




Baseline PSMA tumor volume as a prognostic marker in radical radiotherapy for prostate cancer: a propensity score-weighted retrospective analysis

Francesco Lanfranchi¹ · Liliana Belgioia^{2,3} · Daniele Vita² · Jacopo Passoni² · Sara Mastrogiovanni² · Alessandra Catanoso² · Luca Sofia² · Valentina Pau³ · Stefano Raffa³ · Silvia Chiola³ · Maria Isabella Donegani³ · Roberta Piva³ · Mattia Riondato³ · Michela Marcenaro³ · Giorgia Timon³ · Cecilia Marini^{3,4} · Salvina Barra³ · Gianmario Sambuceti^{2,3} · Matteo Bauckneht^{2,3} 

Received: 3 August 2025 / Accepted: 1 October 2025
© The Author(s) 2025

Abstract

Objective Next-generation imaging with prostate-specific membrane-antigen Positron Emission Tomography/Computed Tomography (PSMA PET/CT) has emerged as an imaging modality offering high diagnostic accuracy and prognostic biomarkers in the primary staging of prostate cancer (PCa). Among these, PSMA-positive tumor volume (PSMA-TV) may carry prognostic significance but has been poorly investigated in patients receiving radical-intent radiotherapy (RT).

Methods Patients with biopsy-proven unfavorable intermediate-to-high-risk PCa staged as non-metastatic (T1-4 N0-1 M0) at [⁶⁸Ga]PSMA-11 or [¹⁸F]PSMA-1007 PET/CT before definitive RT plus androgen deprivation therapy (ADT) at our Institution (2019–2024) were retrospectively recruited. Following RECIP criteria, semi-quantitative PET parameters extracted were: maximum and mean standardized uptake value (SUVmax and SUVmean), PSMA-TV, and total lesion PSMA uptake (PSMA-TL) [PSMA-TV*SUVmean]. We assessed the association between PET-derived semi-quantitative parameters and clinical outcomes, including time to treatment failure (TTF) and PSA response. Inverse probability of treatment weighting (IPTW) was adopted to address confounders, namely, initial PSA, ISUP score, T stage, and N stage.

Results Among 145 patients recruited, median age was 76 years and median initial PSA 8.9 ng/mL. Most patients had ISUP grade ≥ 3 (39.3%), and 28.3% presented with nodal involvement at staging. Concurrent androgen deprivation therapy was administered in all patients, and the most common duration was 12–24 months (60.7%). The median follow-up was 20.5 months. While unadjusted analyses showed no significant association between PET parameters and treatment outcomes, IPTW-adjusted survival analysis revealed that high PSMA-TV was significantly associated with shorter TTF ($p < 0.05$). Other PET-derived metrics were not predictive of outcomes.

Conclusion Our findings highlight PSMA-TV as an independent predictor of treatment failure following definitive RT in PCa, supporting its potential role as a risk-stratifying biomarker, paving the way for individualized therapeutic strategies. Prospective validation is warranted to confirm its clinical utility and guide future radiotherapy personalization.

Keywords Prostate cancer · Prostate-specific membrane-antigen · Positron emission tomography · PSMA-tumor volume · Radiotherapy

✉ Matteo Bauckneht
matteo.bauckneht@unige.it

- ¹ Department of Experimental Medicine (DIMES), University of Genova, Genoa, Italy
- ² Department of Health Sciences (DISSAL), University of Genova, 16132 Genoa, Italy
- ³ IRCCS Ospedale Policlinico San Martino, Genoa, Italy
- ⁴ Institute of Bioimaging and Complex Biological Systems, National Research Council (CNR), Milan, Italy

Introduction

Radiation therapy (RT) with or without androgen deprivation therapy (ADT) is a standard approach for the radical treatment of patients with non-metastatic (M0) prostate cancer (PCa) [1]. However, the growing diffusion of next-generation imaging techniques has shown how the definition of M0 patients relies on the diagnostic modalities adopted. In particular, Prostate-Specific Membrane Antigen (PSMA)

Positron Emission Tomography/Computed Tomography (PET/CT) showed a higher accuracy in the clinical definition of the stage of disease with respect to conventional imaging [2–4].

Beyond its superior diagnostic performance, PSMA PET/CT also offers quantitative imaging biomarkers that may carry prognostic significance. Recent multicenter studies have demonstrated that total PSMA-positive tumor volume (PSMA-TV), a measure of disease burden derived from PET/CT, is associated with overall survival in patients with PCa, including those undergoing initial staging [5, 6]. Nevertheless, these studies did not include stratified analyses based on the definitive treatment received, and data on the prognostic utility of PSMA PET/CT-derived parameters in patients undergoing radical-intent radiotherapy remain lacking.

In this context, our study aimed to investigate whether semi-quantitative parameters obtained from pre-treatment PSMA PET/CT could provide independent prognostic information in patients with newly diagnosed PCa treated with radical-intent RT. By evaluating the association between PSMA-TV and time to treatment failure, we sought to explore its potential role as a risk-stratifying biomarker to guide personalized therapeutic strategies.

Materials and methods

Study design and patient population

Patients with biopsy-proven unfavorable intermediate-to-high-risk PCa submitted to PSMA PET/CT at the most six months before definitive radiotherapy, with or without ADT, at IRCCS Ospedale Policlinico San Martino (Genoa, Italy) between 2019 and 2024 were retrospectively recruited. Inclusion criteria were: i) biopsy-proven new diagnosis of unfavorable intermediate-to-high-risk PCa; ii) staging with PSMA PET/CT with either [⁶⁸Ga]Ga-PSMA-11 or [¹⁸F]F-PSMA-1007 staging; iii) PSMA PET/CT clinical stage T1-4, N0-N2 (N+), M0; iv) radical treatment with radiation therapy with or without ADT. Patients with age < 18 years, PCa with non-adenocarcinoma histology, and metastatic disease (M1a, M1b, or M1c) at staging PSMA PET/CT were excluded.

The Local Ethics Committee (Regione Liguria Ethical Committee, registration number 5/2023–DB id 12,914, date of approval 19-Jun-2023) approved the study. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Due to the study's retrospective design, informed consent was waived from the Ethical Committee.

PSMA PET/CT imaging acquisition

For study enrollment, patients submitted to PSMA PET/CT with either [⁶⁸Ga]Ga-PSMA-11 or [¹⁸F]F-PSMA-1007 were considered. [⁶⁸Ga]Ga-PSMA-11 and [¹⁸F]F-PSMA-1007 PET/CT scans were acquired about 60 and 90 min after the tracer administration, according to the current guidelines [7].

PSMA PET/CT hybrid scans were acquired using either Siemens Biograph MCT Flow (matrix size 200 × 200, PSF-TOF reconstruction with 3 iterations and 21 subsets) or GE Healthcare Omni Legend (matrix size 256 × 256, VUE Point HD iterative reconstruction with 4 iterations and 8 subsets).

PSMA PET/CT image analysis

All PET/CT images were visually assessed and semiquantitatively analyzed by a nuclear medicine physician with more than 10 years of experience (MB) according to the current reporting guidelines [8]. For visual analysis, areas presenting a focal uptake higher than the background were reported as suspected of malignancy. Images were evaluated for the detection of the primary tumor, locoregional and extra-pelvic lymph nodes, and bone and visceral metastases. The issue of Unspecific Bone Uptakes (UBU), frequently occurring in [¹⁸F]F-PSMA-1007 scans [9], was addressed using the BUMP score [10], based on lesions' SUVmax and mean Hounsfield unit at co-registered CT images. The following semi-quantitative PET parameters were extracted using the LIFEx software version 7.8.0 [11]: maximum and mean standardized uptake value (SUVmax and SUVmean, respectively) of the dominant intraprostatic lesion, total PSMA-positive tumor volume (PSMA-TV), and total lesion PSMA uptake (PSMA-TL, calculated as the product between PSMA-TV and SUVmean). Semiquantitative parameters were calculated with a variable SUVmax threshold based on the background uptake (liver for [⁶⁸Ga]Ga-PSMA-11 and spleen for [¹⁸F]F-PSMA-1007) as per RECIP criteria [12]. Semi-automatic analysis was visually verified by a nuclear medicine physician with high experience. To avoid the inclusion of prostate areas with parapsychological uptake, only regions defined as PRIMARY score of at least 3 were segmented [13]. Supplementary Fig. 1 shows an example of prostate gland segmentation.

Clinical and treatment data

The clinical variables collected for analysis included: initial PSA level (ng/mL), ISUP grade group, T stage, N stage, and concurrent ADT.

After imaging, all patients received RT in accordance with international clinical guidelines for the management

of unfavorable intermediate-to-high-risk PCa. RT was delivered using advanced techniques, either volumetric modulated arc therapy (VMAT) with linear accelerator (LINAC) or helical intensity-modulated radiotherapy (IMRT) by helical tomotherapy. All patients underwent hypofractionated RT schedules, prescribed according to institutional protocols and under the supervision of a board-certified radiation oncologist with expertise in PCa management.

Data analysis

Continuous and categorical characteristics are presented as median (interquartile range [IQR]) and as absolute frequency (percentage), respectively. The PET parameters were binarized according to median values to define “low” and “high” groups. The following endpoints were assessed: PSA response, defined as a reduction of PSA levels of at least 50% (PSA50) or 90% (PSA90) compared to pre-treatment values; PSA relapse, defined as a post-radiotherapy increase of ≥ 2 ng/mL above the nadir (Phoenix criteria); Time to Treatment Failure (TTF), defined as the interval from radiotherapy to either biochemical, radiological, clinical progression, initiation of a new treatment, or death. Time to event was calculated in months from the date of radiotherapy.

Statistical analysis

The inverse probability of treatment weighting (IPTW) approach was used to address confounding. Binary logistic regression was used to compute propensity scores, with the following parameters as covariates: initial PSA, ISUP score, T stage, and N stage. Covariate balance before and after weighting was assessed by calculating standardized mean differences (SMDs) for each confounder included in the propensity score model. SMDs below 0.1 after weighting were considered indicative of adequate balance. A covariate balance plot (Love plot) comparing pre- and post-weighting SMDs was performed. IPTW was applied using both stabilized and trimmed weights to control for baseline confounding while minimizing the influence of extreme propensity scores. Stabilized weights were used to reduce variance and improve estimate precision, whereas trimming excluded patients with extreme scores (below the 1st and above the 99th percentile) to enhance model robustness. Univariate and multivariate logistic regression analyses were performed to assess the association between PET parameters and PSA50 or PSA90 responses, and the accuracy in the prediction of these two endpoints was determined with Receiver-Operating Characteristic (ROC) analysis. Kaplan–Meier curves weighted by IPTW were generated for the binarized PET parameters, and log-rank tests were used to compare survival distributions. Univariate and multivariate Cox proportional hazards models were used to evaluate associations

between PET parameters, PSA relapse, and TTF. Model discrimination was assessed using Harrell’s C-index, and p values < 0.05 were considered statistically significant. All analyses were performed using Python version 3.13.

Results

Patient characteristics

The flowchart showing patients’ selection according to inclusion and exclusion criteria is represented in Fig. 1. A total of 145 patients with unfavorable intermediate to high-risk PCa were included in the study (Table 1). The median age at PSMA PET/CT was 76.0 years (IQR: 73.0–79.0). The median initial PSA was 8.9 ng/mL (IQR: 6.5–15.5). Most patients had an ISUP grade group of 3 (39.3%) or 2 (26.9%). The majority of patients were staged with [^{18}F] F-PSMA-1007 (89.7%). Lymph-node involvement (cN+, including both miN1 and miN2) was present in 28.3% of cases. Median RT doses to prostate and pelvic lymphatics

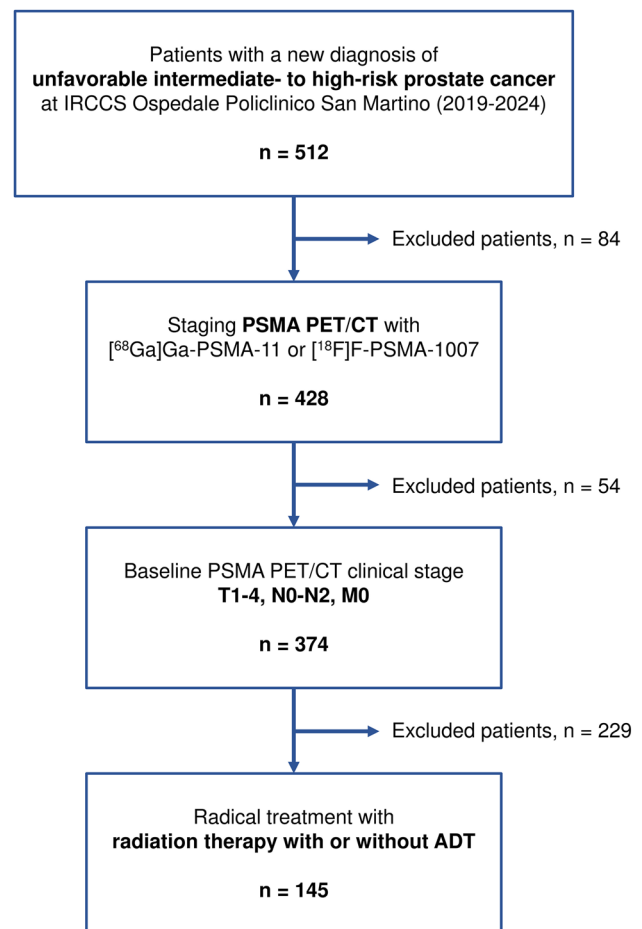


Fig. 1 Flowchart of patients’ selection

Table 1 Clinical characteristics of enrolled patients

Characteristic	Value
Patients, n	145
Age (years)	
Median (IQR)	76.0 (73.0–79.0)
Initial PSA (ng/mL)	
Median (IQR)	8.9 (6.5–15.5)
≤ 10 ng/mL	79 (54.5%)
10–20 ng/mL	23 (15.9%)
> 20 ng/mL	43 (29.6%)
ISUP grade group, <i>n</i> (%)	
Grade 1	3 (2.1%)
Grade 2	39 (26.9%)
Grade 3	57 (39.3%)
Grade 4	38 (26.2%)
Grade 5	8 (5.5%)
PSMA-PET radiopharmaceutical	
[¹⁸ F]F-PSMA-1007, <i>n</i> (%)	130 (89.7%)
Uptake time (minutes), median	95.0 (range 90.0–110.0)
[⁶⁸ Ga]Ga-PSMA-11, <i>n</i> (%)	15 (10.3%)
Uptake time (minutes), median	64.0 (range 53.0–70.0)
Clinical stage at diagnosis, <i>n</i> (%)	
<i>T</i> Stage	
miT2	60 (41.4%)
miT3a	43 (29.6%)
miT3b	39 (26.9%)
miT4	3 (6.1%)
<i>N</i> Stage	
cN0	104 (71.7%)
cN+	41 (28.3%)
PSMA-PET parameters, median (IQR)	
SUVmax (Dominant lesion)	12.2 (8.8–20.6)
PSMA-TV (Total)	5.4 (3.0–13.0)
PSMA-TL (Total)	38.0 (21.6–77.5)
Radiation therapy, median (IQR)	
Dose to prostate (Gy)	64.0 (64.0–64.0)
Dose to pelvic lymphatics (Gy)	46.0 (46.0–46.0)
Fractions (number)	20.0 (20.0–20.0)
Concurrent ADT, <i>n</i> (%)	
< 12 months	32 (22.1%)
12–24 months	88 (60.7%)
> 24 months	25 (17.2%)
Treatment response	
PSA nadir after RT (ng/mL)	
Median (IQR)	0.01 (0.01–0.08)
PSA reduction (%)	
Median (IQR)	99.8 (99.0–99.9)
Outcome	
PSA relapse, <i>n</i> (%)	7 (4.8%)
Treatment failure, <i>n</i> (%)	13 (9.0%)
TTF (months), median	18.1 (1.1–49.8)

Table 2 Cox regression analysis for PSMA-TV as a predictor of TTF

Variable	HR (95% CI)	<i>p</i> value
PSMA-TV (binary)		
Low PSMA-TV	1 (Ref.)	
High PSMA-TV	3.79 (1.04–13.81)	0.043
PSMA-TV (tertiles)		
First tertile	1 (Ref.)	
Second tertile	2.27 (0.41–12.40)	0.345
Third tertile	4.07 (0.84–19.70)	0.081
PSMA-TV (quartiles)		
First quartile	1 (Ref.)	
Second quartile	0.65 (0.06–7.15)	0.727
Third quartile	2.92 (0.57–15.09)	0.200
Fourth quartile	3.00 (0.58–12.79)	0.360

were 64.0 Gy (IQR: 64.0–64.0) and 46.0 Gy (IQR: 46.0–46.0), respectively, both delivered in a median number of 20 fractions (IQR: 20.0–20.0). Concurrent ADT was administered in all patients, and the most common duration was 12–24 months (60.7%). The median follow-up duration was 20.5 months (range 1–50 months).

Predictive value of PSMA-PET parameters

In univariate and multivariate logistic regression models, none of the PET parameters (SUVmax, PSMA-TL, PSMA-TV) were significantly associated with PSA50 or PSA90 responses. Odds ratios were close to 1 (see Supplementary Fig. 2), and area under the curve (AUC) values ranged from 0.49 to 0.55, indicating poor discriminatory power. Similarly, in Cox regression models for PSA relapse and TTF, no significant associations were found. However, PSMA-TV showed the numerically highest C-index (0.704 for PSA relapse, 0.674 for TTF), suggesting a potential prognostic role. Kaplan–Meier curves comparing patients with PET parameters above vs. below the median revealed no statistically significant differences in PSA relapse or TTF for any parameter (Supplementary Fig. 3 and Supplementary Fig. 4). However, the log-rank *p* value for PSMA-TV and TTF was 0.0599, approaching but not reaching significance.

IPTW was applied to control for baseline differences based on initial PSA, ISUP grade, T stage, and N stage. In IPTW-weighted Kaplan–Meier analyses, PSMA-TV was significantly associated with TTF ($p < 0.05$) (Fig. 2a, b). Patients with high PSMA-TV had a shorter time to treatment failure. As shown in Supplementary Fig. 5, Kaplan–Meier curves performed grouping patients according to each individual counfounder used for IPTW calculation reached significance. Cox regression analysis confirmed this result (HR 3.79, 95% CI 1.04–13.81; $p < 0.05$) (Table 2). On

the contrary, no significant differences were observed for PSMA-TV and PSA relapse ($p > 0.3$) (Fig. 2c, d).

An exploratory analysis after grouping patients according to PSMA-TV tertiles and quartiles did not reach statistical significance in the prediction of either PSA relapse or TTF (Supplementary Figs. 6–7). These results were confirmed at Cox regression analysis (Table 2).

SMDs for each covariate included in the propensity score model (initial PSA, ISUP grade, T stage, and N stage), comparing high- and low-PSMA-TV groups before and after IPTW adjustment, are presented in Table 3 and Fig. 3. Following IPTW, all covariates achieved SMD showing an adequate balance between the two groups (Fig. 3).

Table 3 SMDs for prognostic variables included in the propensity score model before and after IPTW weighting in patients grouped according to median PSMA-TV

Variable	SMDs before IPTW weighting	SMDs after IPTW weighting
Initial PSA	0.177	0.009
ISUP grade	0.251	-0.106
T stage	0.503	0.069
N stage	-0.430	-0.082

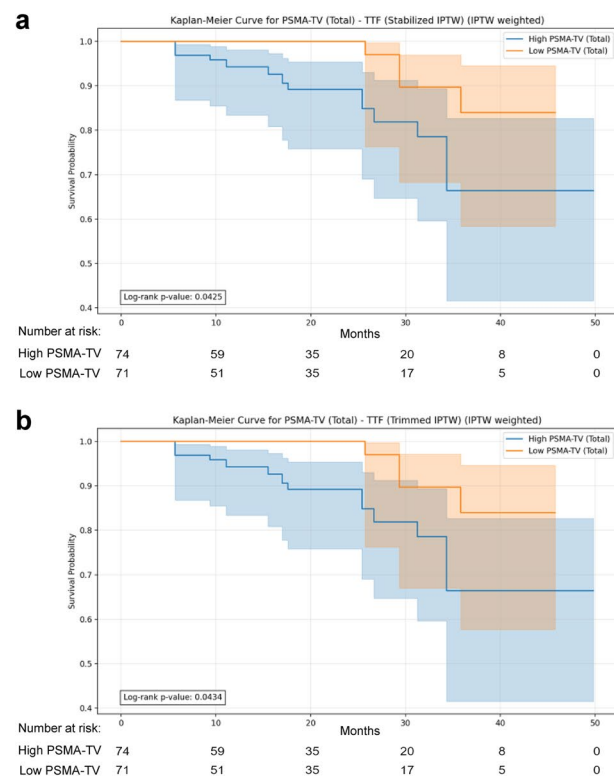


Fig. 2 IPTW-weighted Kaplan–Meier curves for TTF (on the left) and PSA relapse (on the right), stratified by PSMA-TV (high vs. low, dichotomized at the median). IPTW was applied using stabilized

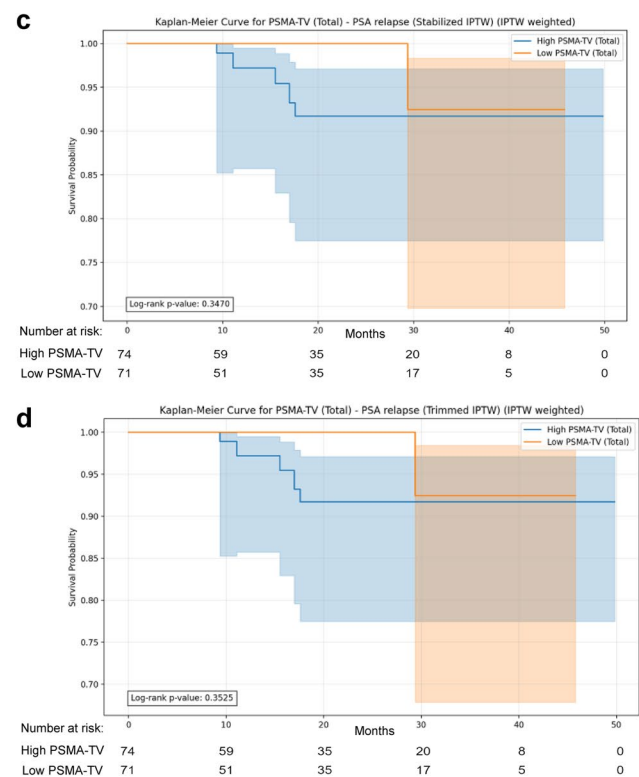
Representative images of two patients presenting the same clinical stage at PSMA-PET performed for staging purposes, but with different total PSMA-TV (below and above the median value) are displayed in Fig. 3.

SUVmax and PSMA-TL were not significantly associated with either outcome (all $p > 0.2$).

These results suggest that PSMA-TV may be a significant prognostic factor for TTF when accounting for potential confounding variables through IPTW, but not for PSA relapse.

Discussion

In this retrospective study, we investigated the prognostic significance of PSMA PET/CT-derived quantitative parameters in patients with unfavorable intermediate to high-risk PCa undergoing curative-intent RT with ADT. Among the parameters analyzed, total PSMA-TV emerged as a statistically significant independent predictor of TTF. This result is in line with the previous findings highlighting the prognostic role of PSMA-TV in several clinical settings, while SUVmax and SUVmean (which is incorporated in the computation of PSMA-TL) showed a lower prognostic power [5, 6, 12]. Moreover, this association remained robust



(panels a-c) and trimmed weights (panels b-d) to adjust for baseline differences in initial PSA, ISUP grade, T stage, and N stage, while reducing the influence of extreme propensity scores

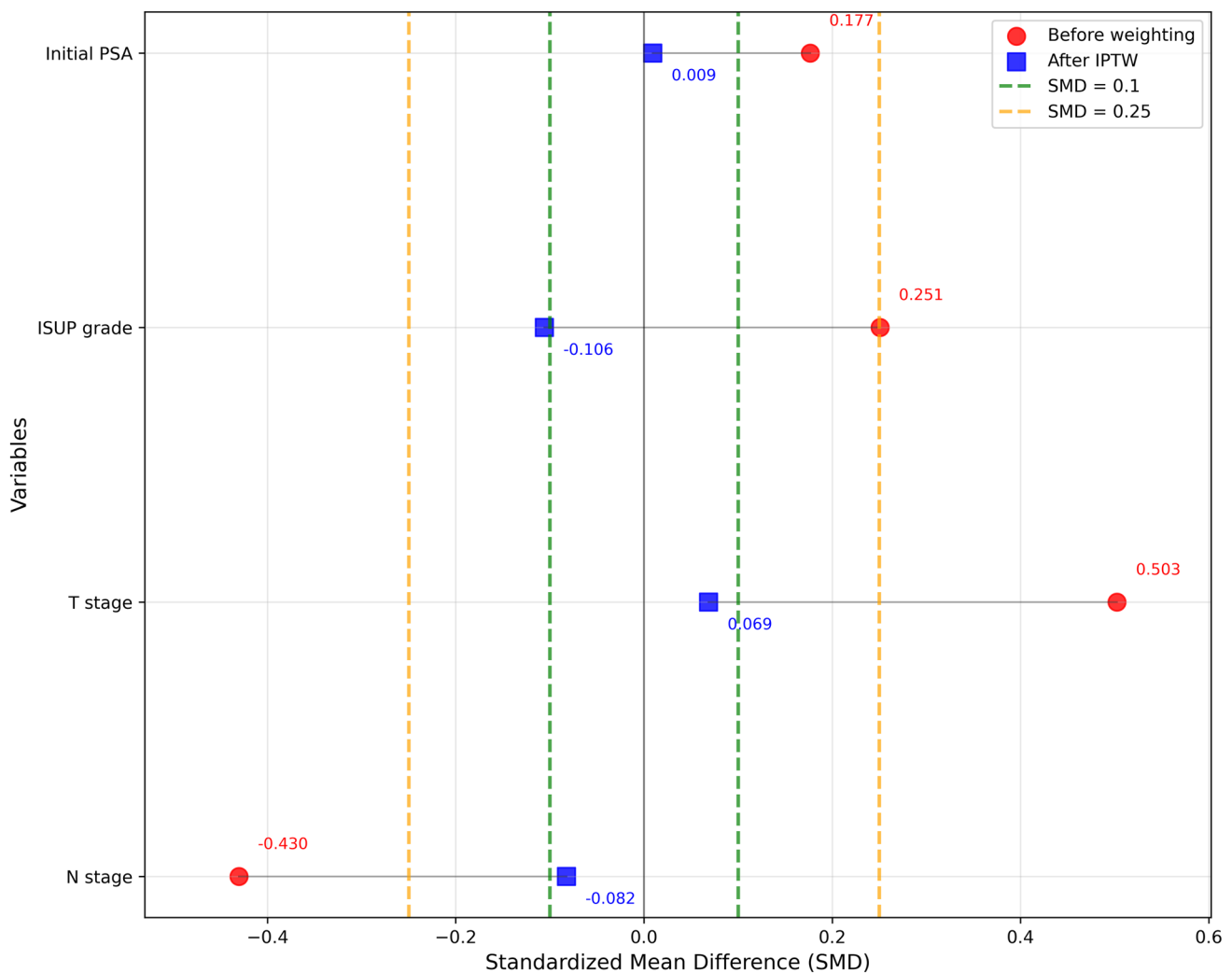


Fig. 3 Love plot showing SMDs for prognostic variables included in the propensity score model before and after IPTW weighting in patients grouped according to median PSMA-TV

after IPTW, which adjusted for key clinical confounders including initial PSA, ISUP grade, and TNM staging. Notably, this association was not observed in unweighted analyses, reinforcing the importance of adjusting for baseline risk factors in observational cohorts [14]. Given the high efficacy of RT combined with ADT, PSA declines below the detection limit in nearly all patients. Consequently, PSA kinetics alone provide limited information for predicting treatment outcome. This highlights the need to investigate additional predictive parameters, such as PSMA-TV or other imaging-based biomarkers, to better stratify patients at risk of treatment failure.

The observed relationship between higher PSMA-TV and shorter TTF aligns with the existing literature demonstrating the value of PSMA PET/CT in the initial staging of PCa [2, 15–17], particularly in detecting nodal and distant metastases, surpassing conventional imaging modalities [4] and

providing prognostic insights [5, 6]. Notably, in 16–48% of cases, the standard treatment planning might be modified according to PSMA PET/CT findings, due to the common identification of metastatic localizations outside the standard boundaries of pelvic lymph-node dissection or RT fields [18, 19]. However, the impact of these differences on the long-term outcome remains unclear.

In recent years, large multicenter initiatives, such as the CO-IMPACT consortium (<https://www.coimpact-project.com/>), have been launched to systematically evaluate how PSMA PET can inform RT in diverse clinical scenarios, including the initial staging of disease. A central hypothesis shared by these initiatives is that image-guided focal dose escalation targeting macroscopic PSMA-avid disease may improve oncological outcomes while minimizing toxicity to adjacent organs-at-risk.

Early studies have already demonstrated that the integration of PSMA PET/CT and/or multiparametric MRI (mpMRI) into RT workflows can significantly alter salvage treatment plans [20, 21]. However, while phase III clinical trials on focal dose escalation in localized PCa are ongoing, robust clinical evidence supporting dose escalation in nodal or low-volume metastatic settings—guided by advanced imaging—remains limited. The extent to which targeted intensification based on PSMA PET/CT or mpMRI influences long-term oncological outcomes or treatment-related toxicity has yet to be conclusively established.

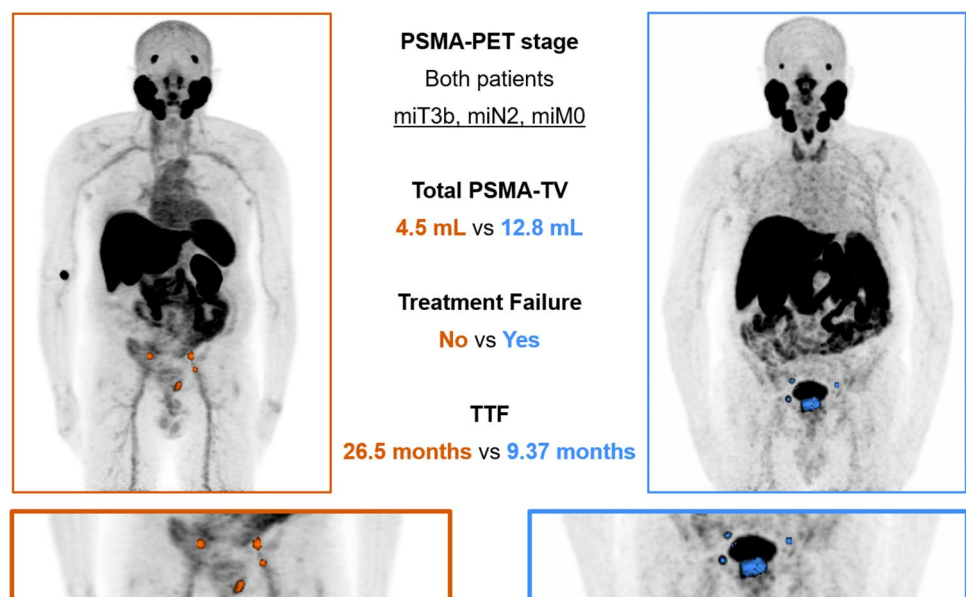
The present study contributes to this evolving landscape by demonstrating that PSMA-TV is independently associated with time to treatment failure (Fig. 4), supporting its potential role as a risk-stratifying biomarker. This finding is in line with the well-established prognostic role of the metabolic tumor volume (MTV), a volumetric measure derived from [¹⁸F]-Fluorodeoxyglucose (FDG) PET, in other solid neoplasms [22, 23], often outperforming SUV-based indices for patients' risk stratification.

From a clinical perspective, the identification of PSMA-TV as a significant prognostic biomarker opens the door to risk-adapted strategies in PCa management. In fact, our patients received a standard RT protocol, while new approaches that modulate the treatment according to imaging findings are emerging. Incorporating PSMA-TV into clinical workflows could facilitate individualized treatment strategies, including focal dose escalation guided by PSMA-PET, integration with systemic therapies in patients with imaging-based high risk of treatment failure, or tailored surveillance based on the individual risk of recurrence. This personalized approach may be especially relevant given the limitations of uniform dose escalation in the pelvic region,

where critical structures such as the bladder and rectum constrain the ability to safely increase radiation doses to the entire prostate or nodal basin [24, 25]. In this context, accurate volumetric assessment of intra- and extraprostatic tumor burden via PSMA PET/CT may guide selective intensification. Prospective validation in multicenter cohorts and exploration of correlations with other endpoints, such as progression-free survival, time to systemic therapy, or castration resistance, are essential to confirm the generalizability of our findings and may further reinforce the application of PSMA-TV in clinical practice.

Several limitations of the present study should be considered. First, the retrospective design is inherently susceptible to confounding and selection bias, despite the application of IPTW. Second, the sample size may limit the power to detect smaller effect sizes, particularly in subgroup analyses. External validation using independent, prospective datasets with scanners' harmonization is necessary before PSMA-TV can be incorporated into routine clinical workflows. Potential interactions between PSMA-TV and the duration of androgen deprivation therapy were not explored, as ADT duration was determined according to NCCN risk classification and not influenced by PSMA-PET findings. Furthermore, the limited number of events did not allow the calculation of specific PSMA-TV cut-offs for building a model with reliable performances. Similarly, we did not assess the added prognostic value of PET-derived parameters using formal methods such as net reclassification improvement or decision curve analysis, due to the limited sample size and number of events. Future studies with larger cohorts are warranted to explore this aspect. Standardization of PSMA-TV measurement [26], segmentation criteria

Fig. 4 Maximum intensity projection images of PSMA-PET scans of two PCa patients submitted to initial staging before radical RT



accounting for different radiopharmaceuticals, or eventual integration with AI-based segmentation tools [27] may improve reproducibility in future studies. Finally, in the present study, due to the relatively small patient sample, we were unable to perform sensitivity analyses to assess potential differences in the predictive value of PSMA-TV depending on the specific PSMA-targeted radiopharmaceutical used. On one hand, this issue may be clinically relevant: in the oligorecurrent setting, where PET/CT is used to guide metastasis-directed therapy, several studies have shown that the choice of PET tracer can impact oncological outcomes [28–32]. Specifically, the use of [⁶⁸Ga]Ga-PSMA-11 versus [¹⁸F]F-PSMA-1007 has been associated with differing long-term prognoses [33, 34]. However, data from the PROMISE registry [5] indicate that PSMA-TV remains a significant prognosticator with similar hazard ratios across patient groups stratified by [⁶⁸Ga]Ga-PSMA-11 or [¹⁸F]-based PSMA tracers. Thus, although further studies are warranted to clarify these findings, it may be hypothesized that the prognostic value of PSMA-derived volumetric parameters such as PSMA-TV is independent of the tracer used.

Conclusions

Our findings highlight PSMA-TV as a promising imaging-derived biomarker independently associated with time to treatment failure. While further prospective validation is needed, its integration into clinical workflows could support more personalized and risk-adapted RT strategies in PCa management.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s12149-025-02118-4>.

Author contributions Conceptualization, F.L., L.B., and M.B.; methodology, F.L., L.B., V.P., and M.B.; formal analysis, F.L. and M.B.; investigation, D.V., J.P., S.M., L.S., S.R., S.C., M.I.D., M.R., M.M., G.T., C.M., S.B., and G.S.; data curation, F.L., L.B., V.P., and M.B.; writing—original draft preparation, F.L., L.B., G.T., and M.B.; writing—review and editing, all authors; funding acquisition, M.B. All authors have read and agreed to the published version of the manuscript.

Funding Open access funding provided by Università degli Studi di Genova within the CRUI-CARE Agreement. This research was supported by the University of Genova through the University Research Fund (FRA) granted to Matteo Bauckneht. and by Project – PNC- E3-2022-23683266 – DIAGNOSTICA AVANZATA (HLS-DA) “INNOVA” financed by the Ministry of Health as part of the National Supplementary Plan for the Innovative Health Ecosysteme, granted to Gianmario Sambuceti.

Data availability M.B. is responsible for data integrity and accuracy of the analyses. Raw data are available upon specific requests.

Declarations

Conflict of interest M.B. reports personal fees for advisory board participation and speaker’s honoraria from Novartis, Bayer, Telix Pharmaceuticals, and Johnson & Johnson. All other authors report no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Institutional review board statement The study was conducted in accordance with the Declaration of Helsinki, and approved by the Local Ethics Committee (Regione Liguria Ethical Committee, registration number 5/2023–DB id 12914, date of approval 19-Jun-2023).

Informed consent statement The Local Ethical Committee (Regione Liguria Ethical Committee) waived informed consent due to the study’s retrospective design.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Prostate cancer. European Association of Urology website. Available online: <https://uroweb.org/guidelines/prostate-cancer>. Accessed March 15, 2025.
2. Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet*. 2020;395:1208–16. [https://doi.org/10.1016/s0140-6736\(20\)30314-7](https://doi.org/10.1016/s0140-6736(20)30314-7).
3. Chow KM, So WZ, Lee HJ, Lee A, Yap DWT, Takwoingi Y, et al. Head-to-head comparison of the diagnostic accuracy of prostate-specific membrane antigen positron emission tomography and conventional imaging modalities for initial staging of intermediate- to high-risk prostate cancer: a systematic review and meta-analysis. *Eur Urol*. 2023;84:36–48. <https://doi.org/10.1016/j.eururo.2023.03.001>.
4. Bauckneht M, Checcucci E, Cisero E, Rizzo A, Racca M, De Cillis S, et al. The prognostic role of next-generation imaging-driven upstaging in newly diagnosed prostate cancer patients. *Eur J Nucl Med*. 2023;51:864–70. <https://doi.org/10.1007/s00259-023-06490-z>.
5. Karpinski MJ, Rahbar K, Bögemann M, Nikoukar LR, Schäfers M, Hoberück S, et al. Updated prostate cancer risk groups by prostate-specific membrane antigen positron emission tomography prostate cancer molecular imaging standardized evaluation

- (PPP2): results from an international multicentre registry study. *Eur Urol.* 2025. <https://doi.org/10.1016/j.eururo.2025.04.017>.
6. Karpinski MJ, Hüsing J, Claassen K, Möller L, Kajüter H, Oesterling F, et al. Combining PSMA-PET and PROMISE to re-define disease stage and risk in patients with prostate cancer: a multicentre retrospective study. *Lancet Oncol.* 2024;25:1188–201. [https://doi.org/10.1016/s1470-2045\(24\)00326-7](https://doi.org/10.1016/s1470-2045(24)00326-7).
 7. Fendler WP, Eiber M, Beheshti M, Bomanji J, Calais J, Ceci F, et al. PSMA PET/CT: joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.0. *Eur J Nucl Med.* 2023;50:1466–86. <https://doi.org/10.1007/s00259-022-06089-w>.
 8. Seifert R, Emmett L, Rowe SP, Herrmann K, Hadaschik B, Calais J, et al. Second version of the prostate cancer molecular imaging standardized evaluation framework including response evaluation for clinical trials (PROMISE V2). *Eur Urol.* 2023;83:405–12. <https://doi.org/10.1016/j.eururo.2023.02.002>.
 9. Rizzo A, Morbelli S, Albano D, Fornarini G, Cioffi M, Laudicella R, et al. The homunculus of unspecific bone uptakes associated with PSMA-targeted tracers: a systematic review-based definition. *Eur J Nucl Med.* 2024;51:3753–64. <https://doi.org/10.1007/s00259-024-06797-5>.
 10. Bauckneht M, D'aMico F, Albano D, Balma M, Cabrini C, Dondi F, et al. Composite prediction score to interpret bone focal uptake in hormone-sensitive prostate cancer patients imaged with [18F]PSMA-1007 PET/CT. *J Nucl Med.* 2024;65:1577–83. <https://doi.org/10.2967/jnumed.124.267751>.
 11. Nioche C, Orhac F, Boughdad S, Reuzé S, Goya-Outi J, Robert C, et al. LIFEx: a freeware for radiomic feature calculation in multimodality imaging to accelerate advances in the characterization of tumor heterogeneity. *Cancer Res.* 2018;78:4786–9. <https://doi.org/10.1158/0008-5472.can-18-0125>.
 12. Gafita A, Rauscher I, Weber M, Hadaschik B, Wang H, Armstrong WR, et al. Novel framework for treatment response evaluation using PSMA PET/CT in patients with metastatic castration-resistant prostate cancer (RECIP 1.0): an international multicenter study. *J Nucl Med.* 2022;63:1651–8. <https://doi.org/10.2967/jnumed.121.263072>.
 13. Emmett L, Papa N, Buteau J, Ho B, Liu V, Roberts M, et al. The PRIMARY score: using intraprostatic 68Ga-PSMA PET/CT patterns to optimize prostate cancer diagnosis. *J Nucl Med.* 2022;63:1644–50. <https://doi.org/10.2967/jnumed.121.263448>.
 14. Chesnaye NC, Stel VS, Tripepi G, Dekker FW, Fu EL, Zoccali C, et al. An introduction to inverse probability of treatment weighting in observational research. *Clin Kidney J.* 2021;15:14–20. <https://doi.org/10.1093/ckj/sfab158>.
 15. Hope TA, Eiber M, Armstrong WR, Juarez R, Murthy V, Lawhn-Heath C, et al. Diagnostic accuracy of 68Ga-PSMA-11 PET for pelvic nodal metastasis detection prior to radical prostatectomy and pelvic lymph node dissection. *JAMA Oncol.* 2021;7:1635–42. <https://doi.org/10.1001/jamaoncol.2021.3771>.
 16. Surasi DS, Eiber M, Maurer T, Preston MA, Helfand BT, Josephson D, et al. Diagnostic performance and safety of positron emission tomography with 18F-rhPSMA-7.3 in patients with newly diagnosed unfavourable intermediate- to very-high-risk prostate cancer: results from a phase 3, prospective, multicentre study (LIGHTHOUSE). *Eur Urol.* 2023;84:361–70. <https://doi.org/10.1016/j.eururo.2023.06.018>.
 17. Pienta KJ, Gorin MA, Rowe SP, Carroll PR, Pouliot F, Probst S, et al. A phase 2/3 prospective multicenter study of the diagnostic accuracy of prostate specific membrane antigen PET/CT with 18F-DCFPyL in prostate cancer patients (OSPREY). *J Urol.* 2021;206:52–61. <https://doi.org/10.1097/ju.0000000000001698>.
 18. Calais J, Kishan AU, Cao M, Fendler WP, Eiber M, Herrmann K, et al. Potential impact of ⁶⁸Ga-PSMA-11 PET/CT on the planning of definitive radiation therapy for prostate cancer. *J Nucl Med.* 2018;59:1714–21. <https://doi.org/10.2967/jnumed.118.209387>.
 19. Yaxley JW, Raveenthiran S, Nouhaud F, Samarasinghe H, Yaxley WJ, Coughlin G, et al. Risk of metastatic disease on 68gallium-prostate-specific membrane antigen positron emission tomography/computed tomography scan for primary staging of 1253 men at the diagnosis of prostate cancer. *BJU Int.* 2019;124:401–7. <https://doi.org/10.1111/bju.14828>.
 20. Habl G, Sauter K, Schiller K, Dewes S, Maurer T, Eiber M, et al. 68Ga-PSMA-PET for radiation treatment planning in prostate cancer recurrences after surgery: individualized medicine or new standard in salvage treatment. *Prostate.* 2017;77:920–7. <https://doi.org/10.1002/pros.23347>.
 21. Henkenberens C, Von Klot CA, Ross TL, Bengel FM, Wester HJ, Hüper K, et al. 68Ga-PSMA Ligand PET/CT-based Radiotherapy for lymph node relapse of prostate cancer after primary therapy delays initiation of systemic therapy. *Anticancer Res.* 2017;37:1273–80. <https://doi.org/10.21873/anticancerres.11444>.
 22. Pak K, Cheon GJ, Nam HY, Kim SJ, Kang KW, Chung JK, et al. Prognostic value of metabolic tumor volume and total lesion glycolysis in head and neck cancer: a systematic review and meta-analysis. *J Nucl Med.* 2014;55:884–90. <https://doi.org/10.2967/jnumed.113.133801>.
 23. Im HJ, Pak K, Cheon GJ, Kang KW, Kim SJ, Kim IJ, et al. Prognostic value of volumetric parameters of (18)F-FDG PET in non-small-cell lung cancer: a meta-analysis. *Eur J Nucl Med Mol Imaging.* 2015;42:241–51. <https://doi.org/10.1007/s00259-014-2903-7>.
 24. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constone LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys.* 2010;76:S10–9. <https://doi.org/10.1016/j.ijrobp.2009.07.1754>.
 25. Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. *Lancet Oncol.* 2012;13:43–54. [https://doi.org/10.1016/s1470-2045\(11\)70293-5](https://doi.org/10.1016/s1470-2045(11)70293-5).
 26. Wang F, Liu C, Vidal I, Mana-Ay M, Voter AF, Solnes LB, et al. Comparison of multiple segmentation methods for volumetric delineation of primary prostate cancer with prostate-specific membrane antigen-targeted 18F-DCFPyL PET/CT. *J Nucl Med.* 2023;65:87–93. <https://doi.org/10.2967/jnumed.123.266005>.
 27. Gafita A, Bieth M, Kroenke M, Tetteh G, Navarro F, Wang H, et al. qPSMA: semiautomatic software for whole-body tumor burden assessment in prostate cancer using 68Ga-PSMA11 PET/CT. *J Nucl Med.* 2019;60:1277–83. <https://doi.org/10.2967/jnumed.118.224055>.
 28. Hegemann N-SS, Rogowski P, Eze C, Schäfer C, Stief C, Lang S, et al. Outcome after 68Ga-PSMA-11 versus choline PET-based salvage radiotherapy in patients with biochemical recurrence of prostate cancer: a matched-pair analysis. *Cancers.* 2020;12:3395. <https://doi.org/10.3390/cancers12113395>.
 29. Deijen CL, Vrijenhoek GL, Schaake EE, Vogel WV, Moonen LM, Pos FJ, et al. PSMA-11-PET/CT versus choline-PET/CT to guide stereotactic ablative radiotherapy for androgen deprivation therapy deferral in patients with oligometastatic prostate cancer. *Clin Transl Radiat Oncol.* 2021;30:1–6. <https://doi.org/10.1016/j.ctro.2021.06.004>.
 30. Mazzola R, Francolini G, Triggiani L, Napoli G, Cuccia F, Nicosia L, et al. Metastasis-directed therapy (SBRT) guided by PET-CT 18F-choline versus PET-CT 68Ga-PSMA

- in castration-sensitive oligorecurrent prostate cancer: a comparative analysis of effectiveness. *Clin Genitourin Cancer*. 2021;19:230–6. <https://doi.org/10.1016/j.clgc.2020.08.002>.
31. Lanfranchi F, Belgioia L, Marcenaro M, Zanardi E, Timon G, Riondato M, et al. Oligometastatic prostate cancer treated with metastasis-directed therapy guided by positron emission tomography: does the tracer matter? *Cancers*. 2023;15(1):323. <https://doi.org/10.3390/cancers15010323>.
 32. Metz R, Rauscher A, Vaugier L, Supiot S, Drouet F, Campion L, et al. Comparison of hormone-sensitive oligorecurrent prostate cancer patients based on routine use of choline and/or PSMA PET/CT to guide metastasis-directed therapy. *Cancers*. 2023;15:1898. <https://doi.org/10.3390/cancers15061898>.
 33. Bauckneht M, Lanfranchi F, Albano D, Triggiani L, Linguanti F, Urso L, et al. Diverse imaging methods may influence long-term oncologic outcomes in oligorecurrent prostate cancer patients treated with metastasis-directed therapy (the PRECISE-MDT study). *J Nucl Med*. 2024;65:1202–9. <https://doi.org/10.2967/jnumed.124.267586>.
 34. Lanfranchi F, Belgioia L, Albano D, Triggiani L, Linguanti F, Urso L, et al. Impact of metastasis-directed therapy guided by different PET/CT radiotracers on distant and local disease control in oligorecurrent hormone-sensitive prostate cancer: a secondary analysis of the PRECISE-MDT study. *Radiol Imaging Cancer*. 2025;7:e240150. <https://doi.org/10.1148/rycan.240150>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.