDT (ng/ml)	1.95±7.93	2.67±11.28	1.32±2.48	0.218
Propensity score matching				
Propensity score	0.54±0.13	0.54±0.13	0.54±0.13	0.987

ADT: Androgen deprivation therapy; AJCC: American Joint Committee on Cancer; BED: biologically effective dose; CRPC: castration-resistant prostate cancer; ISUP: International Society of Urological Pathology; MDT: metastasis-directed therapy; PSA: prostate-specific antigen. Continuous and categorical variables are expressed as the mean±standard deviation, and as number (percentage). Comparisons were performed with chi-square test and with Student's *t*-test, respectively.

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Table II. *Clinical, imaging, treatment and follow-up characteristics of patients submitted to ^{18}F- or ^{68}Ga prostate-specific membrane antigen (PSMA)-positron-emission tomography/computed tomography-guided metastasis-directed therapy (MDT) after propensity score matching.*

		MDT		
	Overall (n=88)	^{18}F-PSMA-1007-guided (n=44)	^{68}Ga-PSMA-11-guided (n=44)	*p*-Value
Pre-imaging clinical characteristics				
Age (years)	73.07±6.42	73.2±7.23	72.94±5.56	0.850
Initial AJCC stage				
I	4 (4.55%)	3 (6.82%)	1 (2.27%)	0.308
II	22 (25.00%)	9 (20.45%)	13 (29.55%)	0.327
III	54 (61.36%)	26 (59.09%)	28 (63.64%)	0.663
IV	8 (9.09%)	6 (13.64%)	2 (4.54%)	0.140
ISUP grade				
1	10 (11.36%)	4 (9.09%)	6 (13.64%)	0.504
2	19 (21.59%)	10 (22.73%)	9 (20.45%)	0.796
3	25 (28.41%)	12 (27.27%)	13 (29.55%)	0.814
4	19 (21.59%)	10 (22.73%)	9 (20.45%)	0.796
5	15 (17.05%)	8 (18.18%)	7 (15.91%)	0.778
Primary treatment				
Surgery	74 (84.09%)	34 (77.27%)	40 (90.91%)	0.080
Radiotherapy (±ADT)	14 (15.91%)	10 (22.73%)	4 (9.09%)	
CRPC at MDT	15 (17.05%)	7 (15.91%)	8 (18.18%)	0.778
PSA at MDT (ng/ml)	2.42±5.01	2.27±3.80	2.58±6.05	0.769
Imaging findings				
Number of metastases				
1	69 (78.41%)	34 (77.27%)	35 (79.55%)	0.796
2	13 (14.77%)	6 (13.54%)	7 (15.91%)	0.755
3-5	6 (6.82%)	4 (9.09%)	2 (4.54%)	0.400
Site of metastases				
Lymph node	59 (67.04%)	27 (61.36%)	32 (72.73%)	0.259
Bone	28 (31.82%)	16 (36.36%)	12 (27.27%)	0.367
Visceral	1 (1.14%)	1 (2.27%)	0 (0.00%)	0.318
MDT parameters and clinical follow-up				
MDT total dose, Gy (per lesion)	34.02±4.86	33.84±5.22	34.20±4.51	0.731
MDT BED, Gy (per lesion)	117.89±20.18	115.40±11.77	120.11±25.64	0.492
Concurrent systemic treatment in addition to MDT	29 (32.96%)	14 (31.82%)	15 (34.09%)	0.822
PSA nadir after MDT (ng/ml)	1.093±1.77	1.70±2.24	0.53±0.91	**0.003**
Propensity score matching				
Propensity score	0.52±0.15	0.52±0.15	0.52±0.15	0.988

ADT: Androgen deprivation therapy; AJCC: American Joint Committee on Cancer; BED: biologically effective dose; CRPC: castration-resistant prostate cancer; ISUP: International Society of Urological Pathology; MDT: metastasis-directed therapy; PSA: prostate-specific antigen. Continuous and categorical variables are expressed as the mean±standard deviation, and as number (percentage). Comparisons were performed with chi-square test and with Student's *t*-test, respectively. Significant *p*-values are shown in bold.

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Background/Aim: Clinical trials showed metastasis-directed therapy (MDT) as an effective treatment for oligo-recurrent prostate cancer (PCa). However, there is an ongoing debate regarding the impact of using different imaging techniques interchangeably for defining lesions and guiding MDT within clinical trials. Thus, we aimed to assess the impact of different imaging tools in guiding MDT and their effects on oncological outcomes in patients with oligo-recurrent PCa. *Patients and Methods*: We retrospectively analysed patients with hormone-sensitive or castration-resistant oligo-recurrent PCa who underwent ^{18}F-fluorocholine, ^{68}Ga-prostate-specific membrane antigen (PSMA)-11 or ^{18}F-PSMA-1007 positron-emission tomography/computed tomography (PET/CT)-guided MDT across eight Italian tertiary-level cancer centers between July 2012 and May 2023. Inclusion criteria were: (i) histologically confirmed PCa, (ii) ≤5 nodal, bone or visceral metastases at choline or PSMA PET/CT, (iii) MDT through stereotactic body radiation therapy with or without systemic therapy, and (iv) ≥6 months clinical follow-up. To compare treatment groups, we calculated a propensity score using multivariable logistic models, including PET tracers used as independent variables, and well-known prognostic factors as dependent variables: International Society of Urological Pathology grade at baseline, and, at the time of MDT, castration-resistant status, prostate-specific antigen level, concurrent systemic treatment, and number of metastases. Propensity-matched cohorts on a one-to-one basis with a 0.01 calibration were then created. Through Cox-regression and Kaplan–Meier analyses, imaging-guided MDT was assessed as progression-free survival (PFS), time to systemic treatment change due to polymetastatic conversion (PFS2), and overall survival predictor. The inverse probability of treatment weighting approach was employed as a sensitivity analysis. *Results:* Out of 402 patients, 232 (57.7%) and 170 (42.3%) were submitted to MDT guided by ^{18}F-fluorocholine and PSMA PET/CT, respectively. Matched and unmatched variables across the two groups were superimposable (Table I). After propensity-score matching, PSMA PET/CT was associated with significantly longer PFS [hazard ratio (HR)=0.49, 95% confidence interval (CI)=0.36-0.67; $p<0.0001$], PFS2 (HR=0.42, 95% CI=0.28-0.63; $p<0.0001$) and overall survival (HR=0.39, 95% CI=0.15-0.99; $p<0.05$) compared to choline PET/CT-guided MDT (Figure 1). We then matched

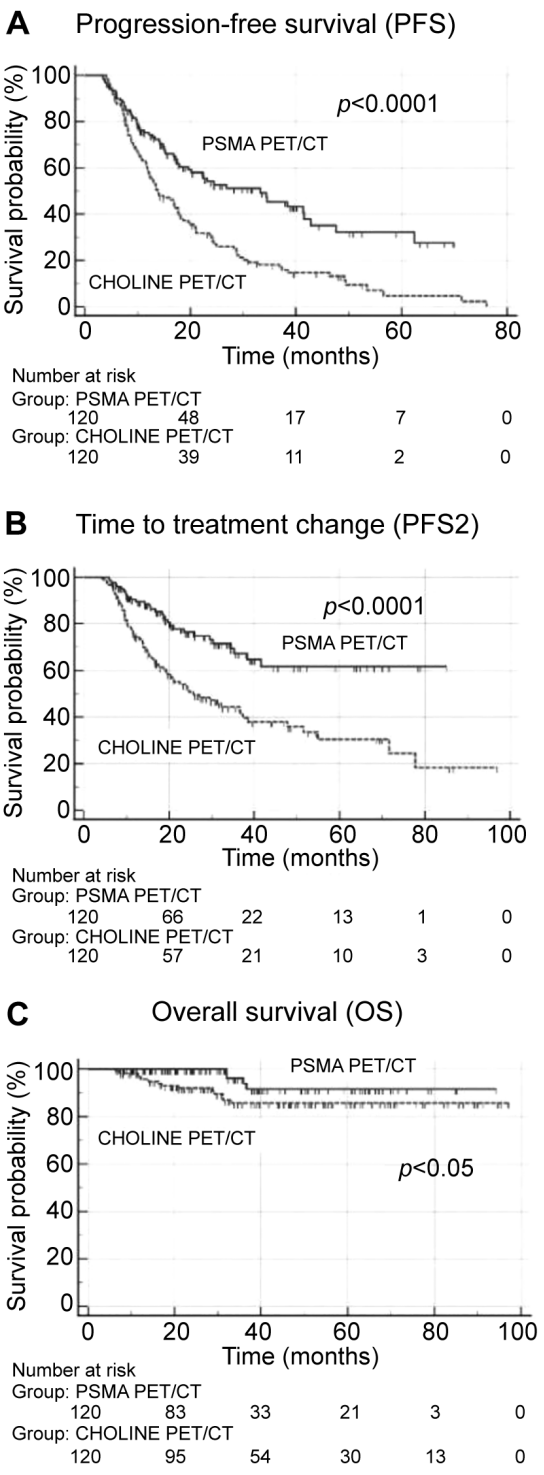

Figure 1. *Kaplan–Meier survival curves according to the imaging modality guiding MDT in the prostate-specific membrane antigen (PSMA) and choline positron-emission tomography/computed tomography (PET/CT) propensity score-matched cohorts (n=120). (A) Progression-free survival. (B) Time to systemic treatment change due to polymetastatic conversion (PFS2). (C) Overall survival according to the imaging modality guiding metastasis-directed therapy. Comparisons were performed with the log-rank test. mo: Months.*

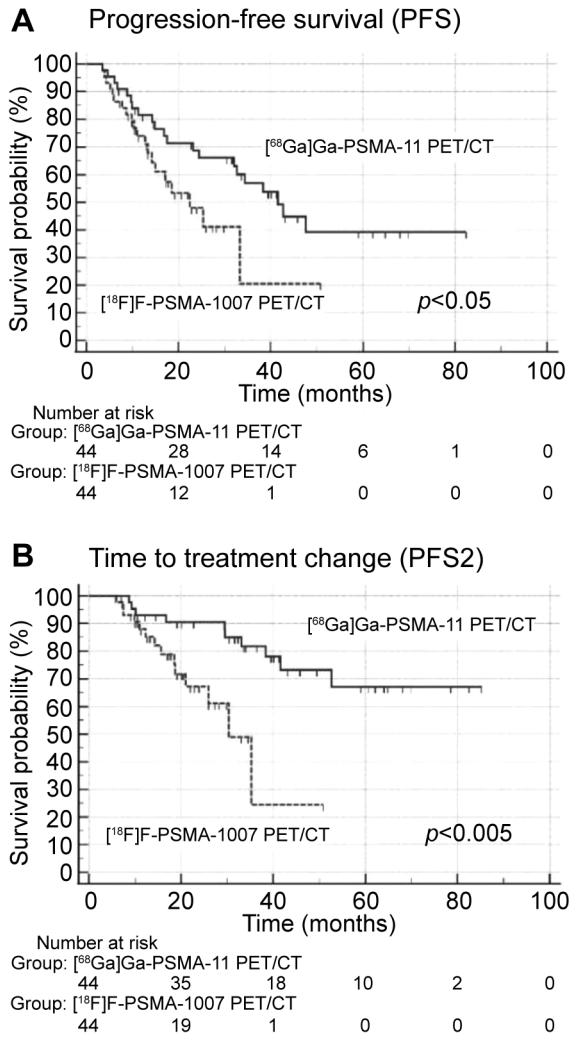

Figure 2. *Kaplan–Meier survival curves according to the imaging modality guiding MDT in the ^{18}F- or ^{68}Ga-prostate-specific membrane antigen (PSMA)-positron-emission tomography/computed tomography (PET/CT) propensity score-matched cohorts (n=44). (A) Progression-free survival. (B) Time to systemic treatment change due to polymetastatic conversion (PFS2) according to the imaging modality guiding metastasis-directed therapy. Comparisons were performed with the log-rank test. mo: Months.*

patients submitted to ^{68}Ga-PSMA-11 *vs.* ^{18}F-PSMA-1007 PET/CT (Table II), showing that MDT based on the former provided higher PFS and PFS2 compared to the latter (HR=0.51, 95% CI=0.26-1.00, and HR=0.24, 95% CI=0.09-0.60, respectively; $p<0.05$ and $p<0.005$, respectively) (Figure 2). In the whole cohort of unmatched patients, inverse probability of treatment weighting-based sensitivity analyses confirmed all these findings. *Discussion and Conclusion*: Diverse PET/CT methods influence the long-term oncological outcome in a real-world, multi-institutional, propensity score-matched sample of patients with oligometastatic PCa undergoing MDT. Additional studies with prospective and randomised designs are necessary to provide more evidence for the practical implementation of the obtained findings.

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THE ROLE OF HOLEP IN INCIDENTAL PROSTATE CANCER

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Background/Aim: Holmium laser enucleation of the prostate (HoLEP) represents a well-established and effective tool in the treatment of lower urinary tract symptoms and bladder outlet obstruction related to benign prostatic hypertrophy. We analyzed patients with symptomatic benign prostatic hypertrophy and concomitant or incidentally detected prostate cancer (PCa) treated with HoLEP and the subsequent clinical management. *Patients and Methods:* From a prospectively maintained database, we retrospectively evaluated patients treated with HoLEP at a single institution with a complete follow-up of 36 months. We evaluated total pre- and postoperative prostate-specific antigen, multiparametric magnetic resonance imaging and pathology results. We compared patients with a PCa diagnosis received before HoLEP (group 1) and patients with PCa diagnosis incidentally at HoLEP (group 2). *Results*: We evaluated a total of 470 consecutive patients: 58 (12.3%) had a PCa diagnosis before HoLEP (group 1), while 67 (14.2%) received a PCa diagnosis at the time of HoLEP (group 2). Grade Group ≤1 was reported in 56.2% and 87.5% of PCa cases in group 1 and group 2, respectively ($p<0.05$) (Table I). The total PSA level at 3 months after HoLEP dropped by 84.3% (from 11.6 to 1.82 ng/ml) in patients of group 1 and by 71.3% (from 3.1 to 0.9 ng/ml) in patients of group 2 (Figure 1); the values remained almost stable up to 36 months after HoLEP [at 0.9 (interquartile range=0.59-2.25) and 0.8 (interquartile range=0.42-1.97) ng/ml in group 1 and in group 2, respectively]. By including even those patients who underwent cancer treatment post-HoLEP, all patients in both groups survived without cancer progression (based on their initial PCa status). *Conclusion*: More than 10% of patients undergoing HoLEP might receive a PCa diagnosis. Furthermore, HoLEP can be performed even in patients with PCa, at any stage of the disease, in order to treat lower urinary tract symptoms. The procedure does not negatively impact oncological outcomes,

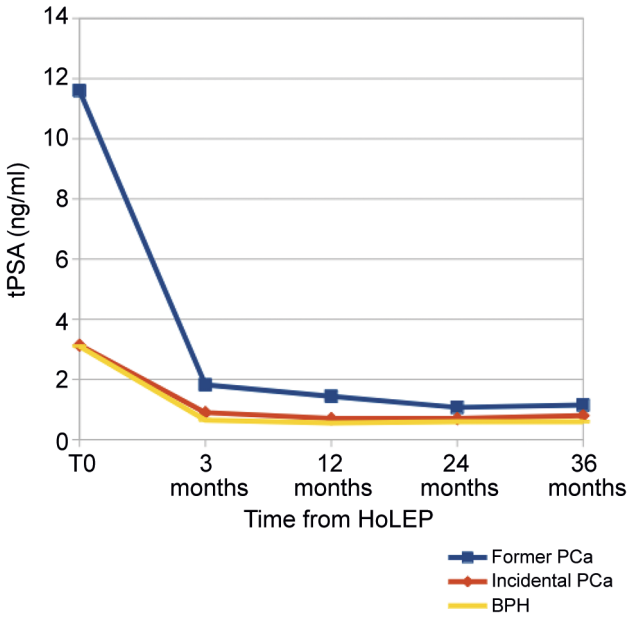

Figure 1. *Total prostate-specific antigen levels after Holmium laser enucleation of the prostate in patients with benign prostate hyperplasia (BPH) and prostate cancer (PCa).*

regardless of whether PCa is diagnosed before or at HoLEP. The durability of the feasibility of this management needs further investigation.

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VOLUMETRIC-MODULATED ARC THERAPY WITH HYPOFRACTIONATED RADIATION REGIMEN FOR TREATMENT OF LOCALIZED PROSTATE CANCER: ACUTE AND LATE URINARY AND GASTRO-INTESTINAL TOXICITY

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Table I. *Descriptive characteristics of the study population.*

	BPH	Pca		*p*-Value (BPH *vs.* Group 1)	*p*-Value (Group 1 *vs.* Group 2)
		Group 1	Group 2		
Patients, n	345	58	67	-	-
Median age (range), years**	69 (47-87)	68.5 (53-84)	72 (58-82)	0.87	0.56
Median total PSA (range), ng/ml**	3.1 (0.13-32.25)	11.6 (0.80-100)	3.14 (1.10-8.45)	0.26	0.09
Median prostate volume (range), cc**	70 (20-263)	74.5 (21-194)	80 (40-250)	0.63	0.07
Median PSA density (range)**	0.048 (0.003-0.205)	0.111 (0.006-4.667)	0.098 (0.009-1.670)	0.95	0.3
Pre-HoLEP mpMRI, n (%)*	20.4%	100%	44.4%	<0.05	0.32
Positive mpMRI§ n (%)*	11.5%	100%	33.3%	<0.05	0.17
Median mpMRI PI-RADS score (range)**	3 (1-5)	4 (1-5)	3 (3-5)	0.98	0.31
Lesions on positive mpMRI (range), n**	1 (1-2)	1 (1-3)	1 (1-2)	0.94	0.92
Pre-HoLEP biopsy, n (%)*	6.2%	100%	11.1%	<0.05	<0.05
Negative, n (%)	6.2%	0%	11.1%	0.95	<0.05
Positive, n (%)	0%	100%	0%	<0.01	0.12
≤GG1, n (%)	-	56.2%	-	-	-
≥GG2, n (%)	-	43.8%	-	-	-
Positive HoLEP histopathology*					
Total	-	43.8%	100%	-	<0.05
≤GG1 (included ASAP, HGPIN, STUMP) n (%)	-	25.0%	87.5%	-	<0.05
≥GG2, n (%)	-	18.8%	12.5%	-	<0.05
Median tPSA post-HoLEP (range), ng/ml**					
3-Months	0.65 (0.23-6.80)	1.82 (0.33-6.47)	0.09 (0.59-2.25)	0.75	0.10
12-Months	0.55 (0.33-2.32)	1.44 (0.04-3.30)	0.7 (0.31-3.04)	0.81	0.25
24-Months	0.6 (0.42-1.15)	1.07 (0.11-2.82)	0.7 (0.48-2.12)	0.83	0.31
36-Months	0.6 (0.28-2.12)	1.15 (0.29-2.35)	0.8 (0.42-1.97)	0.77	0.29

§PIRADS ≥3; *Chi-square test; **Student's *t*-test. mpMRI: Multi-parametric magnetic resonance imaging; GG: grading group; HGPIN: high grade prostatic intraepithelial neoplasia; ASAP: atypical small acinar proliferation; STUMP: prostatic stromal tumor of uncertain malignancy; BPH: benign prostatic hyperplasia; PCa: prostate cancer.

Background: Several studies reported that localized prostate adenocarcinoma can be managed by radical prostatectomy or radiotherapy (1). The most common radiotherapy schedule is moderate hypofractionation. External beam radiotherapy with/without androgen-deprivation therapy (ADT) may be an appropriate treatment for men with confined organ prostate cancer diagnosis; this approach is optimal in men over the age of 70 years, the combination of radiotherapy and ADT prolongs survival and metastasis-free survival in intermediate- and high-risk patients with prostate cancer. *Aim*: To evaluate the impact of hypofractionated schedule of radical high-quality volumetric-modulated arc therapy radiotherapy (VMAT-RT) on urinary and gastrointestinal acute toxicity in patients diagnosed with localized prostate adenocarcinoma (T1c-T3a, N0, M0) through a mono-institutional experience at radiotherapy ASL Frosinone over 22 months from May 2022 to March 2024 (follow-up from 1 to 22 months). *Patients and Methods:* This case study reviewed 81 patients (average age=74.9 years, range=64-84 years) newly diagnosed, biopsy proven, staged as localized prostate cancer and treated with radical radiotherapy from May 2022 to March 2024. All 81 patients underwent pelvic-magnetic resonance imaging, 57 patients were staged by conventional imaging (computed tomography and bone scintigraphy) and 24 patients (29.63%) were staged by choline or prostate-specific membrane antigen positron-emission tomography/computed tomography. The patients were grouped by prostate cancer risk according to National Comprehensive Cancer Network guidelines version 4.2024 (2) (low-risk, six patients; favorable intermediate-risk, 10 patients; unfavorable intermediate-risk, 18 patients; high/very high-risk, 47 patients). VMAT-RT was an exclusive treatment for low and favorable intermediate-risk groups; short-term (6-9 months) ADT in combination with radiation therapy was administered to patients in the unfavorable intermediate-risk group; long-term (18-24 months) ADT in combination with radiation therapy was administered to patients in the high-/very high-risk group. ADT was luteinizing hormone-releasing hormone agonist triptorelin, usually administered once every month, once every 3 months or every 6 months; in total 67/81 patients (82.7%) received ADT. The clinical target volume was the entire prostate for both low-risk and favorable intermediate-risk groups, and the entire prostate and the proximal third of seminal vesicles for both unfavorable intermediate- and high/very high-risk groups. The planning target volume was obtained with expansion of clinical target volume of 0.7 mm in all directions and 0.5 mm posterior *versus* the anterior rectal wall. All patients underwent a preparation aimed at keeping the rectum free of feces and gases, and maintained a full bladder during the radiation therapy session, verified daily by image-guided radiotherapy-cone beam computed tomography (IGRT-CBCT). Radiotherapy was delivered to a VMAT technique with hypofractionated schedule 60 Gy in 20 fractions according to the CHHIp trial (3); daily IGRT-CBCT was performed. Acute and late toxicity was scored according to Common Terminology Criteria for Adverse Events Version 5.0 (4). The patients evaluated for late toxicity had a minimum follow-up of 4 months. *Results*: Data for a total of 81 patients were analyzed. Acute urinary toxicity was noted in 70% of the patients: G1 in 53%, G2 in 12.3% and G3 in 4.9%. Acute gastrointestinal toxicity was G0 in 56.79%, G1 in 28.39%, G2 in 14.81%. Late urinary toxicity was G0 in 45.67%, G1 in 18.51% and G2 in 13.58; 22.4% of patients were not evaluated because they did not have the minimum follow-up. Late gastrointestinal toxicity was G0 in 62.9%, G1 in 7.29% and G2 in 4.05%; 25.5% of patients were not evaluated because they did not have the minimum follow-up. No patients experienced G4 acute or late toxicity; G3 toxicity was only acute urinary toxicity observed in 4.9% of patients. The major symptoms were pollakiuria, nocturia, stranguria, hematuria, urinary urgency, diarrhea, rectal bleeding and rectal tenesmus. The symptom resulting in diminished health-related subjective quality of life were: urinary urgency, stranguria, hematuria, rectal bleeding and transient urinary and fecal incontinence. No patients reported definitive urinary or fecal incontinence. The ADT triptorelin was well tolerated; hot flashes and sexual dysfunction were the most common side-effects. *Discussion and Conclusion*: It is crucial to use advanced radiotherapy techniques to obtain good oncological outcomes and low toxicity. IGRT-CBCT increases the quality of treatment, improves set-up accuracy by repeated imaging of the target anatomical area every day, immediately before the radiation therapy session, allowing position verification and correction of any discrepancies, sparing normal tissue and organs at risk (reducing toxicity) and favoring dose escalation schedules with better oncological outcomes. VMAT with moderate hypofractionated radiation regimen for treatment of localized prostate cancer has been used as a definitive treatment with acceptable acute and late toxicity results. Our results were comparable to those of other trials reported in the literature for similar treatments. Biochemical outcomes are awaited.

Key Words: VMAT, acute and late toxicity, prostate cancer.

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17

A PHASE III PROSPECTIVE RANDOMIZED TRIAL TO EVALUATE THE IMPACT OF AUGMENTED REALITY DURING ROBOT-ASSISTED RADICAL PROSTATECTOMY ON THE RATES OF POSTOPERATIVE SURGICAL MARGINS

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Background/Aim: Positive surgical margin (PSM) rates remain a concern following robot-assisted radical prostatectomy (RARP). Limited research has explored the potential of augmented reality (AR) during surgery and intraoperative frozen section (IFS) analysis to improve outcomes. *Materials and Methods*: This ongoing, single-center, prospective, double-blinded randomized trial (NCT06059859) investigates the efficacy of AR-RARP compared to standard RARP in reducing PSM rates. Patients with low- or intermediate-risk prostate cancer, pre-operative erectile function scores ≥20, and at least one visible lesion on magnetic resonance imaging (mpMRI) are randomized (1:1) to either: AR-RARP or Standard RARP. AR-RARP: A 3D prostate model reconstructed from mpMRI is projected onto the surgical field using TilePro™ technology. During IFS analysis, mixed reality with HoloLens glasses (Microsoft, Redmond, WA, USA) is utilized. Standard RARP: A nerve-sparing approach with IFS analysis guided by mpMRI is performed. The primary outcome is the rate of PSMs. Secondary outcomes include nerve-sparing rates and erectile function recovery at 3, 6, and 12 months post-surgery. Subgroup analyses will identify patient populations potentially benefiting most from AR-RARP. With a projected 10% difference in PSM rates, a total of 159 patients per group is required for sufficient statistical power (80%). Interim analyses are planned after enrolling 159 patients. *Results* (*Preliminary*): As of now, 115 patients have been enrolled, with 58 (50.4%) undergoing AR-RARP and 57 (49.6%) undergoing standard RARP. Baseline characteristics were identical between groups. Surgical times were comparable (212 minutes for AR-RARP *vs*. 213 min for standard RARP, p=0.9). No significant difference was observed in nerve-sparing approaches (p=0.8). Overall PSM rates were lower in the AR-RARP group (13 patients, 22.5%) compared to standard RARP (18 patients, 31.5%), but not statistically significantly so (p=0.18). Interestingly, the AR-RARP group had a higher rate of positive IFS analysis (36% *vs*. 19%, p=0.06). However, final pathology revealed significantly lower PSM rates at the level of the mpMRI index lesion in the AR-RARP group (8.5%) compared to standard RARP (14%). *Conclusion (Preliminary)*: Early data suggest AR-RARP with AR-guided IFS analysis may be beneficial in reducing PSM rates, particularly for the mpMRI index lesion, compared to standard RARP in patients suitable for nerve-sparing surgery. The study is ongoing, and final conclusions will be drawn upon completion.

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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: Current practices rely on bone scintigraphy and abdominopelvic computed tomography (CT) to stage unfavorable intermediate- and high-risk prostate cancer. This study explores the potential of a streamlined approach using a single 'all-in-one' whole-body magnetic resonance imaging (WB-MRI) combined with multiparametric MRI (mpMRI) to assess lymph node and metastatic spread. *Patients and Methods:* This ongoing multicenter study compares the accuracy of all-in-one MRI staging against the standard methods (CT and bone scan) in patients with unfavorable intermediate- and high-risk prostate cancer. All participants should undergo all three imaging modalities within a 6-week window. Radiologists are blinded to the results of other imaging tests. The primary outcome is the sensitivity, specificity, and accuracy of WB-MRI compared to bone scan and CT for detecting lymph node and distant metastases. Secondary outcomes include changes in disease management based on WB-MRI findings, the frequency of inconclusive results, cost analysis, radiation exposure, patient preference, side effects, and interobserver variability among radiologists. A multidisciplinary team reviews all cases and recommends treatment based on either WB-MRI or standard staging results. For patients initially diagnosed as having non-metastatic disease, the accuracy of WB-MRI will be confirmed by final pathology and prostate-specific antigen levels during follow-up. Differently, for patients with initial evidence of metastasis, treatment response will be monitored through changes in the radiological appearance of metastases. The study started on 1st January 2023 and will continue recruiting participants for up to 3 years. All patients will be monitored for at least 1 year post-treatment. With a target enrollment of 350 patients, the study aims to achieve an 80% power level. *Results (Early findings):* As of this preliminary analysis with 70 enrolled patients, two (2.8%) refused WB-MRI because of claustrophobia, in 25 (37%) there were discrepancies between all-in-one WB-MRI staging and standard methods. Notably, compared to bone scintigraphy with CT, 19 (76%) of these patients experienced upstaging with WB-MRI, while six (24%) experienced downstaging. Among those experiencing upstaging after WB-MRI, the most frequent change (79%) involved a shift from cN0M0 to cN1M0, indicating newly detected lymph node involvement. Among the remaining upstaged patients, two (10.5%) switched from cN0M0 to cN0/1M1, while the other two (10.5%) switched from cN0M0 to cN0/1M1b. On the contrary, downgrading to cN0M0 from cN0M1b was observed in six patients, suggesting potential overestimation of metastatic spread with standard methods. A total of 16 (23%) of patients had their treatment plans modified based on WB-MRI findings. Patients with higher-grade cancers (International Society of Urological Pathology 4-5) were more likely to have staging variations detected by WB-MRI (50%) compared to those with lower-grade cancer (International Society of Urological Pathology ≤3) (25%; $p<0.01$). *Conclusion*: Preliminary data from this ongoing study suggest that all-in-one WB-MRI for staging unfavorable intermediate- and high-risk prostate cancer reveals significant rates of discordance compared to standard methods. This may lead to adjustments in treatment plans for a substantial proportion of patients. These promising early results require additional research and may be confirmed once the study is completed.

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A DETAILED ANALYSIS OF PERIOPERATIVE COMPLICATIONS, LENGTH OF STAY, RE-ADMISSION RATES AND TREATMENT TIME AFTER PERCUTANEOUS THERMAL ABLATION FOR SMALL RENAL MASSES

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Background/Aim: Detailed and standardized complication reports derived from large series are needed and of paramount actual relevance to further explore the role of percutaneous thermal ablation (PTA) in treatment of small renal masses (SRMs). Our objective was to report PTA complication rates, management and predictors in a standardized and systematic fashion. Additionally, we investigated re-admission rates and independent predictors of longer length of stay (LOS) and treatment time. *Patients and Methods:* Overall, 553 patients with SRMs were treated with PTA (radiofrequency or microwave) between 2008 and 2022. Treatment time, overall (stratified according to the Society of Interventional Radiology classification) intraoperative (coded according to the European Association of Urology intraoperative adverse incident classification) and postoperative complications (coded according to Clavien–Dindo classification), LOS and

re-admission rates were recorded. Multivariable logistic regression models predicting overall complication occurrence were fitted. Additionally, Poisson and linear regressions tested for independent predictors of LOS and treatment time, respectively. *Results*: Overall, 100 (18%) patients experienced a complication. According to the Society of Interventional Radiology classification, 12% of patients had minor complications and 6% had major complications. Fifty (9.0%) and 60 (11%) patients harbored intraoperative and postoperative complications, respectively. Tumor size [cm; odds ratio (OR)=1.22, p=0.03], RENAL moderate (OR=1.5, p=0.02) and high (OR=2.5, p=0.03) complexity classes emerged as independent predictors of overall complications. Intraoperative (incidence rate ratio=1.22, p=0.02) and postoperative (incidence rate ratio=17, p<0.001) complications were independent predictors of longer LOS. RENAL complexity class in relation to treatment time (moderate: 23.0 min; high: 51.0 min), tumor size (cm), radiofrequency and intraoperative complications were independent predictors of longer treatment time. Limitations include the retrospective and monocentric nature of the study. *Conclusion*: These findings may help to improve clinical decision-making, patient selection and counselling.

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MANAGEMENT OF OLAPARIB-RELATED ADVERSE EVENTS IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER: A SINGLE-CENTER EXPERIENCE

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Background/Aim: The phase III Profound trial (1) established the use of olaparib for patients with advanced castration-resistant prostate cancer harboring *BRCA* mutations, determining its approval for patients who had disease progression while receiving abiraterone or enzalutamide. We describe our experience of patients receiving olaparib at the Department of Oncology of the University Hospital of Ancona, focusing on the reported adverse events (AEs) and their management. *Patients and Methods:* Three patients at our center are actually receiving olaparib at the standard dose (300 mg *bid*) or at the primary dose reduction (250 mg *bid*). One patient had received first-line therapy with apalutamide; the other two had previously received therapy with enzalutamide. Safety was assessed through monthly clinical examinations, AE reporting and laboratory analyses. *Results*: The most common reported AEs were anemia, nausea, fatigue/asthenia and decreased appetite, as reported in the Profound trial. All of them were mostly grade 1 and 2 and peaked within the first 2-3 months of treatment. AEs were generally manageable without treatment discontinuation. One patient was treated with dose reductions. *Conclusion*: The AEs reported in this study were consistent with previous clinical trials. Considering the limited number of patients treated with olaparib, no relevant (grade ≥3) or unusual toxicities were observed. The future goal will be the possibility to implement the cohort of patients receiving poly (ADP-ribose) polymerase inhibitors due to the more extensive mutational testing in patients with prostate cancer; this will allow a better understanding and management of the toxicities of this drug.

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LYMPH-NODAL OLIGOMETASTASES FROM PROSTATE CANCER: DIFFERENT OUTCOMES AND PATTERNS OF RELAPSE BETWEEN PELVIC AND PARA-AORTIC DISEASE

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Background/Aim: Lymph-nodal prostate cancer oligometastases are differently treated according to their site: pelvic are locoregional lymph nodes, whilst para-aortic lymph nodes are considered as distant metastases. The aim of this study was a comparison between para-aortic and pelvic oligometastases treated with stereotactic body radiation therapy (SBRT). *Patients and Methods:* This is a retrospective analysis. Patients with *de-novo* metastatic or extra-nodal disease were excluded. Univariate and multivariate analyses were performed; pattern of recurrence was also evaluated. Propensity-score matching was applied to create comparable cohorts. The primary end-point was progression-free survival (PFS). Secondary end-points were

biochemical relapse-free survival (BRFS), androgen-deprivation therapy-free survival (ADTFS), polymetastasis-free survival (PMFS), local progression-free survival (LPFS) and pattern of relapse. *Results*: A total of 240 lymph-nodal oligometastases in 164 patients (127 pelvic and 37 para-aortic) were treated. The median PFS in patients with pelvic and those with para-aortic metastases was 20 and 11 months, respectively (p=0.042). The difference was not confirmed at the multivariate analysis (p=0.06). The median BRFS was 16 and 9 months, respectively (p=0.07). No statistically significant differences for ADTFS or PMFS were detected. The cumulative 5-year LPFS was 90.5%. At PSM, no statistically significant differences for any of the study end-points were detected. *Conclusion*: Patients affected by para-aortic disease might have PFS comparable to those with pelvic disease; local control is high in both cohorts. Our results support the use of SBRT for para-aortic metastases.

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FIRST CLINICAL APPLICATION OF COMPREHENSIVE MOTION MANAGEMENT WITH 1.5T MR-LINAC ON 50 PROSTATE CANCER PATIENTS TREATED WITH DAILY ADAPTED SBRT

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Background/Aim: Stereotactic body radiation therapy (SBRT) is a common treatment option in localized prostate cancer (PC). The MR-linac technology is showing promising results in terms of accuracy in dose delivery due to the possibility of online daily plan adaptation and the unprecedent possibility to correctly visualize organs at risk (OARs) and prostate boundaries. Prolonged treatment times may lead to target displacement related to abrupt prostate shifts due to bladder and/or rectum filling change. Very recently, comprehensive motion management (CMM) has been introduced in clinical practice. This new tool, available for 1.5T MR-linac, allows for real-time target tracking and intrafraction motion (IFM) correction through drift correction (baseline shifts, BLS). *Patients and Methods*: In September 2023, CMM was installed at our Institution and used for all PC patients treated on the MR-linac. Patients included in this study had the following characteristics: 1) diagnosis of low-to-intermediate risk PC; 2) suitable or SBRT treatment; 3) completion of the entire RT course. The SBRT schedules consisted of 35 Gy and 36.25 Gy in five fractions for low and intermediate risk, respectively. The treatment could be administered either daily or every other day. This study analyzed the first 50 patients treated with daily-adapted SBRT on a 1.5T MR-Linac, utilizing CMM for target tracking. The following variables were reported: patient and treatment characteristics, beam-on time (treatment administration duration), beam-hold (time of beam interruption due to gating) duty cycle (% of the total beam-on time of the entire delivery phase), and positioning shifts. The data were calculated and described per treatment fraction since every RT session corresponded to a newly adapted treatment plan. *Results*: Between October 2023 and March 2024, 50 PC patients were treated with prostate SBRT at our Institution on 1.5T MR-linac using daily CMM. The median age was 71 years (range=61-86 years). Thirty-seven (74%) out of 50 patients were treated with 5-fraction SBRT every day and thirteen (26%) every other day. In 40 patients (80%), the target was the prostate only, while in 10 cases (20%), the target included both the prostate and the seminal vesicles (one third to the entire seminal vesicles, depending on the risk class). All patients completed the planned treatment, except for one temporary interruption in a single fraction due to technical issues. The mean duty cycle for the 250 treatment fractions was 98.9% (95%CI=98.6-99.2%). The mean beam-on time was 515.7 s (8.5 min; 95%CI=497.5-534 s). Globally, beam-hold occurred in 94 (38%) out of 250 treatment fractions for a mean beam-hold count of 24.5 instances (95%CI=16-32). The mean beam-hold time of those 94 treatment fractions was 109 s (95%CI=75-143). At the last treatment session, the treatment-related toxicity was as follows: 10 cases (17.5%) of grade 1 cystitis, 2 cases (3.5%) of grade 2 cystitis requiring a temporary bladder catheter, 6 cases (10.5%) of grade 1 proctitis, and 2 cases (3.5%) of grade 2 proctitis. No grade 3 or higher toxicity occurred. *Conclusion*: This is the first report of a clinical application of CMM in a series of 50 PC patients treated with prostate SBRT on 1.5T MR-linac. The implementation of CMM represented an essential step towards empowering the potential of MR-guided RT. Indeed, while the current system effectively manages interfraction motion with daily contouring and replanning, the relatively long treatment sessions on a MR-linac might increase the risk of intrafraction motion. In the present clinical series, we demonstrated that intrafraction motion can be effectively managed by CMM with no significant reduction in duty cycle or increase in beam-on time. The mean duty cycle in this series was 98.9% and the majority of the positioning modification were corrected in real time with a minimal treatment elongation. In conclusion, CMM was effectively implemented in our daily clinical routine. Treatment duration was minimally modified, as well as adaptive team active workload. Future developments should focus on progressively reducing margins.

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COMPARISON OF MICROWAVE AND RADIOFREQUENCY ABLATION FOR SMALL RENAL MASSES: PERIOPERATIVE AND ONCOLOGICAL OUTCOMES

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Background/Aim: This study compared the efficacy of microwave ablation (MWA) *versus* radiofrequency ablation (RFA) for treating small renal masses. TRIFECTA achievement was evaluated, which includes: 1) complete ablation, 2) absence of Clavien-Dindo ≥3 complications, and 3) absence of ≥30% decrease in eGFR. Local recurrence rates, and operative times (min) were also assessed. *Patients and Methods:* We retrospectively analyzed data from 531 patients with small renal masses (cT1a-b) treated either with MWA or RFA at a single center (2008-2022). First, multivariable logistic regression models (MVLRMs) were used for testing TRIFECTA achievement. Second, multivariable Poisson regression models were used to evaluate variables associated with longer operative time. Finally, Kaplan–Meier plots (KM) depicted local recurrence rates over time according to the different ablation techniques. All analyses were repeated after 1:1 propensity score matching (PSM). *Results:* Of 531 patients with small renal masses, 373 (70%) underwent MWA *vs*. 158 (30%) RFA. MWA patients achieved TRIFECTA status more frequently compared to RFA patients, with rates of 314 (84%) *vs*. 114 (72%), respectively (p=0.001). This difference was primarily attributed to higher rates of incomplete ablation in RFA patients compared to MWA patients [25 (16%) *vs*. 21 (6%); p<0.001]. In MVLRMs, RFA was associated with higher rates of no TRIFECTA achievement compared to MWA before [odds ratio (OR)=1.92; p=0.008] and after PSM (OR=1.99; p=0.023). Moreover, median operative time was superior for RFA *vs*. MWA (115 *vs*. 105 min; p=0.002). In Poisson regression analyses, RFA predicted longer operative times both before [incidence rate ratio (IRR)=1.14, p<0.001] and after PSM (IRR=1.18, p<0.001). Finally, we observed 38 (7%) local recurrences [17(5%) in MWA patients and 21 (13%) in RFA patients] after a median follow-up of 24 (IQR=8-46) months. No differences in recurrence rates were observed in KM before and after PSM. *Conclusion:* MWA provides higher TRIFECTA rates, and shorter operative time compared to RFA even after strict methodological approaches to reduce selection bias (multivariable and PSM). However, they provided virtually the same oncologic outcomes.

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INTRAOPERATIVE EVALUATION OF SURGICAL MARGINS DURING ROBOT-ASSISTED RADICAL PROSTATECTOMY: COMPARISON BETWEEN FLUORESCENCE CONFOCAL MICROSCOPY AND FROZEN SECTION ANALYSIS WITH FINAL PATHOLOGY AS STANDARD

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Background/Aim: Positive surgical margins (PSM) at final pathology after robot-assisted radical prostatectomy (RARP) are associated with higher rates of biochemical recurrence (BCR) during follow-up. Intraoperative evaluation of surgical margins requires time, incurs costs, and necessitates specialized pathologists. Novel technologies are therefore required for optimizing surgical margins evaluation during radical prostatectomy (RP). This study tested the accuracy of fluorescence confocal microscopy (FCM), as compared to intraoperative frozen section analysis (IFS), using final pathology as the standard reference. *Materials and Methods*: This is a secondary analysis of a monocentric, prospective, double-blinded randomized trial (NCT06059859) evaluating the role of augmented reality during RP. Overall, 45 men with EAU low- or intermediate-risk prostate cancer, each having at least one visible lesion on multi-parametric magnetic resonance imaging (mpMRI), underwent RP and intraoperative evaluation for surgical margins. Surgical margins evaluation consisted of: 1) fluorescence confocal microscopy (FCM) and, subsequently, 2) IFS. All surgical margins then underwent final pathology. All FCM images were evaluates by two pathologists (blinded): a young (<3 years of experience) and a senior pathologist (>30 years of experience in genitourinary cancers). FCM sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were evaluated for both pathologists, and compared to those of IFS. Agreement between

pathologists, in evaluating FCM images, was evaluated with Cohen's K. The same analysis was used for testing agreement between FCM and IFS. *Results*: Overall, 54 surgical margins were evaluated. At final pathology, 19 (35%) margins were positive for prostate cancer. IFS was positive in 16 (29%) cases. Conversely, FCM was positive in 15 (27.7%) of the patients according to both the young and senior pathologists. The inter-reader agreement between pathologists when evaluating FCM images was strong (k=0.82). Sensitivity *vs*. specificity *vs*. PPV *vs*. NPV were, respectively, 64% *vs*. 89% *vs*. 73% *vs*. 84% and 70% *vs*. 91% *vs*. 80% *vs*. 87% for FCM images, as compared to final pathology, in young and senior pathologists. Conversely, sensitivity, specificity, PPV, and NPV for IFS were, respectively, 88% *vs*. 100% *vs*. 100% *vs*. 94%. The agreement between fluorescence confocal microscopy (FCM) and intraoperative frozen section analysis (IFS) was moderate (κ=0.63) for the young pathologist and strong (κ=0.86) for the senior pathologist. *Conclusion*: The agreement between pathologists in evaluating FCM images appears to be optimal. Moreover, FCM appears to be a valid, but still suboptimal alternative to IFS, when evaluating intraoperative surgical margins after RP.

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PERIOPERATIVE OUTCOMES AFTER RETROPERITONEAL LYMPH NODE DISSECTION FOR TESTICULAR CANCER: A COMPARISON BETWEEN OPEN AND ROBOT-ASSISTED APPROACHES

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Background/Aim: Retroperitoneal lymph node dissection (RPLND) is an integral part of the multimodal and multidisciplinary treatment of testicular cancer (TC). Since the advent of robotic surgery, only a few studies compared traditional open RPLND (O-RPLND) with minimally invasive approach. Available studies often rely on a small number of patients or case series. This study investigated the surgical outcomes and complication rates of patients with TC treated with O-RPLND or robot-assisted RPLND (RA-RPLND). *Patients and Methods*: We performed a retrospective analysis of all consecutive patients who underwent RPLND for TC, between 2001 and 2023. Patient demographics and peri-and postoperative data were recorded. Intraoperative and postoperative variables consisted of: operative time (OT), estimated blood loss (EBL), haemoglobin (Hb) drop, days of use of nonsteroidal anti-inflammatory drugs (NSAIDs), length of stay (LOS), drain indwelling days, final pathology and intra- (EAUiaiC) and post-operative complications (Clavien-Dindo). Descriptive statistics depicted differences between O-RPLND and RA-RPLND. Multivariable Poisson regression models (MPRMs) tested for predictors of surgical drain permanence, NSAIDs use (days), LOS, EBL, and OT. Additionally, multivariable logistic regression models (MLRM) tested for post-operative and post-discharge complications. All models were adjusted for age, BMI, cN staging, residual mass, and surgical side. *Results*: Of 144 patients who underwent RPLND, 53 (36.4%) were treated with RA-RPLND and 91 (63.6%) with O-RPLND. OT and lymph node yield were similar between the two groups, while the RA-RPLND group had significantly lower median EBL (50 ml *vs*. 150 ml in ORPLND; $p<0.01$), median LOS (4 days *vs*. 5.5 days in O-RPLND; $p<0.01$), median drain indwelling days (4 *vs*. 5 in O-RPLND; $p=0.03$), Hb drop (1.5 g/dl *vs*. 1.9 g/dl; $p=0.02$) and median NSAIDs use (1 day *vs*. 3 days in O-RPLND; $p<0.01$). No difference in intra- and postoperative complication rates was recorded between the two groups. In MPRM, RA-RPLND was associated with shorter LOS (RR: 0.28; $p<0.01$), drain permanence time (RR: 0.83; $p=0.01$), NSAIDs use (RR: 0.63; $p<0.01$), and OT (RR: 0.85; $p<0.01$), when compared to O-RPLND. Conversely, in MLRMs, RA-RPLND was not associated with higher overall complications (OR: 0.86, $p=0.71$), relative to O-RPLND. *Conclusion*: RA-RPLND appears to lead to a shorter length of stay, reduced need for painkillers, shorter duration of surgical drain, lower blood loss, and reduced operative time compared to O-RPLND. However, the robotic approach does not appear to be associated with lower complication rates compared to O-RPLND. Our findings require prospective validation in future randomized trials.

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RETROPERITONEAL LYMPH NODE DISSECTION FOR POST-CHEMOTHERAPY RESIDUAL MASSES: COMPARISON OF PERI-OPERATIVE OUTCOMES AFTER OPEN *VERSUS* ROBOT-ASSISTED APPROACH

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Background/Aim: Retroperitoneal lymph node dissection (RPLND) is a viable surgical option within a multidisciplinary approach for treating testicular cancer (TC), particularly for managing residual masses (RM) after chemotherapy. Since the advent of robotic surgery, only a few studies have compared traditional open RPLND (O-RPLND) with a minimally invasive approach. Available studies often rely on limited cohorts or case series. We compared surgical outcomes and complication rates of patients with RM treated with O-RPLND and robot-assisted RPLND (RA-RPLND). *Patients and Methods*: We performed a retrospective analysis of all consecutive TC patients who underwent RPLND for RM (2001-2023). Patient demographics, peri- and post-operative data were recorded. Intraoperative and postoperative variables consisted of: operative time (OT), estimated blood loss (EBL), hemoglobin (Hb) drop, days of use of nonsteroidal anti-inflammatory drugs (NSAIDs), length of stay (LOS), drain indwelling days, final pathology, intra- (EAUiaiC) and post-operative complications (Clavien-Dindo). Descriptive statistics depicted differences between O-RPLND and RA-RPLND. Univariable linear regression models (ULRM) tested for predictors of surgical drain permanence, NSAIDs use (days), LOS, EBL, OT, and overall complications. *Results*: Of the 67 patients treated with RPLND for RM, 20 (30%) underwent RA-RPLND and 47 (70%) underwent O-RPLMD. The two groups were similar in terms of body mass index, Charlson Comorbidity Index (CCI), and oncologic characteristics (prognostic group, RM size, TNM score, and histology at orchiectomy). OT and lymph node yield were similar between the two groups, while the RA-RPLND group had significantly lower EBL ($p<0.01$), LOS ($p<0.01$), drain indwelling days ($p<0.01$), and Hb drop ($p=0.03$). We recorded fewer intraoperative complications in the RA-RPLND [1 (5%) *vs*. 10 (21.3%) in the O-RPLND] but no significant difference in terms of postoperative complications ($p=0.08$). In ULRM, RA-RPLND was associated with shorter LOS (OR=0.7; $p<0.01$), EBL (OR=0.19; $p<0.01$), days of NSAIDs therapy (OR: 0.6; $p=0.02$) and drain permanence (OR=0.6; $p<0.01$). Moreover, in ULRM, RA-RPLND was associated with lower OT (OR=0.78, $p<0.01$) and overall complications rate (OR=0.29, $p=0.03$). *Conclusion*: RA-RPLND in TC appears to be associated with lower estimated blood loss, length of stay, drain indwelling days, and hemoglobin drop. Moreover, the procedure appears to lead to a shorter operative time and a lower number of overall complications. Our findings require prospective validation in future randomized trials.

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ANDROLOGICAL OUTCOMES AFTER RETROPERITONEAL LYMPH NODE DISSECTION FOR TESTICULAR CANCER: A COMPARISON BETWEEN OPEN AND ROBOT-ASSISTED APPROACHES

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Background/Aim: Sexual disorders following retroperitoneal pelvic lymph node dissection (RPLND) for testicular cancer can affect the quality of life of patients. The aim of the current study was to compare several different andrological outcomes between the open (O-RPLND) and robotic (RA-RPLND) approaches for RPLND. *Patients and Methods*: We performed a retrospective analysis of 107 patients who underwent O-RPLND and RA-RPLND for testicular cancer between 2001 and 2023 in our Institution. Modified unilateral RPLND nerve-sparing template was preferred, while radical template resection was performed in case of contralateral spread or larger residual tumors. A nerve-sparing procedure was always attempted. Preoperative patient demographics, comorbidities, tumor characteristics, clinical stage, and previous chemotherapy regimens were recorded. Major variables of interest were erectile dysfunction (ED), anorgasmia (AO), hypoposia, and dry ejaculation (DE). Finally, fertility as well as the fecundation process [sexual intercourse or medically-assisted procreation (MAP)] was investigated. Chi-squared, Wilcoxon or Mann–Whitney tests estimated differences in proportions or medians. All statistical tests were two-sided, with the level of significance set at $p<0.05$. *Results*: A total of 107 patients underwent RPLND, 61 (57%) with the open approach and 46 (43%) with the robot-assisted approach. Overall, 32 patients (29.9%) presented an andrological disorder of any type after RPLND, with no difference between the two

Table I. *Overall andrological problems after surgery.*

	O-RPLND (n=61; 57%)	RA-RPLND (n=46, 43%)	*p*-Value
	Median (IQR)	Median (IQR)	
Andrological problems after surgery		0.3	
No	40 (65.6)	35 (76.1)	
Yes	21 (34.4)	11 (23.9)	
Infertility			

techniques (21 for O-RPLND and 11 for RA-RPLND, p=0.3) (Table I). Hypoposia was present in 13 (12.1%) patients, 8 (13%) in the O-RPLND group and 5 (10.9%) in the RA-RPLND group; p=0.9. Six (5.6%) patients presented DE after surgery, 5 (8.2%) after O-RPLND and 1 (2.2%) after RA-RPLND (p=0.3). Only one patient (0.9%) presented with anorgasmia, in the O-RPLND group. Eight patients (7.5%) suffered from ED, 6 (9.8%) in the O-RPLND group and 2 (4.3%) in the RA-RPLND group (p=0.4). Similar median age at surgery, body mass index (BMI), number of nodes removed, and preoperative risk factor rates were identified between groups (all p>0.05). Infertility was observed in 14 (13.1%) patients with no difference between the two groups (13.1% for O-RPLND and 13% for RA-RPLND). Of all 107 patients, 30 (28%) successfully fathered children after surgery, but two required a MAP. No preoperative or perioperative characteristics were significantly associated with any of the described complications. *Conclusion*: In conclusion, no significant differences were found in terms of andrological complications after RPLND between the open and robot-assisted approaches. A non-negligible number of events were recorded, mainly represented by ejaculation disorders; however, ED occurrence and overall sexual satisfaction deficit should be definitely considered. Infertility was reported after both techniques, however, with a similar rate than that in the general population. Our findings require prospective validation in future trials.

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THE IMPACT OF INCOMPLETE ABLATION IN PATIENTS TREATED WITH THERMAL ABLATION FOR SMALL RENAL MASSES ON PERIOPERATIVE OUTCOMES AND THE FEASIBILITY OF RE-TREATMENT

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Background/Aim: Thermal ablation (TA) offers an alternative to partial nephrectomy for the treatment of small renal masses (SRMs). However, little is known about the perioperative outcomes of incomplete TA or the outcomes of re-treatment for residual tumors. *Patients and Methods:* We retrospectively analyzed 551 SRMs (cT1a-b) patients treated with TA at a single center (2008-2022). First, multivariable logistic regression models were fitted in a stepwise fashion for testing for predictors of incomplete ablation. Second, Kaplan–Meier plots (KM) depicted survival rates for local recurrence (LRR), systemic recurrence (SR), cancer-specific survival (CSS), and overall survival (OS). For patients with incomplete ablation, survival analyses considered the time from re-treatment to event. Third, scatter plots were used to depict the relation between preoperative and postoperative kidney function. *Results:* Of 551 patients with SRMs, 49 (9%) had incomplete ablation. Incomplete ablation patients were older (73 *vs*. 67 years), had larger tumor size (3.7 *vs*. 2.40 cm), higher age-adjusted CCI (6 *vs*. 5), higher RENAL classifications class [moderate complexity (57 *vs*. 27%) and high complexity (12 *vs*. 6%)], longer operative time (160 *vs*. 104 min), and higher intraoperative complications rate (24 *vs*. 8%). Of these 49 patients, 27 (55%) had to undergo a re-treatment. In multivariable logistic regression models, tumor size [odds ratio (OR)=1.69, p<0.001], RENAL classification (moderate complexity OR=3.96, p<0.001 and higher complexity OR=3.47; p=0.026), and Charlson Comorbidity Index (CCI), age-adjuster (OR=1.27, p=0.004) were predictors of incomplete ablation. No differences in LRR (p=0.81), SR (p=0.73), and CSS (p=0.45) were observed in KM. Conversely, patients with incomplete ablations had worst OS

(p<0.001). Scatter plots demonstrated no significant impact of re-treatment on kidney function compared to a single treatment. *Conclusion:* Advanced age, large tumor size, and higher RENAL score were predictors of incomplete TA. Patients who underwent a re-treatment for incomplete ablation exhibited comparable oncological outcomes.

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THERMAL ABLATION FOR LOCAL TUMOR RECURRENCE AFTER PREVIOUS PARTIAL NEPHRECTOMY: PERIOPERATIVE AND ONCOLOGICAL OUTCOMES

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Background/Aim: The management of local tumor relapse after partial nephrectomy (PN), for localized renal cell carcinoma (RCC), at the site of the primary surgical resection still represents a challenging situation. Often, a radical nephrectomy (RN) is offered to these patients. This approach usually leads to higher morbidity and has a strong impact on residual renal function. As percutaneous thermal ablation (PTA) has recently emerged as an intriguing alternative to salvage surgery, we report perioperative and oncological outcomes of patients treated with PTA for local kidney recurrence. *Patients and Methods*: We retrospectively analyzed 27 patients with local recurrence on surgical site, who received either radiofrequency (RF) [8 (29.6%)] or microwaves (MW) [19 (70.4%)], from 2008 to2022 in a high-volume center. The primary endpoint was the perioperative outcomes following PTA. We specifically evaluated the median treatment time, intraoperative and postoperative complications and their management, length of stay (LOS), and readmission rates. The secondary outcome was the oncological results. Specifically, we focused on in-site tumor recurrence, defined as a relapse in-site of a previously completely ablated zone, and out-site recurrence. Last, we collected renal function outcomes after PTA. *Results*: Median (IQR) treatment time was 75 (63-106) min and median LOS was 3 days. Intraoperative complications occurred in one (3.7%) patient (urinary leakage that did not require additional treatments: EAU intraoperative adverse incident Classification grade 0), while postoperative complications occurred in two (7.4%) patients [one urinary leakage requiring ureteral double J stent placement: Clavien-Dindo (CD) grade III; one bleeding necessitating blood transfusions: CD grade II]. According to Society of Interventional Radiology (SIR) classification, one (3.7%) patient had minor complications (grade A) and two (7.4%) had major complications (grade C and D). Of all patients, three (11%) received incomplete ablation. Of those, local control was achieved after one adjunctive MW session in one patient and after RN in two patients. Overall, four (16%) patients developed in-site recurrence with a median (IQR) time of 29 (6-31) months. Of these, complete local control was achieved with PTA in three, while one patient developed bone metastases and, therefore, no other local treatments were performed. Moreover, six (24%) patients developed out-site recurrences with a median time of 11 (9-23) months. Last, median (IQR) creatinine drop at 1 month and at 1 year after surgery were respectively –0.03 (–0.11-0.01) and –0.11 (–0.20-–0.05), while median (IQR) eGFR drop at 1 month and at 1 year were respectively 2 (0-7.65) and 9.5 (5-13.45). *Conclusion*: PTA is a safe and feasible approach for the management of recurrences on surgical site after PN. In the current series, a low perioperative complication rate and an optimal local cancer control was achieved in the majority of patients, without a significant impairment in residual renal function.

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APPARENT DIFFUSION COEFFICIENT (ADC) AT MRI FOR OPTIMIZING ACTIVE SURVEILLANCE INCLUSION IN PATIENTS DIAGNOSED WITH ISUP GG1 AND ISUP GG2 PROSTATE CANCER

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Background/Aim: PI-RADS categories at baseline multiparametric magnetic resonance imaging (mpMRI) are associated with varying risks of disease progression in men undergoing active surveillance (AS) for prostate cancer (PCa). However, mpMRI, and especially PI-RADS score assignment, are subjected to significant heterogeneity among readers. Apparent diffusion coefficient (ADC) is an objective functional mpMRI variable that was previously

associated with tumor aggressiveness. We therefore tested the role of mpMRI ADC in in selecting patients with ISUP GG 1 and ISUP GG 2 PCa for AS. We then compared its predictive accuracy with following criteria for each group: (i) Prostate Cancer Research International: Active Surveillance (PRIAS) criteria, (ii) Johns Hopkins (JH) criteria, (iii) European Association of Urology (EAU) low-risk classification, and (iv) EAU low-risk or low-volume with ISUP GG 2 classification. *Patients and Methods*: We selected 802 patients with ISUP GG1 or GG2 prostate cancer (PCa), treated with radical prostatectomy (RP) between 2012 and 2015. The outcomes of interest were: 1) the presence of clinically significant PCa (csPCa) at RP, defined as: ISUP GG 3 and/or pT ≥3a and/or pN1; 2) Biochemical recurrence (BCR) during follow-up, defined as two consecutive PSA values 0.2 ng/ml. First, logistic regression and Cox regression models testing, respectively, csPCa and BCR, including PRIAS, JH, EAU low-risk, and EAU low-risk or low-volume ISUP GG2 binary classifications (not eligible *vs*. eligible) were used. Second, we fitted separate multivariable logistic and Cox regression models to test for csPCa and BCR over time. These models included all clinical variables (age, PSA-D, ISUP GG, and percentage of positive cores) and mpMRI variables (PI-RADS categories, EPE categories, and ADC values). The area under the receiver operating characteristic curve (AUC) was calculated for all models. *Results*: Of the 802 patients, 423 (52.7%) had csPCa at RP. Median ADC values were, respectively 875 (749-968) and 940 (839-1,076) in csPCa *vs*. non-csPCA patients (p<0.001). The proportion of csPCa amongst the EAU low-risk, EAU low-risk or low-volume ISUP GG2, PRIAS and JH candidates was 39.5%, 51.6%, 37.8%, and 28.2%, respectively. A simplified multivariable model (in which only PSA-D, ISUP GG, ECE score and ADC values were retained) had a greater AUC (0.74), compared to the four proposed AS criteria (all p<0.001). Moreover, the AUC value of this simplified model (0.74) was comparable to a model in which PI-RADS categories were used instead of ADC (0.73). After a median follow-up time of 4.58 years, 195 (24%) men developed BCR. Again, the same simplified multivariable model had a greater AUC (0.66), compared to the four proposed AS criteria (all p<0.001). Moreover, the AUC value of this simplified model (0.66) was comparable to a model in which PI-RADS categories were used instead of ADC (0.65). *Conclusion*: Low ADC values at mpMRI were associated with higher risk of csPCa at RP and BCR during follow-up in men with ISUP GG1 and ISUP GG2 PCa. Specifically, ADC performance was comparable to the one of PI-RADS categories in multivariable models adjusted for clinical and mpMRI variables. Therefore, ADC should be considered as a valid alternative to PI-RADS categories for selecting patients suitable for AS.

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EVALUATION OF THE M371 TEST UNDER REAL LIFE CONDITIONS FOR THE DIAGNOSIS OF TESTICULAR GERM CELL CANCER

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Background/Aim: Testicular germ cell cancer (GCT) represents the most frequently diagnosed group of neoplasms in men aged 15 to 50 years with a survival rate above 90% for clinical stage (CS) I and II, and above 80% for CS III. Currently, the gold standard for the clinical management of GCT includes surgery, computed tomography (CT) or magnetic resonance imaging (MRI), and tumor markers alpha fetoprotein (AFP), beta-human chorionic gonadotropin (b-HCG), and lactate dehydrogenase (LDH). However, tumor markers are positive in only 50-60% of cases. For these reasons, new methods for early detection of possible metastasis at diagnosis or recurrence have been studied for many years. Recently, miRNA-371a-3p has been shown to be a very reliable tumor marker for the diagnosis of testicular tumors, performing better than the conventional markers. The purpose of the study was to establish the performance of M371-Test on the Thermocycler Rotor-Gene Q (Qiagen) platform and to analyze the test under real life conditions, comparing it to the classical markers AFP, b-HCG, and LDH. *Materials and Methods*: Forty-nine M371 tests were performed in 47 patients (median age 37 years) and were included in this prospective study. All patients presented with suspicion of testicular cancer. The results of M371, AFP, b-HCG, LDH were compared with the histology, which was considered the gold standard. Four samples were excluded from the analysis due to non-diagnostic/indeterminate M371 (two samples) or LDH (two samples) results. The cut-off for the M371 test was set at >5 RQ. *Results*: In the patients with suspicion of TC, the M371 test showed an overall sensitivity of 89.3%, AFP of 17.9%, LDH of 42.9%, and b-HCG of 53.6% (Table I). Specificity of the markers was 88.2% for M371, 94.1% for both AFP and LDH, and 100% for b-HCG. In addition, positive predictive value was 92.6% for M371, 83.3% for AFP, 92.3% for LDH, and 100% for b-HCG. The M371 test showed a negative predictive value of 83.3%, while the negative predictive values for AFP, LDH, and b-HCG were 41%, 50%, and 56.7%, respectively. *Discussion and Conclusion*: In terms of sensitivity, the M371 test performs excellently compared to traditional markers such AFP, LDH, and β-HCG. This holds true even under real-life conditions,

making the M371 test a highly effective marker for the diagnosis of GCTs. It has high specificity and negative predictive value, which outperform the classical markers. However, this study has some limitations. It is a single-center study, and the sample size of enrolled patients is small. Furthermore, the need of experienced molecular pathology technicians with a learning curve could have also affected the initial results performed without the support of the manufacturer's laboratory. Another limitation may be due to the possible delay between the collection and processing of blood samples in the early period of the study, which could influence the quality of miRNA. In conclusion, even when using the real-time Thermocycler Rotor-Gene Q (Qiagen) platform under real life conditions, the M371 test showed an excellent performance, especially when compared with classical markers.

Table I. *Sensitivity, specificity, and predictive values of M371, alpha fetoprotein (AFP), lactate dehydrogenase (LDH), and beta-human chorionic gonadotropin (bHCG) in 47 patients with suspicion of testicular cancer.*

	Sens	Spec	PPV	NPV
miRNA	89.3	88.2	92.6	83.3
AFP	17.9	94.1	83.3	41
LDH	42.9	94.1	92.3	50
b-HCG	53.6	100	100	56.7

PPV: Positive predictive value; NPV: negative predictive value.

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PROSTATE STEREOTACTIC BODY RADIOTHERAPY DELIVERED WITH 1.5T MR-LINAC OR CYBERKNIFE IN PATIENTS AFFECTED BY LOCALIZED PROSTATE CANCER: A PROPENSITY SCORE MATCHING ANALYSIS

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Aim: To compare the acute and late toxicity of prostate cancer (PCa) stereotactic body radiotherapy (SBRT) delivered using daily-adaptive MR-guided radiotherapy (MRgRT) with a 1.5T MR-linac *versus* robotic SBRT with CyberKnife (CK). *Patients and Methods*: This multi-institutional analysis included 238 PCa patients treated with 5 fractions of SBRT. The treatment doses were: 35 Gy for low-risk and favorable intermediate-risk patients and 36.25 Gy unfavorable intermediate-risk and high-risk patients. 120 patients were treated with MRgRT and 118 with CK at two Institutions. The primary endpoint was the comparison of acute toxicity (required follow-up of six months). Toxicity assessment was measured by CTCAE v5.0 scale. The secondary endpoint was late toxicity. A propensity score matching (PSM) analysis was performed by matching patients 1:1 according to the following characteristics: prostate volume (threshold 50 cc), IPSS before SBRT (threshold 7), and total treatment dose (35 Gy *versus* 36.25 Gy). *Results*: The population after PSM was represented by 150 individuals. The median prostate volume was 50 cc (range=20-113.5 cc). The PTV margin was 5 mm in all directions and 3 mm posteriorly in both groups. In the CK, the median maximal dose administered to the CTV was 44.3 Gy (range=42.6-46.7 Gy), compared to 38.7 Gy in MRgRT. Globally, acute G1, G2, and G3 genitourinary (GU) toxicity occurred in 49.3%, 12%, and 2.7% cases, respectively. Acute G1, and G2 gastrointestinal (GI) toxicity occurred in 18%, and 6%, cases, respectively. In the univariate analysis, MRgRT patients had a significantly lower acute GU toxicity (G1: 37.3% *versus* 61.3%, G2: 10.7% *versus* 13.3%; p=0.007), while G3 toxicity was 2.7% in both groups. Acute GI toxicity did not differ significantly (p=0.28). Late GU toxicity was significantly lower in MRgRT patients (G1 18.7% *versus* 50%, G2: 9.3% *versus* 10.6%, G3 2.7% *versus* 0%; p=0.0001). There was no difference in late GI toxicity (p=0.39). In the multivariate analysis (MVA), treatment technique was the only factor associated with acute (OR=2.645, 95%CI=1.099-6.365; p=0.02) and late (OR=4.578, 95%CI=2.063-10.162; p=0.000) GU toxicity. No factors were associated with acute and late GI toxicity in the MVA. *Conclusion*: MRgRT using homogenous planning might be associated with lower moderate GU toxicity. However, no significant differences in high-grade acute and late GU and GI toxicities were reported in both groups. Both techniques, prostate SBRT with the 1.5TMR-linac or the CK, exhibit a satisfactory late toxicity profile with rare severe adverse events.

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ELECTIVE HYPOFRACTIONATED HEMIPELVIC IRRADIATION WITH SIMULTANEOUS INTEGRATED BOOST IN THE NODAL OLIGORECURRENT PROSTATE CANCER: AN INSTITUTIONAL EXPERIENCE

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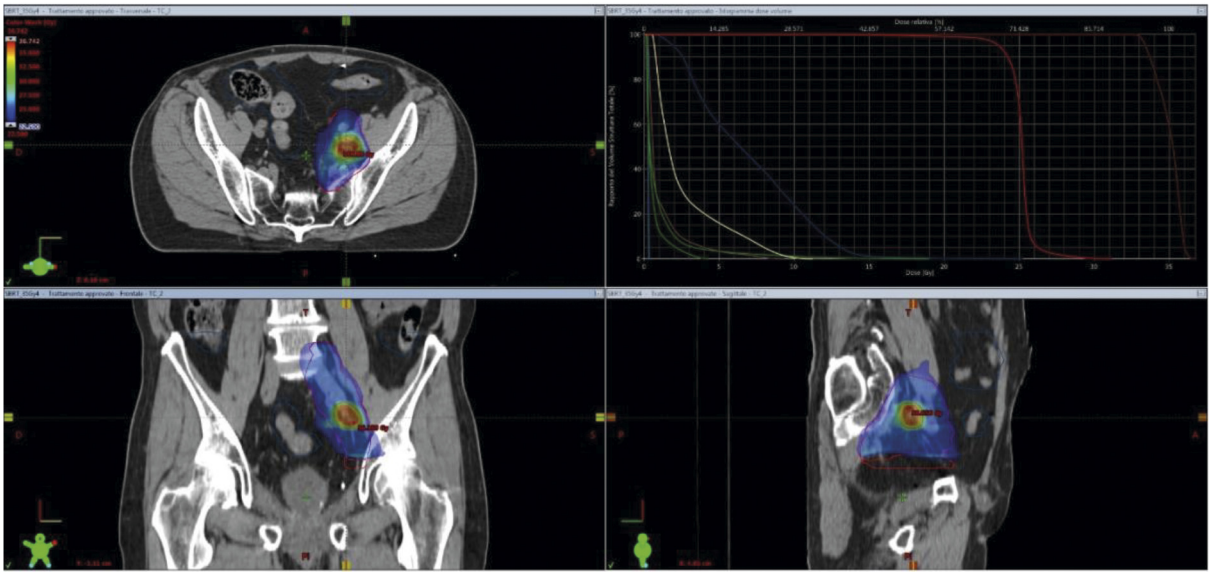

Figure 1. *Treatment plan of elective hypofractionated hemipelvic nodal irradiation.*

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Background/Aim: Patients with recurrence following primary prostate cancer (PCa) treatment often experience a relapse in the pelvic lymph nodes (LNs). Radiotherapy (RT) is an emerging treatment strategy for patients with nodal oligorecurrent PCa. However, the optimal RT strategy – whether stereotactic body radiotherapy (SBRT) or elective nodal radiotherapy (ENRT) – remains to be determined in this setting of patients (1-4). This study aimed to evaluate the clinical outcomes of elective hypofractionated hemipelvic nodal irradiation (EHhpNRT) with simultaneous integrated boost (SIB) in patients (pts) with Prostate-specific membrane antigen positron emission tomography (PSMA-PET) positive (PSMA+) nodal oligorecurrence after primary local treatment for PCa. *Patients and Methods*: We retrospectively evaluated data of patients treated with EHhpNRT and SIB for a LN oligorecurrence of PCa (1 node) after prostatectomy, prostate radiotherapy or their combination. All patients were staged with a PSMA-PET following a biochemical relapse. No concomitant androgen deprivation therapy (ADT) was administered. Toxicity (CTCAE 4.0), biochemical progression-free survival (BPFS, defined as an increase in PSA after a biochemical response), and time to castration-resistant prostate cancer (CRPC) free survival were the endpoints analyzed. *Results*: From March 2021 to October 2023, nine patients were treated with 25 Gy in 5 daily fractions to the ipsilateral hemipelvis (including internal and external iliac, obturator, and common iliac LNs) with a SIB of up to 35 Gy on the PSMA-PET positive nodal oligorecurrences (Figure 1). Median PTVs were 276.9 cc (range=207.2-415.1 cc) for the elective hemipelvic volume and 8.7 cc (range=6.1-16.9 cc) for the nodal PSMA+ target volume. Mean doses to the bowel ranged from 3.02 Gy to 10.41 Gy with a median of 5.66 Gy. After a median follow up of 25.5 months (range=3.7-34.6 months) no acute or late significant toxicities were detected. At the time of the analysis, all the patients were alive: 4/9 pts were biochemical or disease-free; 5/9 pts had relapsed as diagnosed by PSMA-PET (3 pts in contralateral hemipelvic nodes, 1 with M1a, and 1 with M1b). Among these, three pts were on ADT, one patient was treated with EHhpNRT on the contralateral pelvis, and the remaining one was treated with SBRT only. Median pre-RT PSA was 1.14 ng/ml (range=0.34-8.46). Median post-RT PSA was 0.39 ng/ml (range=0.07-3.72 ng/ml). 1-yr, 2-yr and median BPFS for the whole population were 75%, 56.3%, and 25 months, respectively. So far, no patients have developed CRPC. *Conclusion*: The optimal radiotherapy approach for nodal oligorecurrence in pts previously treated for primary prostate cancer – whether SBRT or ENRT – remains an open question. This uncertainty extends to not only oncological outcomes and relapse patterns but also differences in toxicity and overall treatment duration. According to our experience, EHhpNRT with a SIB in selected pts with nodal prostate cancer oligorecurrence is safe and feasible, providing a good biochemical control with a short overall treatment time.

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UPDATE OF THE MICROSTYLE STUDY: A RANDOMIZED CONTROLLED TRIAL ON LIFESTYLE INTERVENTION IN PROSTATE CANCER PATIENTS

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Background/Aim: Health-related quality of life (QoL) of prostate cancer is affected by radiotherapy (RT). The aim of this study was to report preliminary data from a clinical trial (the MICROSTYLE study) in prostate cancer (PCa) patients (pts) undergoing RT designed to investigate whether changes towards a healthy lifestyle improve QoL (1). *Patients and Methods*: PCa pts undergoing adjuvant/salvage or curative RT were recruited in two comprehensive Italian Cancer Centers (Millan and Naples). Participants were randomized in two arms: Intervention Group (IG) who received personalized counseling on diet and exercise to improve overall lifestyle and to reduce eventual RT-related toxicities or the Control Group (CG). The primary outcome was assessed after six months by measuring the change in healthy lifestyle adherence (HLA) score between groups (Figure 1). The score was calculated according to the World Cancer Research Fund recommendations (2018). Each component is worth one point: 1, 0.5, and 0 points for fully, partially, and not meeting each recommendation, respectively. The score ranged from 0 to 7 points, from minimal to maximal adherence (2). *Results*: Recruitment ended on December 2023 with the enrollment of 311 patients (155 in the GI and 156 in the GC) with a median age of 71 years. Compared to the baseline, there was a significant increase in the DM score in the GC group (+0.4±1.7, p=0.0015) with a greater increase in the GI group (+0.7±1.6, p=0.0011). The HLA score resulted significantly higher at six months with respect to baseline (4.4 *vs*. 4.8, p<0.0001) (Figure 2). High risk NCCN patients (very high to intermediate unfavorable) *vs*. low (low to intermediate favorable) presented significantly different cholesterol levels (196 *vs*. 186, p=0.05) and wine intake (80 *vs*. 66 score, p=0.04). *Conclusion*: The promotion of healthy behavior will be started before the initiation of standard care to achieve long-lasting impacts. This approach aims to manage side effects, address feelings of anxiety and depression, and enhance the effectiveness of radiotherapy.

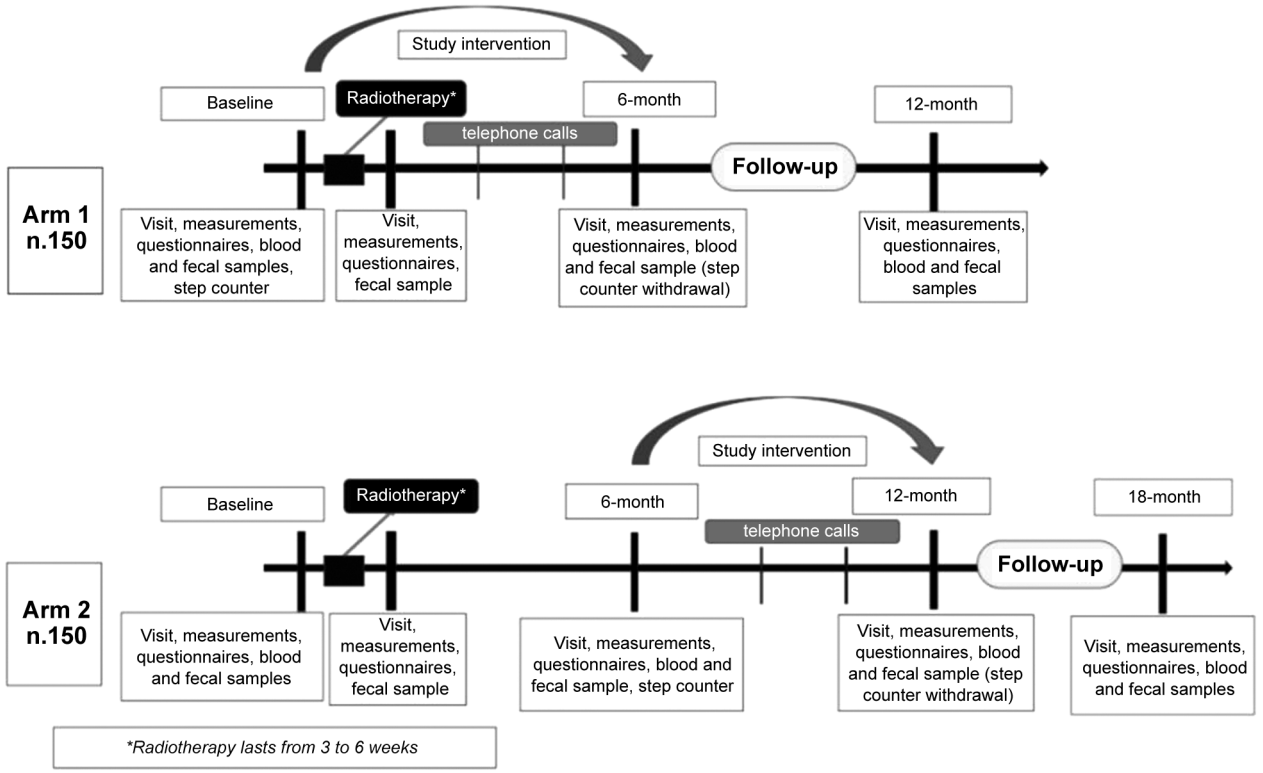

Figure 1. *Schematic representation of the study design.*

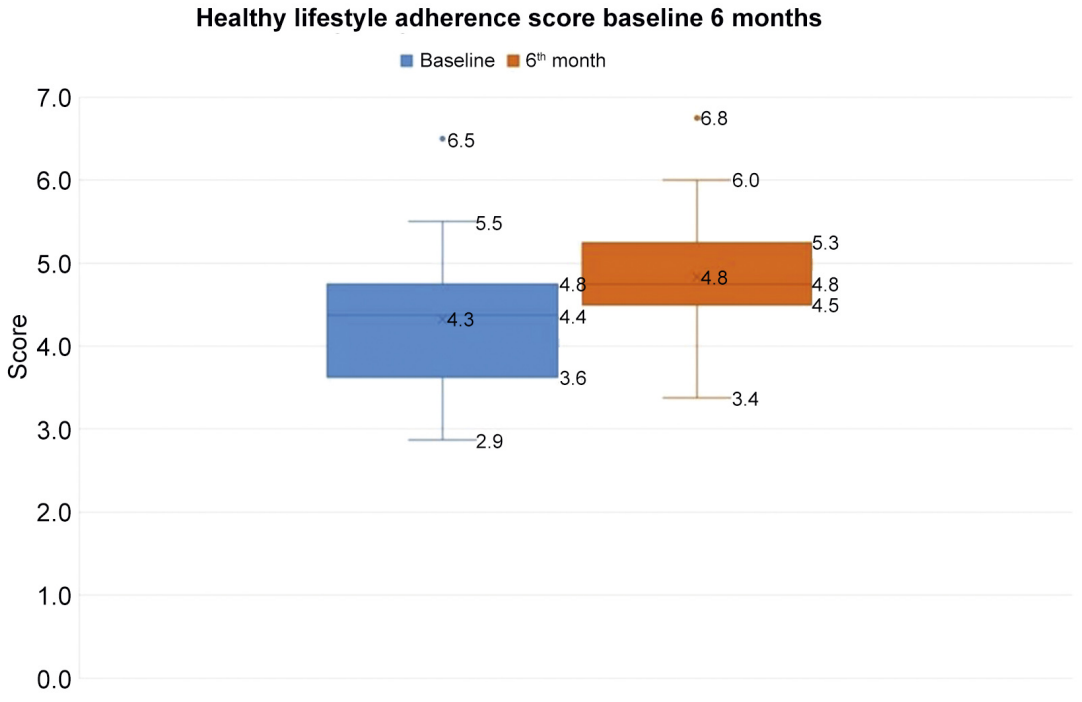

Figure 2. *HLA score at baseline and at six months.*

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STEREOTACTIC BODY RADIATION THERAPY (SBRT) IN THE MANAGEMENT OF RENAL CELL CARCINOMA (RCC): A REPORT FROM AN ITALIAN SINGLE INSTITUTION

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Background/Aim: Stereotactic body radiation therapy (SBRT) is an emerging non-invasive alternative to surgical resection in the management of renal cell carcinoma (RCC). This is significantly useful in an aging population where patients with RCC often have multiple comorbidities and are therefore not surgical candidates. *Patients and Methods*: This retrospective analysis is focused on the experience of a single Italian Radiotherapy Centre. From 2018 to 2023, 12 patients deemed unfit for surgery underwent SBRT for RCC. Median age was 79 years (range=62-89 years). Tumor location was on the left in four cases (33.3%) and on the right in eight cases (66.7%). The median tumor dimension was 32 mm (range=17-50 mm). Five patients had biopsy-confirmed RCC whilst seven had a radiological diagnosis based mainly on dimensional progression at computed tomography. Three patients had previously undergone contralateral nephrectomy for kidney cancer and thus had a single kidney. When considering the whole patient population, baseline mean estimated glomerular filtration rate (eGFR) was 60.2 ml/min/1.73 m^2. Median follow up was 30 months (range=15-64 months). *Results*: The prescribed dose was 42 Gy/3 fractions in eight patients (66.6%), 39 Gy/3 fractions in three patients (25%), and 40 Gy/5 fractions in one patient (8.4%). All patients were treated using volumetric modulated arc radiotherapy and image-guided radiotherapy. A cone-beam computed tomography was performed before each treatment. Flattening Filter Free 6 MV were used. Local control and cancer-specific survival were 100% at one year. Two patients died of unrelated causes (COVID infection complications). Freedom from distant failure was 75% at two years. SBRT had a favorable toxicity profile with no grade 3-5 toxicity. Kidney function preservation was especially favorable, with only a 6 ml/min decrease in eGFR from baseline, and no patients underwent dialysis. *Conclusion*: For both disease control and toxicity profile, our data suggest that SBRT can be a valid non-invasive treatment in patients with RCC who are deemed unfit for surgery or have a single kidney. Furthermore, SBRT can be given also to patients with large kidney tumors and/or central location of the tumor. Our data are consistent with those reported in the Fastrack trial.

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IMPACT OF TRANSRECTAL *VERSUS* TRANSPERINEAL APPROACH ON PATHOLOGICAL CONCORDANCE BETWEEN MRI-ULTRASOUND FUSION PROSTATE BIOPSY AND RADICAL PROSTATECTOMY: RESULTS FROM THE PROMOD WORKING GROUP

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Background/Aim: The study of pathological concordance rates between transperineal (TP) and transrectal (TR) magnetic resonance imaging (MRI)-ultrasound (US) fusion prostate biopsy (PBx) compared with radical prostatectomy (RP) specimen has led to contradictory results. This study aimed to assess whether the type of approach (TP *vs*. TR) in MRI-US fusion PBx has an impact on the final pathological concordance with radical prostatectomy (RP) in patients diagnosed with prostate cancer (PCa). *Patients and Methods*: We retrospectively reviewed data from the Prostate MRI Outcome Database (PROMOD) database, including all men who underwent MRI-US Fusion PBx for positive MRI (PIRADS ≥3) at 24 institutions between 2013 and 2022. We included only patients who were diagnosed with PCa and underwent RP. The primary endpoint was the International Society of Urological Pathology (ISUP) grade concordance between PBx and RP specimens. Patients were stratified based on the type of PBx approach used (TP *vs*. TR). Pathologic concordance, as well as grade upstaging and downstaging between PBx and RP specimens, were assessed for each individual patient. The overall diagnostic concordance was assessed using Kappa's coefficient for the TP and TR groups. Multivariable Logistic regression analysis on final pathological concordance was calculated using all the available clinicopathological covariates, including type of MRI-fusion PBx performed (TR *vs*. TP). The concordance rate was further analyzed separately for standard biopsy (SBx) cores and TBx cores. *Results*: We included 1,512 men, of whom 553 (37%) underwent TP PBx. Pathological concordance, grade upstaging, and downstaging at RP were observed in 59%, 30%, and 11% of men who underwent TP-PBx, respectively, compared to 58%, 28%, and 14% in the TR-PBx group (p=0.4). The overall ISUP concordance coefficient between biopsy and RP were 57% for TP and 53% for TR. When focusing on SBx cores exclusively, pathological concordance, upstage and downstage were 47%, 47%, and 6% for TP-PBx, *versus* 41%, 51%, 8% for TR-PBx (p=0.1). Conversely, TP-TBx was associated with higher pathological concordance (56% *vs*. 48%) and both lower upstaging (36% *vs*. 43%) and downstaging (8% *vs*. 9%) at RP, when compared with TR-TBx (p=0.01). At multivariable analysis, the type of biopsy approach was not an independent predictor for overall diagnostic concordance, although the TP approach was independently associated with higher diagnostic concordance between ISUP at TBx and RP, when compared with TR-TBx (OR=1.4, 95%CI=1.11-1.70, p=0.003). *Conclusion*: The type of PBx approach does not appear to be associated with a difference in ISUP grade concordance between biopsy and RP. However, TP-TBx might improve concordance compared with TR-TBx.

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RISK AND PREDICTORS OF PROGRESSION TO HIGH-GRADE AND MUSCLE-INVASIVE DISEASE IN LOW-GRADE NMIBC: IMPLICATIONS FOR ACTIVE SURVEILLANCE FROM A LARGE BI-CENTRIC COHORT

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Background/Aim: Active surveillance (AS) for low-grade (LG) non-muscle invasive bladder cancer (NMIBC) has recently been proposed as a novel strategy to avoid or delay invasive radical treatments in men with a very low risk of disease progression. However, existing literature primarily consists of small case series with limited follow-up durations (1-3). Our

study investigated the risk of progression to high-grade (HG) and muscle-invasive (MIBC) diseases in a large cohort of patients with primary LG NMIBC. We aimed to identify potential predictors of disease progression, thus better refine the timing strategy for AS. *Patients and Methods*: This retrospective study included patients diagnosed with LG NMIBC (Ta G1-G2) from 2013 to 2022 at two academic Centers. Following transurethral resection for bladder tumor (TURBT), all patients underwent follow-up cystoscopies at 3 and 9 months after diagnosis, then annually, following the European Urology Association NMIBC guidelines. All specimens were analyzed by two dedicated uropathologists at each Center. Primary outcomes were progression to HG disease and MIBC, using Kaplan-Meier curves and multivariable Cox regression analysis, adjusted for all available covariates. Sensitivity landmark analyses at 12-, 18-, 24- and 36-months were also performed. Patients with macroscopic hematuria or positive/suspicious urinary cytology were excluded. *Results***:** A total of 575 LG NMIBC were included in the study. At a median interquartile range (IQR) follow-up of 41 (21-65) months, recurrence-free survival, HG progression-free survival (PFS) and MIBC PFS were 57.7%, 87.3% and 98.4% respectively. The 3-year HG PFS from the 12-, 18-, 24- and 36-month landmark analyses were 93.8%, 95.5%, 95.9% and 92.6% respectively. At the 12-month landmark analysis, the 3-years MIBC PFS was 98.5%, with no progression to MIBC observed in patients without recurrence in the first 18 months post-diagnosis. At multivariable Cox Regression analysis, the number of TURBT was significantly associated with higher hazards for both recurrence (HR=1.45, 95% CI=1.31-1.61, $p<0.001$) and progression to HG (HR=1.55, 95% CI=1.46-1.65, $p<0.001$). *Conclusion:* In this retrospective cohort of primary LG NMIBC, a non-negligible proportion of patients exhibited progression to HG disease over time. PFS was significantly better among patients without any recurrence within the first 18 months post-diagnosis, suggesting that AS could be a feasible option for this group of patients. Both tumor size and multifocality were not reliable predictors of recurrence and progression, which calls for the implementation and validation of AS criteria in larger cohorts than those used in initial studies.

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RE-IRRADIATION FOR PATIENTS WITH ISOLATED LOCAL RELAPSE OF PROSTATE CANCER: A MONOCENTRIC RETROSPECTIVE STUDY

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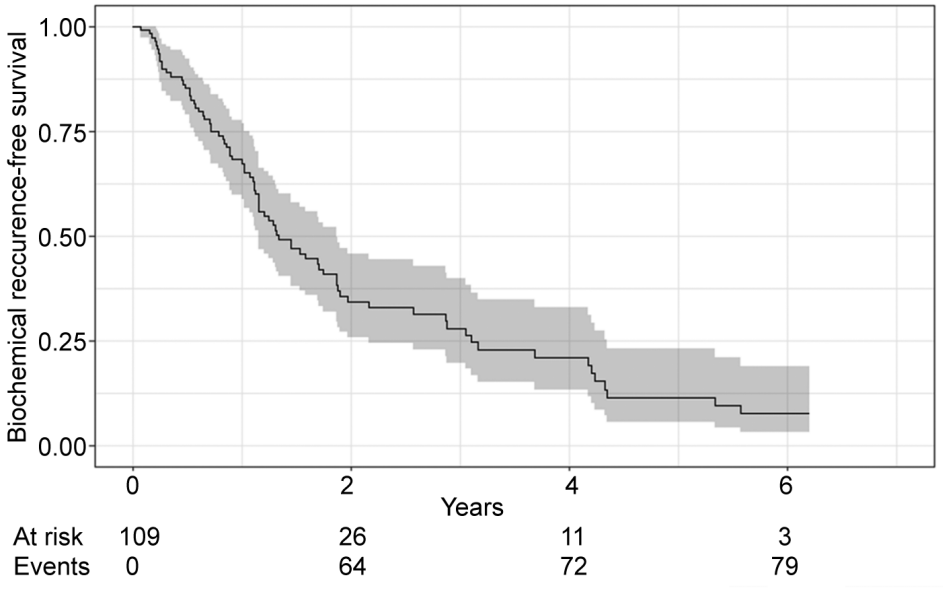
Aim: The objective of the study was to assess the safety and efficacy of re-irradiation for local recurrence in patients previously treated with curative or salvage/adjuvant radiotherapy for prostate cancer (PCa). *Patients and Methods***:** Patients who underwent either salvage/adjuvant radiotherapy after surgery or curative radiotherapy and showed evidence of localized recurrence within the prostate on magnetic resonance imaging (MRI) or positron emission tomography (PET) choline scans, were retrospectively reviewed for inclusion in this study. Re-irradiation was conducted using image-guided techniques (RapidArc®, VERO®, and CyberKnife®) with a dosage ranging from 25 to 35 Gy delivered in 5 fractions. *Results:* A total of 120 patients, with a median age of 73 at salvage re-irradiation, were included in the analysis. Among them, 83 patients (69%) had received curative radiotherapy initially, while 37 underwent radical prostatectomy. The median PSA levels at re-irradiation were 3.7 ng/ml (range=2.2-5.5 ng/ml), with 32 patients (27%) receiving concurrent hormone therapy. Disease staging was determined by PET choline scans in 90 patients (75%) and MRI in 105 patients (88%). Dosage varied with 30 patients receiving 25 Gy/5 fractions, 53 receiving 30 Gy/5 fractions, and 37



Median survival (95% CI)
1.3 (1.2,1.9)

BRFS rates at 1-year (95% CI)	BRFS rates at 2-years (95% CI)
68% (60%, 78%)	34% (26%, 46%)

Figure 1. *Biochemical recurrence-free survival of patients included in the study.*

receiving 35 Gy/7 fractions. Regarding patients initially treated with curative radiotherapy, 62 patients received partial prostate irradiation and 21 patients were re-irradiated in the entire prostate. Median gross tumor volume (GTV) was 17.2 cm^3 for prostate re-irradiation and 5.5 cm^3 for re-irradiation of the prostate bed. At a median follow-up of 4.7 years, the median time to biochemical recurrence (Figure 1) was 1.3 years (95% CI=1.2-1.9 years), with biochemical recurrence-free survival rates of 68% and 34% at 1 and 2 years, respectively. Among recurrences, 19 patients experienced both intraprostatic and metastatic relapse, 13 patients only had metastatic relapse, and 37 patients experienced local relapse. Of the intraprostatic relapses, 17, 26, and 13 were observed in the 25 Gy, 30 Gy, and 35 Gy groups, respectively. One Grade 2 acute genitourinary event was recorded. Regarding maximum toxicity post-treatment, three Grade ≥3 late gastrointestinal events (two resolved at the last follow-up) and twelve Grade ≥3 late genitourinary events (seven resolved at the last follow-up) were reported. *Conclusion:* Salvage re-irradiation for isolated local recurrence of PCa could be a viable treatment option, but careful patient selection is crucial. Future investigations should focus on determining the optimal dosage and identifying ideal candidates for this personalized treatment approach.

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SHORT ADT + SBRT IMPROVES OUTCOMES IN OLIGORECURRENT HORMONE-SENSITIVE PCA: RESULT OF RADIOSA TRIAL

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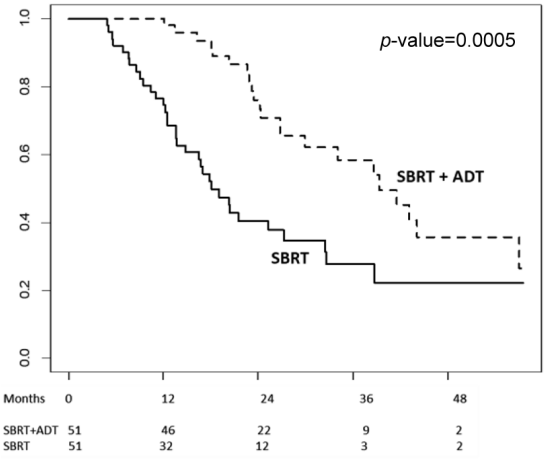
Background/Aim: The RADIOSA trial (1), a monocentric phase II randomized trial, investigated the role of metastasis-directed therapy (MDT) in oligorecurrent hormone-sensitive PCa patients. The aim of the study was to compare the addition of a short-course androgen deprivation therapy (ADT) to stereotactic body radiotherapy (SBRT) to all oligometastatic sites compared to standard SBRT alone in terms of clinical progression-free survival (CPFS). The purpose of the present project

Table I. *Patient characteristics*.

	Overall (n=102) n	SBRT only (n=51) n (%)	SBRT + ADT (n=51) n (%)
Initial T stage			
cT1c	2	1 (2)	1 (2)
cT2	3	-	3 (6)
cT3	1	-	1 (2)
pT2	34	16 (32)	18 (35)
pT3	61	34 (66)	27 (53)
Missing	1	-	1 (2)
Initial N stage			
N0/cN0	63	34 (67)	29 (57)
N1	19	11 (22)	9 (16)
NX	19	6 (12)	13 (26)
Missing	1	-	1 (2)
ISUP grade (primary tumor)			
1	4	1 (2)	3 (6)
2	23	11 (22)	12 (24)
3	37	16 (31)	21 (42)
4	23	12 (24)	11 (22)
5	14	11 (22)	3 (6)
Missing	1	-	1 (2)
Initial management			
Radical prostatectomy only	60	28 (55)	32 (63)
Radical prostatectomy ± adjuvant/salvage RT ± ADT	36	22 (43)	14 (27)
Curative RT ± ADT	6	1 (2)	5 (10)
Salvage treatment (n = 25)			
Salvage RT ± ADT	24	11 (22)	13 (25)
ADT only	1	-	1 (2)
Prior RT on pelvis			
Yes	24	13 (25)	11 (22)
No	78	38 (75)	40 (78)
	Median (IQR)	Median (IQR)	Median (IQR)
Initial PSA at diagnosis	8.18 (5.70; 12.47)	8.72 (5.64; 12.35)	7.48 (5.70; 13.46)
Missing	6	1	5

was to define the optimal management of bone or nodal PCa recurrences in SBRT regimen. *Materials and Methods:* Oligorecurrent PCa patients with up to 3 bone or lymph-node lesions were randomized 1:1 to receive SBRT alone (arm A) or SBRT + 6 months of ADT (arm B). Patients were stratified according to PSA doubling time (≤3 *vs*. >3 months), initial localization of metastases (node *vs*. bone) and diagnostic imaging [positron emission tomography (PET) *vs*. magnetic resonance imaging (MRI)]. The primary endpoint was to compare the CPFS, defined as the absence of new metastatic lesions (local, regional, or distant) between the two arms. Biochemical progression-free survival (BPFS), overall survival (OS), ADT-free survival, local control, treatment-induced acute and late toxicity, time to castration-resistant disease, and quality of life (QoL). For the statistical analysis, Wilcoxon rank-sum tests were used to assess any differences in baseline characteristics of patients among the two arms. Kaplan–Meyer analysis and Cox regression were performed to explore the association between prognostic factors and biochemical progression (BP) and CP. *Results*: Between September 2019 and April 2023, 102 patients were enrolled in the trial. Respectively, 51 and 51 patients were assigned to arms A and B. All patients included in the present analysis completed at least 6 months of follow-up to reach the primary endpoint. Baseline population characteristics were balanced between the two arms (Table I). BP was reported as the first event in 66 patients with a median follow-up of 31 months (IQR=12-39), [40 (60%) enrolled in ARM A *vs*. 26 (40%) in ARM B, respectively]. The median PSA reported at BP was 2.36 ng/ml (IQR=1.31-5.38). Radiological progression was reported as the first CPFS event in 56 patients: 34 (66%) patients enrolled in ARM A and 22 (34%) in ARM B, respectively.

a



b

		clinical recurrence			
		HR B vs A	*Low 95%CI*	*Up 95%CI*	*p-value*
PSA at diagnosis (ng/ml)	≤8	0.42	0.19	0.92	0.029
	>8	0.40	0.18	0.86	0.019
ISUP score	1-3	0.42	0.21	0.83	0.012
	4-5	0.32	0.12	0.89	0.028
N stage at diagnosis	1	0.58	0.17	1.95	0.381
	x	0.78	0.19	3.30	0.737
	0	0.28	0.13	0.60	0.001
Previous RT on the pelvis	Yes	0.18	0.05	0.59	0.005
	No	0.48	0.26	0.91	0.024
PSA at enrollment (ng/ml)	>2	0.30	0.15	0.62	0.001
	0-2	0.49	0.22	1.13	0.096
Type of metastases at enrollment	Bone	0.36	0.15	0.85	0.020
	Lymph	0.43	0.21	0.88	0.021
Site of metastases at enrollment	M1a	0.81	0.27	2.44	0.702
	M1b	0.36	0.15	0.85	0.020
	N1	0.28	0.11	0.72	0.008
Number of metastases	2 or 3	0.25	0.09	0.68	0.006
	1	0.44	0.22	0.88	0.020
Time from first treatment to RT (months)	>43	0.48	0.20	1.15	0.099
	≤43	0.32	0.16	0.64	0.001
Time from last active treatment to RT (months)	>37	0.55	0.24	1.26	0.154
	≤37	0.29	0.14	0.60	0.001

Figure 1. *(a) Kaplan-Meier estimates of the clinical progression-free survival according to treatment arm. (b) Survival analysis of clinical relapse in patients according to main variables.*

Addition of ADT significantly improved CPFS, with a Hazard Ratio in favor of the ADT + SBRT arm B (p<0.0005) (Figure 1a). Median time to CP was 15 months for arm A and 33 months for arm B (SBRT + ADT). ARM of treatment was found to be significantly associated with CPFS, and the result is confirmed also at multivariate analysis. PSA at diagnosis and PSA pre-RT were also found to be associated with CPFS. Survival analysis of CP dividing patients according to the main factors is shown in Figure 1b. The additional advantage of the combined treatment results is evident for all the subgroups of patients, with the exception of the following subgroups: N stage at diagnosis=1, time from first treatment to RT <43 months, site of metastases M1a. The second-line treatment for patients who experienced radiological progression (29 oligo-progression *vs*. 15 poli-progression) was ADT alone, SBRT to metastatic sites alone, and SBRT+ADT in 19, 16, and 9 patients respectively. OS was 98% (2 patients died from non-PCa-related causes). An additional evaluation of testosterone was assessed to compare levels at baseline (Table I) and at 1 year after SBRT for the two arms. Testosterone levels at 1 year were 4.2 ng/ml (IQR=3.0-4.9) and 3.8 ng/ml (IQR=2.1-5.5) for ARM A and ARM B, respectively [data available for 43 patients (ARM A) and 43 patients (ARM B)]. No difference was found between the two arms, confirming a complete testosterone recovery even after a short course of ADT. No significant toxicities related to SBRT were reported. A separate analysis of patients reported that outcomes on QoL is ongoing. *Conclusion*: The RADIOSA trial showed a significant improvement in terms of CP rate in the ADT + SBRT ARM suggesting a clinical advantage for the treatment combination for oligorecurrent hormone-sensitive PCa patients. Considering that almost all ARM B patients achieved testosterone recovery at one year, these results support the safety and effectiveness of adding a short-course (6 months) ADT to SBRT. Longer FU data will provide clearer indication about the safety and effectiveness of such approach. Molecular analyses of biological samples collected within the trial are ongoing, and will hopefully help to identify a genomic signature to be integrated with next-generation imaging allowing for a more refined oligometastatic patients stratification and treatment personalization.

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IMPACT OF COMORBIDITIES ON ULTRA-HYPOFRACTIONATED RADIOTHERAPY TOXICITY PROFILES IN LOCALIZED PROSTATE CANCER: A REAL-WORLD EXPERIENCE

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Background/Aim: Patients with a high number of comorbidities frequently are overlooked for ultra-hypofractionated radiotherapy (UHRT), potentially depriving them of a curative alternative, even though clinical trials have demonstrated that UHRT is not inferior to standard RT in treating localized prostate cancer (PCa). The current study aimed to assess the impact of pre-treatment Charlson Comorbidity Index (CCI) on acute and late RT-related side-effects, as well as the toxicity profiles of a real-world cohort of PCa patients who underwent curative UHRT±simultaneous integrated boost (SIB) on dominant intraprostatic lesion (DIL)±androgen deprivation therapy (ADT). *Patients and Methods*: Patients with localized PCa treated with radical UHRT at a single institute were retrospectively studied. Risk categorization followed National Comprehensive Cancer Network (NCCN) guidelines and baseline age-adjusted CCI was calculated. Maximum gastrointestinal (GI)/genitourinary (GU) acute and late toxicities were assessed *via* the Radiation Therapy Oncology Group (RTOG) scale. Patients were categorized into 5 CCI subgroups and their impact analyzed *via* the Chi-square test. *Results:* From 2012 to 2021, 890 patients met the inclusion criteria. Median age at diagnosis was 76 years (IQR=72-79) with a median initial Prostate Specific Antigen (iPSA) of 7.4 ng/ml (IQR=5.2-10.4). The most common risk class was unfavorable intermediate (327, 37.4%), then favorable intermediate (202, 23.1%), low (188, 21.5%), and high/very high (156, 17.9%). A total of 364 patients (41%) received ADT for a median of 8 months (IQR=6-12). All patients received UHRT on prostate in 5fx on alternate days, with a dose/fraction within 6.5-7.25 Gy±SIB on DIL with a dose within 37.5-40 Gy. Median prostate clinical target volume (CTV) was 60cc (IQR=46-77.15). Median follow-up was 2.48 years (IQR=1.48-3.45). Median baseline CCI score was 4 (IQR 3-5). Diabetes mellitus (14.6%), localized second malignancy (12.9%) and heart failure/myocardial infarction (7.0%) were the most frequent comorbidities. Acute toxicities included 122 (13.7%) G≥2 GU and 43 (4.8%) G≥2 GI events. Larger prostate CTVs were significantly linked to acute GU toxicities ($p<0.05$). Data on maximum late toxicities were available for 565 patients (63.5%), with 53 (9%) experiencing late G≥2 GU toxicities and 25 (3.4%) experiencing G≥2 GI toxicities. Significant correlation was found between acute and maximum late toxicities ($p<0.05$). Toxicity details by CCI-score are shown in Table I, where a significant relationship was observed between higher CCI and higher late GI toxicity ($p<0.05$), but not for late GU toxicity. *Conclusion:* UHRT is a safe and effective treatment, showing excellent GI/GU toxicity profiles. CCI scores have shown low impact on toxicities, thus, UHRT should be proposed as a treatment option independently from patient's comorbidities.

Table I. *Maximum late GU/GI toxicity according to CCI group.*

Late maximum GU Toxicity				
CCI group	G0	G1	G2	G3
1-2	45	22	4	0
3	116	44	19	3
4	119	35	14	1
5-6-7	87	34	8	1
8-9-10-11	7	1	3	0
Late maximum GI Toxicity				
CCI group	G0	G1	G2	G3
1-2	59	10	2	0
3	158	17	4	2
4	152	10	6	1
5-6-7	112	12	4	1
8-9-10-11	10	0	0	5

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PSMA-PET/CT AND WHOLE-BODY MRI FOR STAGING AND RESTAGING OF PROSTATE CANCER PATIENTS

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Background/Aim: Prostate specific membrane antigen – positron emission tomography (PSMA-PET) and whole-body magnetic resonance imaging (wbMRI) are accurate techniques for local prostate cancer (PCa) staging and identification of distant bone, lymph node, and visceral metastases. Despite wbMRI efficacy, a lack of robust recommendations for its integration into routine clinical practice still exists. This study aimed to compare the diagnostic performance of PSMA-PET and wbMRI in detecting PCa localizations in two patient groups: those with high-risk PCa (staging level) eligible for radical treatment and those experiencing biochemical recurrence (BCR) following radical therapies. *Patients and Methods*: This was a prospective single-center study enrolling PCa patients undergoing both PSMA-PET and wbMRI within a 2-month timeframe for staging or BCR. No PCa treatments were allowed between PSMA-PET and wbMRI. Independent readers reviewed the images: 2 nuclear medicine physicians for PET images and 2 radiologists for wbMRI. The concordance of both techniques in assessing local or residual disease (T/Tr), local (N) and distant (M1a) lymph node, bone (M1b) and visceral (M1c) metastasis was evaluated using the Cohen's kappa coefficient. In patients subsequently treated with radical prostatectomy (RP), sensibility, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of PSMA-PET and wbMRI were compared, using histopathology as a gold standard. *Results*: A total of 62 patients were enrolled (median age=70 years): 41/62 (66%) newly diagnosed PCa and 21/62 (34%) BCR. PSMA-PET and wbMRI were performed within a median time-frame of 18 days (IQR=8-29). Overall, PSMA-PET was positive for PCa in 46/62 (74%) patients and wbMRI in 46/62 (74%). PSMA-PET up-staged and down-staged results in 5% (3/62) and in 5% (3/62) patients respectively when compared to wbMRI. The concordance between PSMA-PET and wbMRI for T/Tr, N, M1a, and M1b was 0.84, 0.88, 0.86 and 0.44, respectively (Cohen's kappa). Among the staging cohort, 23/41 (56%) patients underwent subsequent RP. In those patients, PSMA-PET and wbMRI sensitivity for local disease (T) was 96% *vs*. 100% while PPV 100% *vs*. 100%. Furthermore, for pelvic node involvement (N) sensitivity was 44% *vs*. 44%, specificity 100% *vs*. 93%, PPV 100% *vs*. 80%, NPV 74% *vs*. 72% and accuracy 78% *vs*. 74%. *Conclusion*: Although based on a limited sample size, both PSMA-PET and wbMRI demonstrated high agreement in detecting local disease (T and N) and distant lymph node involvement (M1a), while a partial agreement was observed for bone disease. Notably, wbMRI outperformed PSMA-PET for local disease detection, whereas PSMA-PET was superior in nodal metastasis detection showing high specificity, PPV, NPV, and accuracy.

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THE ROLE OF METASTASIS-DIRECTED THERAPY IN THE JOURNEY OF OLIGOMETASTATIC PROSTATE CANCER PATIENTS

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Aim: This study aimed to assess the trajectories of metachronous hormone-sensitive prostate cancer (omHSPCa) patients, concentrating on how various clinical factors affect oncological outcomes – clinical progression-free survival (CPFS) after the first metastasis directed therapy (MDT) treatment, castration resistance-free survival (CRFS), and free survival to polimetastatic state (PMFS). *Patients and Methods*: The study involved patients diagnosed with metachronous omHSPCa, having ≤5 metastases, who underwent MDT by stereotactic body radiation therapy (SBRT) from 2014 to 2022 at the European Institute of Oncology, Milan, Italy. Kruskal-Wallis test, Kaplan-Meier survival curves, and log-rank analyses were used. Univariate Cox regression analyses were performed, and significant features were incorporated into the multivariate Cox regression. Process mining analysis was executed using the pMineR and pMinShiny libraries. *Results*: The study included 248 patients with a median age at primary diagnosis of 64 years [IQR=58-68 years]. Median follow-up was 8.0 years [IQR=5.3-11.9 years], and the median time to first clinical recurrence from the treatment of the primary tumor was 4.24 years [IQR=2.18–7.44 years]. A total of 469

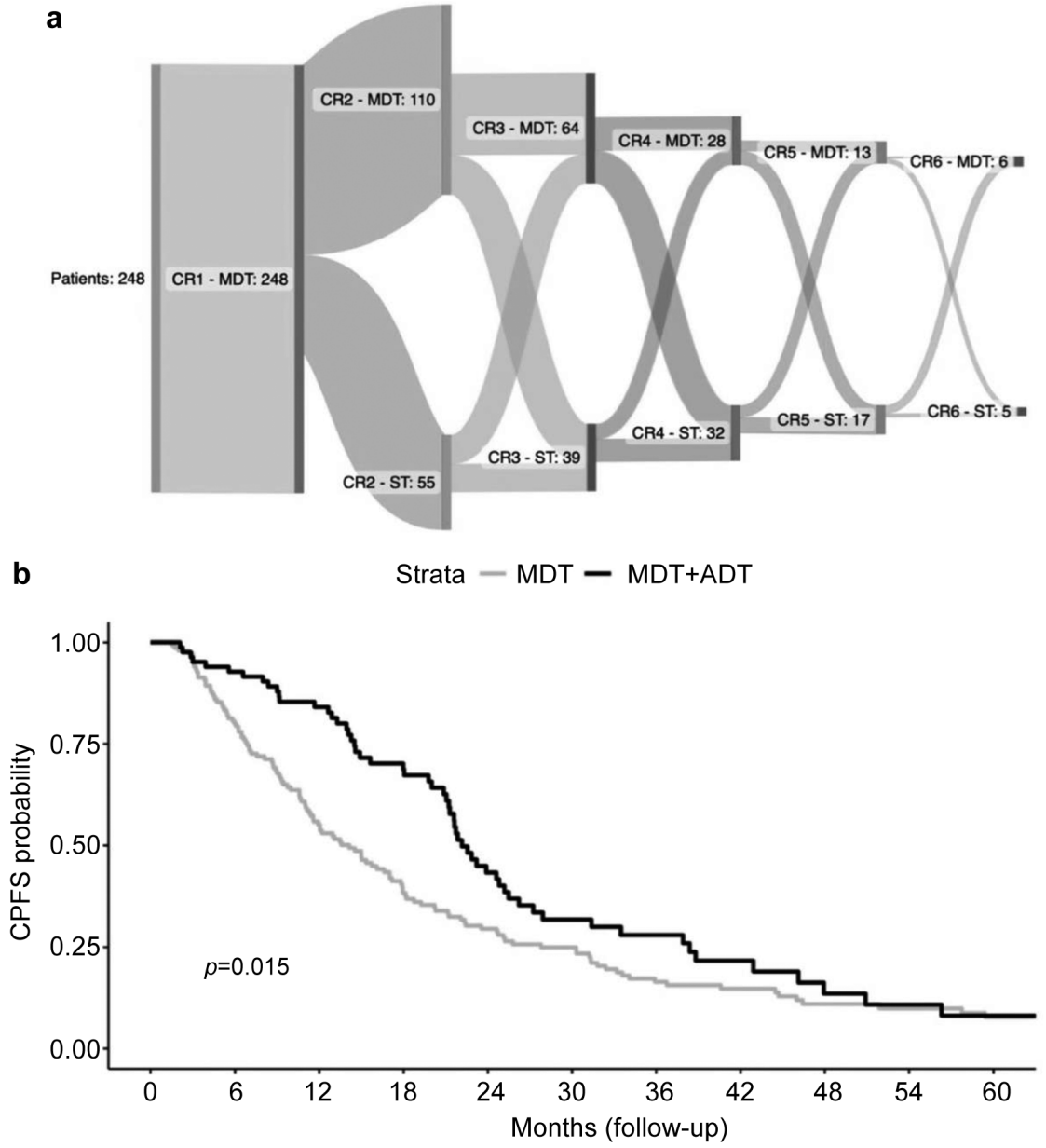

Figure 1. *(a) Sankey plot of the adopted treatment for each CR. (b) Kaplan-Meier analysis of CPFS after first MDT, stratified for patients receiving MDT+ADT versus MDT only. CR: Clinical relapse; sT: Systemic therapy; MDT: metastasis directed therapy; CPFS: clinical progression free survival.*

MDTs were assessed. Specifically, 54% (135 patients) underwent more than one course of MDT (Figure 1a). CPFS median time was 22.1 (95% CI=21.2-26.2) months for patients receiving concurrent androgen deprivation therapy (ADT) and 14.1 (95% CI=11.4-17.8) months for those who did not (p<0.05) (Figure 1b). A total of 60 events were assessed in CRFS analysis, with a median time of 18.7 years. Multivariate Cox analysis identified N1 at primary diagnosis (HR=2.04, 95% CI=1.08-3.86, p=0.03), ISUP4-5 (HR=1.95, 95% CI=1.12-3.38, p=0.02), and ADT usage of ≥2 years (HR=1.76, 95% CI=1.03-3.02, p=0.04) as independent CRFS predictors. PMFS analysis included 72 events with a median time of 17.7 years. Key PMFS predictors included ISUP4-5 (HR=2.34, 95% CI=1.43-3.84, p<0.01), M1b at first recurrence (HR=1.83, 95% CI=1.14-2.94, p=0.01), 4-5 lesions at first recurrence (HR=5.46, 95% CI=1.57-18.97, p<0.01), at least one course of MDT not addressed to all the lesions revealed at imaging (HR=2.70, 95% CI=1.58-4.61, p<0.01). *Conclusion*: The study underscores the comprehensive management of omHSPCa, from diagnosis to treatment outcomes. The findings emphasize the importance of personalized treatment strategies, the potential benefits of integrating ADT, and the critical role of

MDT. Additionally, the analyzed endpoints have significant economic implications. Delaying castration resistance could result in substantial cost savings while improving the patient's quality of life.

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THE ADVANCEMENT OF IMAGING MODALITIES IN OMHSPCA: A SHIFTING PARADIGM

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Aim: This study aimed to evaluate changes in clinical practice concerning the choice of imaging modality prior to metastasis-directed therapy (MDT) in oligometastatic hormone-sensitive prostate cancer (omHSPCa), using a historical cohort of patients. *Materials and Methods:* The study encompassed patients diagnosed with metachronous omHSPCa who had ≤5 metastases, undergoing radiotherapy (RT) MDT treatment between 2014 and 2022 at the European Institute of Oncology (IEO) in Milan, Italy. Statistical tests used included the Kruskal-Wallis and ANOVA tests. *Results:* A total of 248 patients and a total of 469 MDTs were included. Notably, 54% (135 patients) underwent more than one MDT course. Regarding imaging methodologies utilized to determine the indication for MDT at the first clinical recurrence, positron emission tomography with choline (PET Cho) was the predominant technique (111 treatments, 45%), followed by positron emission tomography with prostate-specific membrane antigen (PET PSMA) (92 treatments, 37%), whole-body magnetic resonance (WB RM) (39 treatments, 16%), and conventional imaging techniques (6 cases, 2.4%) were also adopted. No statistically significant difference was found in the average number of lesions detected by each imaging method (p=0.32) (Figure 1a). An evaluation of PSA levels at the time of imaging detection showed that WB RM was performed with an average PSA of 1.62 ng/ml and a median PSA of 1.06 ng/ml. PET PSMA showed an average PSA of 1.72 ng/ml and a median of 1.02 ng/ml. PET Cho had an average PSA of 3.61 ng/ml and a median of 2.22 ng/ml, while traditional imaging methods recorded an average PSA of 4.80 ng/ml with a median of 1.31 ng/ml. A subsequent Kruskal-Wallis analysis showed significant differences in the medians across these groups, with

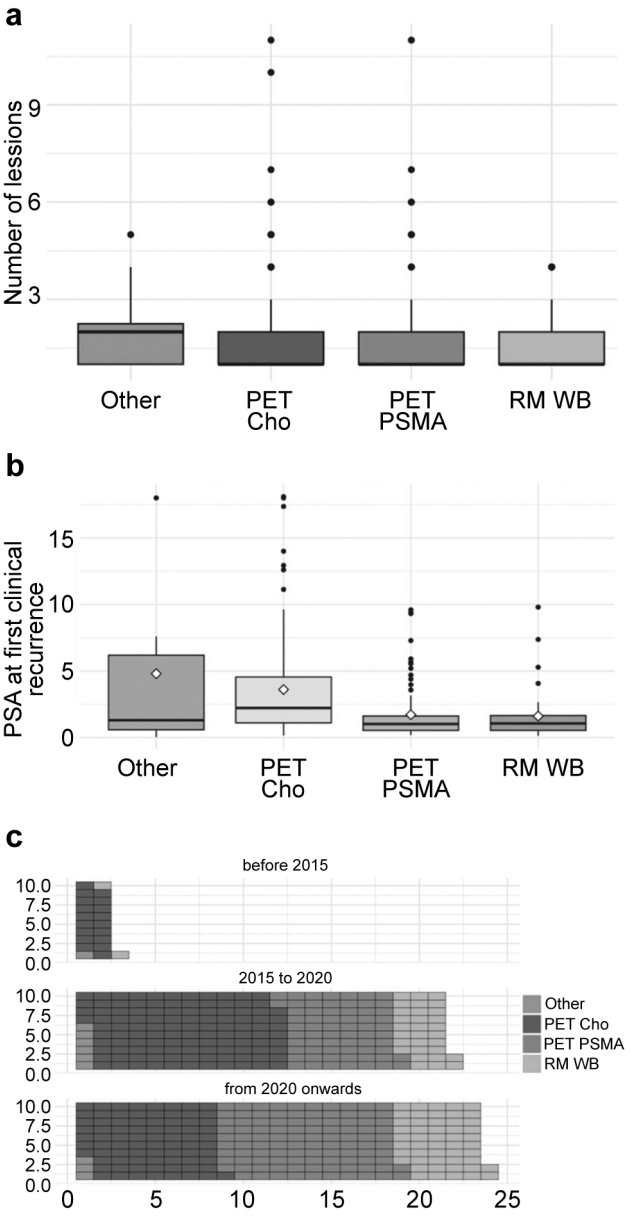

Figure 1. *(a) Number of lesions detected by each imaging methodology. (b) PSA at first clinical recurrence per each imaging methodology. (c) Temporal distribution of the adopted imaging methodology during time.*

$p<0.05$ (Figure 1b). Further analysis revealed shifts in preferred imaging methods for MDTs throughout the study period, segmented into three intervals: before 01/01/2015, between 01/01/2015 and 01/01/2020, and after 01/01/2020 (Figure 1c). *Conclusion*: The clear transition from conventional to new-generation imaging techniques with enhanced sensitivity highlights the evolving landscape of MDT, illustrating the strong correlation between imaging modality and PSA levels. The increased sensitivity of newer imaging methods has resulted in lower PSA levels at the time of detection, making them the preferred choice for directing MDT.

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UHRT IN PCA: A CLINICAL AND TOXICITY IMPACT ANALYSIS FROM REAL WORLD EXPERIENCE

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Background/Aim: Randomized clinical trials have demonstrated the non-inferiority of ultra-hypofractionated radiotherapy (UHRT) compared to conventional RT in patients with localized prostate cancer (PCa). Despite an increased cost-effectiveness and expanded RT access, UHRT adoption remains variable. Notwithstanding, patients with high percentage of comorbidities are not often considered candidates for this approach, thus denying a curative treatment option. The aim of the study was to evaluate the oncological outcomes and toxicity profiles of a real-world cohort of PCa patients who underwent curative UHRT +/– a simultaneous integrated boost (SIB) on dominant intraprostatic lesion(s) (DIL) +/– androgen deprivation therapy (ADT) and assess the influence of pre-treatment Charlson Comorbidity Index (CCI) on acute and late RT-related side-effects. *Patients and Methods:* Patients with localized PCa who underwent radical UHRT in a single Institute were retrospectively included. Risk groups were determined based on NCCN definitions. For all patients age adjusted CCI was calculated at baseline. After treatment, PSA was assessed every 3 months and biochemical progression (BP) was stated according to the Phoenix definition. Clinical progression (CP) was evaluated as the presence of local or distant metastasis at radiological imaging. Maximum acute and late gastrointestinal (GI) and genitourinary (GU) toxicity were collected according to the RTOG scale. The impact of CCI on the acute and late toxicities was explored. Patients were stratified according to CCI into 5 subgroups. Chi square test was performed to test any association among CCI and reported toxicities. All patients signed an informed consent and the study was approved by local Ethics Committee (UID 2684). *Results*: From 2012 to 2022, a total of 824 patients matched the inclusion criteria. General cohort characteristics are reported in Table I. Median age at diagnosis was 76 years (IQR=71-80 years) and median iPSA was 7.3 ng/ml (IQR=5.14-10.30 ng/ml). Patients were stratified according to risk classes (data available for 98.2% of the cohort) as follows: 353 (42.8%) as favorable intermediate, 177 (21.5%) as low, 135 (16.4%) as unfavorable intermediate and 144 (17.5%) as high/very high risk. Median baseline CCI score was 4 (range=1-1). Diabetes mellitus (14.6%) and localized second malignancy (12.9%) were the most frequent comorbidities, followed by heart failure/myocardial infarction (7.0%) and cerebrovascular disease (6.7%). All patients underwent UHRT in 5 fractions with a dose/fx between 6.25 and 7.25 Gy on alternate days. Median prostate CTV volume was 60 ml. A total of 310 (37.6%) patients received a simultaneous integrated boost (SIB) on dominant intraprostatic lesion (DIL) of 7.5/8 Gy. Overall, 322 patients (39.1%) underwent ADT, according to clinical staging and performance status, with a median duration time of 6 months (IQR=5-12, available for 237 patients). Median follow-up (FU), available for 709 (86%) patients, was 30 months (IQR=17-40) with a median PSA (available for 642 patients) of 0.56 ng/ml. A total of 77 patients (9.3%) experienced a BP, with a median time from RT treatment of 26 months (IQR=18-41). CP was observed in 63 patients (8.9%) with a median time from the end of RT of 26 months (IQR=18-41); 30.2% (19 patients) was shown to be unfavorable intermediate, 28.6% (18 patients) high/very-high risk, 25.4% (16 patients) favorable intermediate and 15.9% (10 patients) was shown to be low-risk group. Local recurrence was registered for 39.7% (25) of patients; the other reported CPs were 20.6% (13) lymph nodal, 34.9% (22) bone and 3.2% (2) visceral. At last FU [available for 726 patients (88%)], 14 (2%) patients died for other causes than PCa, 633 (87.2%) are alive with no evidence of disease and 79 (10.8%) are alive with disease. Considering maximum late toxicities [data available for 507 patients (61.5%)], 46 (9%) and 17 (3.4%) patients experienced late ≥G2 GU and GI toxicities, respectively. Toxicities according to CCI-score are reported in Table II. No significant association was found for CCI and both maximum late GI and GU toxicities. *Conclusion:* UHRT is a safe and effective treatment. Despite the high presence of comorbidities, these patients have excellent biochemical control and secure GI/GU toxicity profiles. Moreover, the CCI score showed no impact on reported toxicities, thus, UHRT should be proposed as a treatment option in this group of patients.

Table I. *General cohort characteristics and follow-up data.*

Characteristic	n (%)
Risk class	
Low	177 (21.5)
Favorable intermediate	353 (42.8)
Unfavorable intermediate	135 (16.4)
High	131 (15.9)
Very high	13 (1.6)
Missing	15 (1.8)
Hormone therapy	322 (39.1)
Low risk	32 (9.9)
Favorable intermediate	93 (28.9)
Unfavorable intermediate	67 (20.8)
High	113 (35.1)
Very high	12 (3.7)
Charlson Comorbidity Index	
1	22 (2.7)
2	80 (9.7)
3	260 (31.6)
4	251 (30.5)
5	128 (15.5)
6	41 (5.0)
7	25 (3.0)
8	10 (1.2)
9	5 (0.6)
10	0 (0.0)
11	2 (0.2)
Follow-up data	
Acute maximum GU toxicity	
G0	481 (58.4)
G1	284 (34.5)
G2	50 (6.1)
G3	4 (0.5)
G4	2 (0.2)
Missing	3 (0.4)
Acute maximum GI toxicity	
G0	741 (89.9)
G1	66 (8.0)
G2	13 (1.6)
Missing	4 (0.5)
Late maximum GU toxicity	
G0	326 (64.0)
G1	137 (26.9)
G2	41 (8.1)
G3	5 (1.0)
Late maximum GI toxicity	
G0	450 (88.6)
G1	41 (8.1)
G2	13 (2.6)
G3	4 (0.8)
Last follow-up status	
No evidence of disease (NED)	633 (87.2)
Alive whit disease (AWD)	79 (10.8)
Died for other causes	14 (2%)

GU: Genitourinary; GI: gastrointestinal.

Table II. *Late maximum toxicities according to CCI group.*

Late maximum GU

Charlson Comorbidity index group	Total	G0	G1	G2	G3	Missing
1-2	102	44	20	4	0	34
3	260	104	43	18	3	92
4	251	103	36	10	1	101
5-6-7	194	68	36	8	1	81
8-9-10-11	17	7	2	1	0	7

Late maximum gastro-intestinal (GI) toxicity

CCI group	Total	G0	G1	G2	G3	Missing
1-2	102	56	11	1	0	34
3	260	146	15	4	2	93
4	251	134	9	6	1	101
5-6-7	194	104	6	3	1	81
8-9-10-11	17	10	0	0	0	7

GU: Genitourinary; GI: gastrointestinal.

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LONG-TERM OUTCOMES OF PSMA PET/CT-GUIDED RADIOTHERAPY IN BIOCHEMICAL RECURRENCE PATIENTS POST-RADICAL PROSTATECTOMY: A 5-YEAR FOLLOW-UP ANALYSIS

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Background/Aim: Prostate-specific membrane antigen – positron emission tomography/ computed tomography (PSMA-PET/CT) imaging is increasingly used to guide salvage radiotherapy (s-RT), the main potentially curative option for biochemical recurrence (BCR) after radical prostatectomy (RP) in clinically localized prostate cancer (PCa). Our purpose was to evaluate the role of PSMA-PET/CT-guided salvage radiotherapy (sRT) in improving long-term BCR-free survival in these patients. *Patients and Methods:* We retrospectively screened 240 patients, with 100 meeting inclusion criteria: PSMA-PET/CT performed for biochemical persistence (PERS) or BCR after RP; ≥4 years of follow-up; PSMA-PET/CT-guided sRT; availability of PSA values and clinical data. All PSMA-PET/CT scans were

performed using [68Ga]Ga-PSMA-11. The study endpoint was BCR-free survival (PSA ≤0.2 ng/ml) after PSMA-PET/CT guided sRT. *Results:* Sixty-three percent of patients underwent PET-PSMA for BCR and thirty-seven for PERS. Fifteen patients had PSA pre-RT<0.5 while seventy-five had PSA pre-RT≥0.5. s-RT was performed according to EAU guidelines. PET-PSMA was positive in 52/100 cases. BCR patients were more often PET-negative or, if positive, exhibited a higher frequency of local recurrence (21%BCR *vs*. 8%PERS); with 65%receiving RT as the only treatment. PERS patients were more often PSMA PET positive with nodal involvement (54%PERS *vs*. 21%BCR; *p*<0,001). Patients with PERS received RT and androgen deprivation treatment in 21/37 cases (57%). The hazard ratio (HR) of RT-treatment failure between patients with PSA pre-RT ≥0.5 and patients with PSA pre-RT<0.5 was statistically significant (2.2; *p*<0.039). The overall median time of follow-up was 59 months (IQR=51-67 months) and the median PSA at last follow-up was 0.01 ng/ml (IQR=0.01-0.1ng/ml). We assessed a RT-treatment failure in 36/100 patients (36%) with a median time from RT of 33 months (IQR=18-47 months) without statistically significant differences between BCR and PERS (38%BCR *vs*. 32%PERS); all of them underwent a second PSMA PET/CT. Among all patients who had RT-treatment failure, 23/36 (64%) were PET positive and 14/36 (39%) received a new PSMA PET/CT-based RT. All patients were alive at the last examination. *Conclusion*: PSMA PET/CT-guided radiotherapy demonstrates significant long-term efficacy in patients experiencing BCR or persistence post-RP, eliciting a substantial PSA response over time and serving as a valuable tool in treatment management.

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UTILITY OF MPMRI AND PHI IN DETECTION OF PROSTATE CANCER IN ITALY: A DECISION ANALYTIC MODELING

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Background/Aim: Research indicates that Prostate Health Index PHI can be used alongside imaging technologies to increase diagnostic accuracy (1). This analysis aimed to determine the clinical consequences of different diagnostic strategies, including multiparametric magnetic resonance imaging (mp-MRI) and phi test for diagnosing prostate cancer (PCa) in Italy. *Materials and Methods*: A decision analytical model using a decision tree was developed and validated thanks to 12 Subject Matter Experts (Laboratory, Radiology, Urology, Oncology Specialties). The population included men with PSA >2 – <10 with suspicious or negative digital rectal examination (DRE). Three diagnostic strategies and two phi cut-offs were considered. Positive results of mp-MRI or phi were confirmed by prostate biopsy. Model inputs were obtained from peer-reviewed literature. Outcomes included the numbers of diagnosed and missed overall PCa and clinically significant PCa (csPCa, Gleason Grade ≥7). Analysis was limited to the diagnostic phase of the patient pathway; further diagnostics and treatment of PCa were not considered. *Results*: At phi cut-off=25 mp-MRI followed by phi gave the best clinical outcome results identifying the higher number of PCa (46) and all csPCa, requiring, however, 38 unnecessary biopsies (defined as biopsies performed but no PCa present). At phi cut-off=28 the same performances were obtained: 45 PCa and 19 csPCa were identified, requiring 33 unnecessary biopsies. In both cases mpMRI alone missed 10 and 9 PCa and one csPCa. Other details are represented in Table I. *Conclusion*: A PCa diagnostic strategy of mpMRI followed by phi provides the largest clinical benefit in the Italian healthcare system.

Table I. *Clinical outcomes (per 100 population) by diagnostic strategy.*

	No. of PCa identified	No. of csPCa identified	No. of unnecessary biopsies
PHI cut-off 25			
mp-MRI alone	36	18 of 19	14
mp-MRI followed by PHI	46	19 of 19	38
PHI followed by mp-MRI	32	16 of 19	9
PHI cut-off 28			
mp-MRI alone	36	18 of 19	14
mp-MRI followed by PHI	45	19 of 19	33
PHI followed by mp-MRI	29	13 of 19	8

PCa: Prostate cancer; csPCa: clinically significant PCa; PHI: Prostate Health Index; mp-MRI: multiparametric magnetic resonance imaging.

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FEASIBILITY AND DIAGNOSTIC PERFORMANCE OF PSMA-PET-GUIDED PROSTATE BIOPSY IN PI-RADS SCORES 2-3: PRELIMINARY RESULTS FROM A PROSPECTIVE SINGLE-CENTER STUDY

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Background/Aim: Multiparametric MRI (mpMRI) is used as a guide for prostate biopsy. However, in some cases, clinically significant prostate cancer (csPCa) is not identified by MRI. The aim of the study was to determine the feasibility and diagnostic performance of transperineal prostate biopsy guided by prostate specific membrane antigen-positron emission tomography/computered tomography-ultrasound (PSMA-PET/CT-US) fusion in patients with PI-RADS score 2-3 on mpMRI. *Patients and Methods*: This was a prospective single-center study enrolling patients with serum PSA ≥4 ng/ml, PSA density (dPSA) ≥0,1 and mpMRI PI-RADS 2-3. 68Ga-PSMA-11 PET/CT images were acquired both 60-and-90-minutes post-injection. Prostate contours on CT and PSMA-positive lesions (ROIs) were manually delineated. Transperineal prostate biopsy was performed *via* real-time PET/CT-US fusion (Esaote Urofusion, Bologna, Italy). Biopsy cores were obtained from PSMA-positive regions of interest (at least 3 cores) and systematically. Intra-prostatic PSMA activity was assessed using the PRIMARY score. A PRIMARYscore ≥3 was evaluated as positive and delineated. *Results*: A total of 22 patients were enrolled (mean age=65 years). At the time of the scan the median PSA was 14 ng/ml and median dPSA was 0.24. A total of 19/22 (86%) patients had PI-RADS2 lesions while 3/22 (14%) had PI-RADS3. PSMA-PET and biopsy were performed within a median timeframe of 27 days (IQR=1-70 days). A total of 12/22 (55%) patients had a PRIMARYscore ≥3 and underwent transperineal PET-guided biopsies in addition to systematic biopsies, while 10/22 (45%) were PRIMARY 1-2 and underwent only systematic biopsies. Recorded PRIMARY scores were: score 1-2 in 10/22 patients (none positive for csPCa); score 3 in 5/22 (40% csPCa), score 4 in 4/22 (75% csPCa) and score 5 in 3/22 (100% csPCa). A total of 6/22 (36%) patients showed positive PET-guided biopsies for csPCa. Lesions' median SUV_{max} (PRIMARY score ≥3) was 7.9 (IQR=3-42.5) 60 min post-injection and 8.2 (IQR=4-45.9) 90 min post-injection. Through combination of systematic biopsies and PET-fusion biopsies we had 12/22 PCa detected by biospy; 8/22 (36%) patients had a csPCa (3 ISUP2, 3 ISUP3, 1 ISUP4, 1 ISUP5), while 4/22 was ISUP 1 (18%). PET-fusion only biopsy sensitivity, PPV and accuracy for csPCa were 85% (95% CI=65-96%), 37% (95%CI=33-41%) and 34% (95% CI=23-47%), respectively. Considering both PET-fusion and systematic biopsies, sensitivity, specificity, NPV, PPV and accuracy for csPCa were 85% (95%CI 65-96%), 86% (95% CI=81-90%), 98% (95% CI=96-100%), 37% (95% CI=29-45%) and 86% (95%CI 81-89%), respectively. *Conclusion*: Transperineal PSMA-PET-guided biopsy is feasible. Our preliminary results suggest that adding PSMA-PET-guidance to systematic biopsies in patients suspicious of PCa and PIRADS 2-3 on mpMRI increased csPCa detection will augment diagnostic accuracy.

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OPTIMIZATION OF PSA DENSITY THRESHOLD THROUGH AUTOMATED PROSTATE VOLUME SEGMENTATION WITH DEEP LEARNING FOR THE DIAGNOSIS OF CLINICALLY SIGNIFICANT PROSTATE CANCER

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Aim: To determine the optimal threshold for prostate-specific antigen density (PSAd) using an automated prostate volume measurement obtained through a deep learning (DL) algorithm from T2-weighted MRI (T2W MRI) images, and to evaluate the value of PSAd in combination with other predictors of clinically significant prostate cancer (csPCa). *Patients and Methods*: This was a retrospective multicenter study including patients who underwent MRI before biopsy. Clinically significant prostate cancer (csPCa) was defined as prostate cancer with an ISUP grade group=2 (Gleason=3+4). A DL algorithm based on a 3D U-Net architecture was trained and applied to T2W MRI for the automatic estimation of prostate volume, and evaluated using the Dice Similarity Coefficient (DSC) by comparing it with manual

segmentation by three specialist radiologists. *Results*: A total of 279 patients with a mean age of 65.5±8.0 years were included. The DL algorithm demonstrated a reproducibility of 0.86 (DSC). PSAd values ranged between 0.02 and 2.36 ng/ml/cm^3. The threshold of 0.10 ng/ml/cm^3 showed the best balance between sensitivity (0.66) and specificity (0.64) on an external test set of 86 subjects. Considering the patient's age, the optimal thresholds were 0.11 ng/ml/cm^3 (PSAd) and 67 years, with a sensitivity of 0.84 without a reduction in specificity. *Conclusion:* The results indicate that it is possible to obtain a calibrated PSAd threshold on prostate volumes, automatically through a DL algorithm applied to T2W MRI, and that this threshold can be further optimized by considering patient age. The inclusion of radiomic features extracted from MRI images could further improve optimization.

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