Society of Medical Education & Research

2026, Volume 6, Issue 1, Page No: 154-163
ISSN: 3108-4834

Archive of International Journal of Cancer and Allied Science

Does PET Tracer Selection Matter in Oligometastatic Prostate Cancer Undergoing PET-Guided Metastasis-Directed Therapy?

Charlotte Dupuis[1]*, Hugo Perrin[1], Elise Morel[2], Thomas Martin[3]

[1]Department of Prostate Cancer and PET-Guided Therapy, Faculty of Medicine, University of Lille, Lille, France.
[2]Department of Oligometastatic Disease and PET Tracers, Faculty of Medicine, University of Montpellier, Montpellier, France.
[3]Department of Metastasis-Directed Therapy and Imaging, Faculty of Medicine, University of Nantes, Nantes, France.

***E-mail** ✉ charlotte.dupuis@univ-lille.fr

Abstract

It is well established that [68Ga]Ga-prostate-specific membrane antigen-11 ([68Ga]Ga-PSMA-11) PET/CT offers greater diagnostic precision than [18F]F-Fluorocholine PET/CT for prostate cancer (PCa). Nevertheless, whether this improved accuracy translates into better clinical outcomes in oligometastatic PCa patients managed with [68Ga]Ga-PSMA-11 PET-guided metastasis-directed therapy (MDT) remains unclear. This investigation evaluated the effects of the two imaging modalities on Progression-Free Survival (PFS) in a real-world cohort of oligometastatic PCa patients who received PET-guided MDT. A total of 37 patients were included retrospectively. In eleven cases, MDT was guided by [18F]F-Fluorocholine PET/CT, while [68Ga]Ga-PSMA-11 PET/CT was used in twenty-six. Progression was defined according to biochemical recurrence (BR), new radiological findings on follow-up PET/CT, clinical deterioration, start of androgen deprivation therapy, or death. Various clinical and imaging factors were analyzed as potential predictors of PFS. Patients whose MDT was guided by [18F]F-Fluorocholine PET/CT experienced markedly shorter PFS compared with the [68Ga]Ga-PSMA-11 group (median PFS 15.47 months, 95% CI: 4.13–38.00 versus 40.93 months, 95% CI: 40.93–40.93; $P < 0.05$). Correspondingly, the choice of radiotracer for PET-guided MDT emerged as a predictor of PFS on univariate analysis, along with castration-resistant status at the time of MDT and PSA nadir following MDT. On multivariate analysis, however, only castration resistance and post-MDT PSA nadir remained independent predictors of PFS. In summary, this preliminary proof-of-concept study found that [68Ga]Ga-PSMA-11 imaging was linked to superior PFS rates relative to [18F]F-Fluorocholine in oligometastatic PCa patients treated with PET-guided MDT. Although these results are initial, they indicate that expanding detection of disease extent through next-generation imaging—thereby identifying a larger share of otherwise hidden lesions—may improve oncological outcomes when MDT is applied in oligometastatic PCa.

Keywords: PET/CT, [68Ga]Ga-PSMA-11, [18F]F-Fluorocholine, Prostate cancer, Metastasis-directed therapy, SBRT

Introduction

Androgen deprivation therapy (ADT) constitutes the cornerstone of treatment for metastatic prostate cancer (PCa). Although many patients remain on ADT for extended periods before disease advancement or resistance develops, this approach seldom achieves permanent elimination of metastatic lesions [1]. The same limitation applies when ADT is paired with contemporary androgen receptor pathway inhibitors [2-6]. Furthermore, ADT carries significant adverse effects, including fatigue, emotional changes, and disruptions in metabolism [6]. Consequently, definitive local treatments such as metastasis-directed therapy (MDT) via stereotactic body radiotherapy (SBRT) merit

Access this article online https://smerpub.com/

Received: 01 February 2026; **Accepted:** 08 May 2026

How to cite this article: Dupuis C, Perrin H, Morel E, Martin T. Does PET Tracer Selection Matter in Oligometastatic Prostate Cancer Undergoing PET-Guided Metastasis-Directed Therapy? Arch Int J Cancer Allied Sci. 2026;6(1):154-63. https://doi.org/10.51847/kMBVF5mYOu

consideration in cases where metastases are few and well-defined. Delaying or avoiding ADT in these situations offers a meaningful benefit to patients by limiting exposure to systemic side effects.

The utility of MDT in oligometastatic PCa has been examined extensively. Individuals receiving MDT have demonstrated substantially extended intervals before needing to begin ADT [7-9]. In addition, MDT achieves strong local control with favorable tolerability and contributes positively to long-term disease outcomes in both newly diagnosed and recurrent low-volume metastatic PCa [7, 9]. A key factor influencing MDT success is the accuracy of the imaging modality used to identify target lesions. Greater precision in metastasis detection is thought to increase the proportion of patients who receive appropriate MDT, thereby enhancing overall results. At the 2017 Advanced Prostate Cancer Consensus Conference, oligometastatic disease was characterized using conventional imaging modalities, including bone scintigraphy, contrast-enhanced CT, and MRI [10]. Despite their current endorsement, these methods possess limited sensitivity and frequently underestimate the true metastatic burden [11].

In recent years, PET/CT has substantially enhanced the identification of PCa recurrences beyond what conventional imaging can achieve [12]. It is reasonable to expect that revealing a larger fraction of microscopic metastatic disease via modern imaging techniques could improve oncological results for oligometastatic PCa patients treated with MDT. However, there is currently no consensus on incorporating these advanced imaging tools into routine PCa management, largely because clinical trials evaluating the benefits of treating oligometastases detected by such methods have not yet been completed.

Likewise, the potential superiority of visualizing phospholipid membrane synthesis as a marker of cellular proliferation (via radiolabeled choline) versus targeting Prostate-Specific Membrane Antigen (PSMA) expression on tumor cells using PET/CT requires confirmation in this specific context. For a considerable time, [18F]F-Fluorocholine and [11C]C-choline PET/CT were considered the reference standard for restaging PCa in patients with biochemical relapse, according to international recommendations [13]. More recently, [68Ga]Ga- or [18F]F-labeled PSMA tracers have been designated the preferred imaging approach in updated guidelines, demonstrating superior sensitivity even at low PSA levels (0.2–1 ng/mL) [14]. Given this enhanced detection capability, it can be postulated that earlier MDT applied to PSMA-positive oligometastases could beneficially alter the disease trajectory in oligometastatic PCa, whereas treating only visible choline-avid lesions might merely postpone detectable recurrence while allowing undetected micrometastases to progress.

Based on these considerations, the current study was designed to provide an initial comparison of the effects of these two radiotracers on oncological outcomes in a retrospective, real-world series of oligometastatic PCa patients who underwent PET-guided MDT.

Materials and Methods

Study population and clinical data collection

We conducted a retrospective review of consecutive oligometastatic PCa patients who received PET-guided MDT at our center between June 2017 and December 2021. Participants were notified that their de-identified clinical and imaging information might be utilized for research purposes and provided written informed consent for such use and publication. The study adhered to the principles of the Declaration of Helsinki and received approval from the local ethics committee (Regional Ethical Committee of Liguria, registration number 343/2019).

Eligibility criteria included: (i) histologically verified PCa; (ii) detection of pelvic or extra-regional nodal involvement (M1a) or bone metastases (M1b) on either choline- or PSMA-based PET/CT; (iii) no more than five metastatic lesions visible on the pre-MDT PET/CT scan (defining oligometastatic disease); and (iv) initial treatment with MDT delivered as SBRT, with or without accompanying systemic therapy. The only exclusion criterion was lack of available follow-up data. Application of these criteria yielded a cohort of 37 oligometastatic PCa patients (mean age, 73.7 ± 7.6 years).

Collected variables encompassed: Gleason score and International Society of Urological Pathology (ISUP) grade at initial diagnosis, primary radical treatment received, history of salvage radiotherapy, interval from diagnosis to development of oligometastatic disease, age at MDT, proportion of patients with castration-resistant prostate cancer (CRPC) at the time of MDT, use of additional systemic therapy alongside MDT, number and locations of metastases treated, total MDT dose and biologically effective dose, PSA nadir after MDT, time

to reach PSA nadir, and the number of patients who experienced disease progression during follow-up.

PET/CT images acquisition and analysis

[18F]F-Fluorocholine and [68Ga]Ga-PSMA-11 PET/CT examinations were conducted in accordance with prevailing guidelines [15, 16].

Whole-body PET/CT scans (from skull vertex to upper thighs) were acquired on integrated systems—either a Hi-Rez Biograph 16 or Biograph mCT Flow (Siemens Medical Solutions, Munich, Germany)—using three-dimensional acquisition mode (2 minutes per bed position, 15.6 cm axial field of view). A low-dose CT scan was obtained for attenuation correction and anatomical localization; no contrast-enhanced diagnostic CT was performed. Image reconstruction used an ordered-subset expectation-maximization algorithm (4 iterations, 8 subsets) with corrections for random coincidences and scatter.

Image interpretation was performed consensually by two experienced nuclear medicine specialists using Syngo, via software (Siemens Medical Solutions, Munich, Germany). For each detected lesion on transaxial slices, a volume of interest (VOI) was delineated employing a 40% isocontour threshold of the SUVmax. Parameters recorded included maximum standardized uptake value (SUVmax), total metabolic tumor volume (MTV, summed across all lesions), and total lesion glycolysis (TLG, calculated as MTV multiplied by the corresponding SUVmean).

PET-guided MDT and clinical follow-up

In line with our center's standard procedures, patient management followed established International Guidelines [17] and principles of good clinical practice. Before MDT, all individuals underwent CT simulation for treatment planning with a 2-mm slice thickness while in the supine position. The Gross Tumor Volume (GTV) was contoured by integrating all available anatomical and functional PET/CT data. For bone lesions, an isotropic 3-mm expansion was applied to the GTV to generate the Clinical Target Volume (CTV). A Planning Target Volume (PTV) was then defined by adding isotropic or anisotropic 2-mm margins around the CTV. Treatment delivery involved intensity-modulated radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) with image guidance. Recorded MDT details comprised the cumulative radiation dose, number of fractions, biologically effective dose, and whether ADT was concurrently administered. The predominant fractionation scheme was 35 Gy delivered over 5 sessions.

After MDT, patients were monitored according to our institutional short-term follow-up schedule, which included regular clinical assessments and PSA measurements every 3 to 4 months. Restaging with [18F]F-Fluorocholine or [68Ga]Ga-PSMA-11 PET/CT—using the same radiotracer that had guided the initial MDT—was carried out upon detection of rising PSA or biochemical progression, as defined by the Prostate Cancer Working Group 3 criteria [18]. When oligoprogression occurred post-MDT, additional MDT sessions were typically offered provided that PET/CT identified fewer than five new lesions outside previously irradiated areas. In instances of polymetastatic progression, systemic therapies were introduced. Patients with advancing disease continued long-term monitoring focused on survival outcomes.

Statistical analysis

The main outcome measure was Progression-Free Survival (PFS) among oligometastatic PCa patients treated with MDT guided by either [68Ga]Ga-PSMA-11 or [18F]F-Fluorocholine PET/CT. Progression was evaluated using a composite definition consistent with prior reports [8, 9]. Specifically, progression was recorded upon meeting any of the following: (i) a PSA increase of $\geq$ 2 ng/dL and $\geq$ 25% from the nadir value; (ii) evidence of radiological advancement on PET/CT; (iii) development of symptomatic disease progression; (iv) commencement of ADT or modification of systemic treatment for any indication; or (v) death.

Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Group comparisons for continuous data employed the t-test, whereas categorical variables were analyzed with the chi-square test. Cox proportional hazards regression was utilized with PFS as the outcome variable. Univariate analyses examined associations between PFS and all available clinical and imaging factors. Variables with p-values < 0.100 in univariate testing were included in the multivariate model. Hazard ratios (HRs) from Cox models were presented, along with 95% confidence intervals (CIs) and corresponding p-values. Survival curves were generated via the Kaplan-Meier method and compared using the log-rank test after dichotomizing continuous variables. A threshold of $p < 0.050$ was considered statistically

significant. All statistical computations were performed with SPSS® version 26 (IBM Corp., Armonk, NY, US).

Results and Discussion

Patients' clinical characteristics, PET-guided MDT, and clinical follow-up

Baseline clinical features for the overall cohort are presented in **Table 1**. Eleven patients (29.8%) had restaging performed with [18F]F-Fluorocholine PET/CT, while twenty-six patients (70.2%) underwent restaging with [68Ga]Ga-PSMA-11 PET/CT following their initial definitive treatment.

Table 1. Clinical characteristics of patients enrolled at the time of MDT.

	Overall	[68Ga]Ga-PSMA-11 guided MDT	[18F]F-fluorocholine guided MDT	P-value
Number of patients	37	26	11	
ISUP grade				
ISUP 1	8 (21.6%)	6 (23.1%)	2 (18.2%)	0.747
ISUP 2	8 (21.6%)	5 (19.2%)	3 (27.3%)	
ISUP 3	8 (21.6%)	7 (27.0%)	1 (9.0%)	
ISUP 4	8 (21.6%)	5 (19.2%)	3 (27.3%)	
ISUP 5	5 (13.6%)	3 (11.5%)	2 (18.2%)	
Primary treatment (radiotherapy vs. surgery)				
Surgery	29 (78.4%)	22 (84.6%)	7 (63.6%)	0.157
Radiotherapy (± ADT)	8 (21.6%)	4 (15.4%)	4 (36.4%)	
Previous salvage radiotherapy	29 (78.4%)	20 (76.9%)	9 (81.8%)	0.741
Time to oligometastases, months (range)	91 (2–245)	104 (2–245)	79 (2–209)	0.551
Age at MDT	73.7 ± 7.57	75.08 ± 6.65	70.45 ± 8.9	0.142
CRPC at MDT	8 (21.6%)	5 (19.2%)	3 (27.3%)	0.587
PSA pre-MDT	3.01 ± 6.34	2.5 ± 6.74	4.19 ± 5.38	0.468
Medical therapy in addition to MDT	29 (78.4%)	19 (73.2%)	10 (90.9%)	0.228
PSA nadir after MDT	0.76 ± 0.1	0.43 ± 0.91	1.54 ± 1.83	**0.018**
Time to PSA nadir, months (range)	4 (1–29)	5 (1–29)	4 (1–17)	0.545
Number of metastases treated with MDT				
1 lesion	30 (81.0%)	19 (73.2%)	11 (100%)	0.302
2 lesions	5 (13.6%)	5 (19.2%)	0 (0%)	
3 lesions	1 (2.7%)	1 (3.8%)	0 (0%)	
5 lesions	1 (2.7%)	1 (3.8%)	0 (0%)	
Site of metastases treated with MDT				
Lymph nodes	24 (64.9%)	17 (65.4%)	7 (63.6%)	0.582
Bones	11 (29.7%)	7 (27.0%)	4 (36.4%)	
Both	2 (5.4%)	2 (7.6%)	0 (0%)	
MDT total dose	34.99 ± 3.54	35.37 ± 3.99	34.09 ± 2.02	0.324
MDT biologically effective dose	112.08 ± 14.21	112.56 ± 13.91	111 ± 15.51	0.766
Progression	15 (40.5%)	6 (23.1%)	9 (81.8%)	**0.001**

Continuous and categorical variables were evaluated using the t-test and chi-square test, respectively. Statistically significant p-values are highlighted in bold. Abbreviations: ADT = androgen deprivation therapy; CRPC= castration-resistant prostate cancer; ISUP= International Society of Urological Pathology; MDT= metastasis-directed therapy; PSA= prostate-specific antigen.

The two subgroups demonstrated similar profiles regarding the initial biopsy-derived ISUP grade, type of primary intervention, prior salvage irradiation, and duration from initial PCa diagnosis until the appearance of oligometastatic spread (p = ns across all parameters) **(Table 1)**. When oligorecurrence was identified on PET imaging, both subgroups were equivalent in age and CRPC status (P = ns for each), with no notable difference in serum PSA concentrations (4.19 ± 5.38 versus 2.50 ± 6.74 ng/mL, P = 0.468). In total, PET/CT detected 48 metastatic foci, comprising 37 lymph node sites (77%) and 11 skeletal lesions (23%), with no distant visceral involvement. The large majority of cases involved only a single metastatic focus (100% among those treated

with [18F]F-Fluorocholine-directed MDT), and the relative proportions of nodal and bone disease remained evenly matched between the study arms **(Table 1)**. No further meaningful distinctions emerged between the cohorts **(Table 1)**. Specifically, both the cumulative radiation dose and the biologically effective dose for MDT showed no significant variation (P = ns). Of note, the addition of concurrent systemic medical treatment to MDT occurred at comparable rates (91% in the [18F]F-Fluorocholine cohort versus 73% in the [68Ga]Ga-PSMA-11 cohort, P = ns).

For the study population as a whole, the median time from PET-directed MDT to the lowest PSA value was 4 months (5 months in the [68Ga]Ga-PSMA-11 group and 4 months in the [18F]F-Fluorocholine group; P = ns). However, the actual PSA concentration at this nadir point was markedly reduced in individuals whose treatment was guided by [68Ga]Ga-PSMA-11 PET/CT **(Table 1)**, (P = 0.018). Post-MDT monitoring, encompassing both clinical examinations and laboratory assessments, extended over a median of 20.48 months (range 5.37–60.13 months). During this period, the median PFS for the entire cohort stood at 40.93 months (95% CI: 15.93–40.93) **(Figure 1)**.

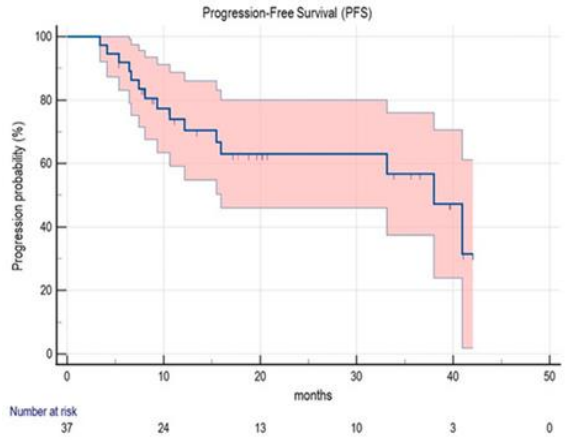

Figure 1. Kaplan-Meier plot illustrating PFS across the complete cohort—abbreviations: PFS= progression-free survival.

Among the 15 patients (40.5%) who experienced biochemical recurrence following MDT, disease progression occurred more frequently in the [18F]F-Fluorocholine group (9 out of 11 patients, 81.8%) than in the [68Ga]Ga-PSMA-11 group (6 out of 26 patients, 23.1%; P = 0.001). Of those who progressed, 14 individuals (93.3%) underwent repeat PET/CT evaluation, which verified advancement in every instance, while one patient (6.7%) succumbed to the disease and belonged to the [18F]F-Fluorocholine arm. In every case, the follow-up PET/CT used the same radiotracer that had initially guided the MDT. Restaging scans demonstrated ongoing oligometastatic disease in 5 patients (2 from the [18F]F-Fluorocholine arm and 3 from the [68Ga]Ga-PSMA-11 arm), prompting delivery of second-line MDT. This repeat MDT targeted the original metastatic locations in 3 of these cases (2 from the [18F]F-Fluorocholine arm and 1 from the [68Ga]Ga-PSMA-11 arm).

Predictors of clinical outcome

Univariate analysis **(Table 2)** identified several factors significantly linked to reduced PFS: CRPC status at MDT (HR: 6.238, 95% CI 1.939–20.073; P = 0.002), PSA nadir value after MDT (HR: 2.979, 95% CI: 1.882–4.717; P < 0.001), and employment of [18F]F-Fluorocholine PET/CT to steer MDT (HR: 3.813, 95% CI: 1.351–10.760; P = 0.011). To further delineate the influence of the radiotracers, Kaplan-Meier curves were constructed **(Figure 2)**. Consistent with the earlier findings, individuals whose MDT was guided by [18F]F-Fluorocholine PET/CT exhibited substantially shorter median PFS relative to those in the [68Ga]Ga-PSMA-11 group (15.47 months, 95% CI: 4.13–38.00 versus 40.93 months, 95% CI: 40.93–40.93; P = 0.047). On multivariate analysis, only CRPC status and post-MDT PSA nadir retained independent prognostic value for PFS (P = 0.024 and P < 0.001, respectively); **(Table 2)**, whereas the remaining clinical and imaging variables did not achieve statistical significance.

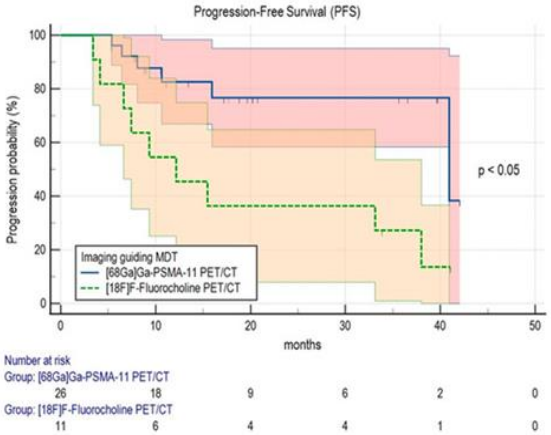

Figure 2. Kaplan-Meier survival curves depicting PFS stratified by the radiotracer used to guide MDT.

The statistical comparison between groups was conducted using the Log Rank test. Abbreviations: MDT= metastasis-directed therapy; PET/CT= positron emission tomography/computed tomography; PFS= progression-free survival.

Table 2. Prognostic values of clinical and imaging characteristics in the prediction of PFS.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**
Age	0.973 (0.914–1.036)	0.390		
ISUP grade				
ISUP 1	1.000 (Ref.)			
ISUP 2	0.694 (0.097–4.972)	0.716		
ISUP 3	0.993 (0.163–6.030)	0.994		
ISUP 4	1.474 (0.268–8.097)	0.656		
ISUP 5	1.536 (0.265–8.916)	0.632		
Primary treatment (radiotherapy vs. surgery)				
Surgery	1.000 (Ref.)			
Radiotherapy (± ADT)	2.617 (0.784–8.736)	0.143		
Previous salvage radiotherapy	0.698 (0.217–2.243)	0.546		
CRPC	6.238 (1.939–20.073)	**0.002**	4.587 (1.226–17.154)	**0.024**
PSA pre-MDT	1.005 (0.922–1.095)	0.907		
Medical therapy in addition to MDT	0.635 (0.142–2.843)	0.553		
PSA nadir after MDT	2.979 (1.882–4.717)	**< 0.001**	2.937 (1.750–4.928)	**<0.001**
PET/CT imaging				
[68Ga]Ga-PSMA-11	1.000 (Ref.)			
[18F]F-Fluorocholine	3.813 (1.351–10.760)	**0.011**	2.603 (0.829–8.172)	0.100
SUVmax	1.031 (0.981–1.084)	0.232		
MTV	0.936 (0.707–1.240)	0.645		
TLG	1.002 (0.977–1.028)	0.870		
Number of metastases treated with MDT				
1 lesion	1.000 (Ref.)			
2 or more lesions	1.550 (0.532–4.518)	0.422		
Site of metastases treated with MDT				
Lymph node	1.000 (Ref.)			
Bones or both	0.926 (0.283–3.031)	0.899		
MDT total dose	0.952 (0.812–1.117)	0.546		
MDT biologically effective dose	0.993 (0.958–1.029)	0.695		

Univariate and multivariate analyses were conducted using Cox regression. Significant p-values are highlighted in bold. Abbreviations: ADT = androgen deprivation therapy; CRPC = castration-resistant prostate cancer; ISUP = International Society of Urological Pathology; MDT = metastasis-directed therapy; MTV = metabolic tumor volume; PET/CT = positron emission tomography/computed tomography; PSA = prostate-specific antigen; SUVmax = maximum standardized uptake value; TLG = total lesion glycolysis.

Although agreement remains lacking on the precise lesion count that defines the oligometastatic condition [19, 20], the rationale for applying MDT is that both the primary tumor and distant metastatic sites can serve as sources of further tumor dissemination [21]. While SBRT is not the sole option for MDT [22, 23], it remains the predominant technique and has seen a substantial increase in adoption, with usage rising fourfold over the past 10 years [24].

In the phase II STOMP trial, MDT notably extended the interval until ADT initiation among PCa patients harboring one to three metastases relative to a surveillance strategy [7]. Beyond delaying ADT, eradication of oligometastatic lesions via MDT also delivered effective local control, demonstrated favorable safety, and contributed positively to extended oncological results in both synchronous and metachronous low-burden metastatic PCa [7]. The ORIOLE phase II trial randomized 54 oligometastatic

PCa patients who had discontinued ADT within six months to either MDT or observation [8]. Progression at six months was recorded in 19% of the MDT arm versus 61% in the observation arm. The durable clinical advantage of MDT was subsequently corroborated through a combined analysis of the STOMP and ORIOLE cohorts [9]. On one hand, these results have heightened interest in the field and spurred additional clinical investigations into the oligometastatic phase of PCa. On the other hand, they have highlighted several unresolved questions, particularly regarding the optimal imaging modality to guide MDT.

Employing PET/CT to guide MDT is anticipated to enhance its efficacy in oligometastatic PCa by minimizing undertreatment and extending long-term disease control. However, PET/CT in PCa can utilize various radiotracers in routine practice. Selection of a particular tracer often hinges on factors such as availability, associated expenses, reimbursement policies, and institutional expertise in image interpretation. Therefore, it is essential to establish whether one tracer offers clear advantages over alternatives. Although extensive evidence has confirmed the superior diagnostic performance of PSMA-directed radiotracers over [11C]C-choline or [18F]F-Fluorocholine for restaging PCa at low circulating PSA concentrations [25], no definitive superiority has been shown in patients with elevated PSA values [25] or advanced castration-resistant disease [26].

Additionally, emerging reports indicate variable PSMA expression in individuals undergoing systemic treatments [27, 28]. Such variability could translate into differing responses to MDT when guided by PSMA-based imaging. Consequently, any presumed benefit of PSMA-targeted tracers over radiolabeled choline agents in the oligometastatic setting amenable to MDT cannot be taken for granted. Thus, direct comparison with the other commonly employed PET tracer for PCa, drawing on real-world evidence, addresses an important clinical gap.

In the current investigation, [68Ga]Ga-PSMA-11 PET/CT was associated with improved PFS compared with [18F]F-Fluorocholine PET/CT among oligometastatic PCa patients undergoing PET-guided MDT. In keeping with this, the PSA nadir achieved after MDT was substantially lower when [68Ga]Ga-PSMA-11 guided the procedure, reflecting a stronger biochemical response. This observation holds importance because the PSA nadir emerged as the strongest independent predictor of outcome in our multivariable model. Unlike the ORIOLE and STOMP trials [7-9], our cohort included patients treated with MDT alone or MDT combined with systemic agents. This approach precluded evaluation of ADT-free survival as an endpoint.

Nevertheless, since concurrent systemic therapy was similarly distributed across the two imaging groups, the radiotracer choice for PET-guided MDT appears to carry independent prognostic significance, irrespective of accompanying systemic treatment. Due to limited statistical power, however, we were unable to conduct subgroup analyses to detect differential effects within specific patient subsets. Likewise, the real-world retrospective design incorporated both hormone-sensitive and castration-resistant cases, which were evenly represented across groups. As anticipated, CRPC status was a robust prognostic factor in both univariate and multivariate models, yet the small sample size precluded dedicated subgroup analyses.

A recent retrospective study by Mazzola *et al.* [29] employed a comparable approach. Their analysis, restricted to oligorecurrent hormone-sensitive PCa, demonstrated that [68Ga]Ga-PSMA-11 PET/CT-guided stereotactic radiotherapy conferred an advantage in ADT-free survival over [18F]F-Fluorocholine PET/CT. Notably, that study found no significant differences in ADT-free survival or PFS between groups when baseline PSA exceeded 0.5 ng/mL [29]. While our results did not mirror this PSA-related pattern, the observation warrants further examination, as it could imply that the clinical benefit of [68Ga]Ga-PSMA-11 PET/CT varies with pretreatment PSA levels.

It is worth mentioning that, despite relying on early data, the incremental benefit of [68Ga]Ga-PSMA-11 PET/CT in this context has already gained some acceptance in clinical practice. In 2019, the RADAR (Radiographic Assessments for Detection of Advanced Recurrence) III Group issued a paper strongly advocating next-generation imaging for patients with biochemically recurrent prostate cancer [30]. Subsequently, a survey by the AIRO (Italian Association of Radiotherapy and Clinical Oncology) genitourinary working group revealed a growing inclination among radiation oncologists to incorporate molecular imaging both before and after MDT [31]. More recently, the European Society for Radiotherapy and Oncology (ESTRO) Guidelines Committee, using the Delphi consensus process, released recommendations to standardize

radiotherapy for oligometastatic PCa [17]. The expert panel reached agreement on PSMA-targeted PET/CT as the preferred modality for staging and restaging in oligometastatic, oligorecurrent, and oligoprogressive disease [17]. Our findings align with this preference. Nonetheless, retrospective evidence of improved clinical outcomes alone is inadequate to justify alterations in standard care. As previously noted, larger prospective trials are required to resolve outstanding questions, such as the relative benefit of [68Ga]Ga-PSMA-11 PET/CT for guiding MDT as monotherapy versus MDT plus systemic therapy, its performance in hormone-sensitive versus castration-resistant populations, and its utility across varying baseline PSA levels.

Furthermore, routine application of highly sensitive next-generation imaging for MDT planning may trigger a "stage migration phenomenon," reclassifying some patients from oligometastatic to polymetastatic status [32]. This shift could preclude MDT in those with widespread disease, leaving systemic therapy as the primary option and potentially advancing its initiation. Therefore, any potential gains from next-generation imaging-guided MDT must be weighed against the long-term implications of earlier systemic treatment exposure. Simply increasing cohort size in future observational studies of PET-guided MDT may prove insufficient to resolve this issue and justify widespread implementation of [68Ga]Ga-PSMA-11 PET/CT-directed MDT. Dedicated prospective randomized trials will be essential to fully evaluate the consequences of stage migration induced by advanced imaging [33].

Limitations

The principal drawback of this investigation is the modest sample size. Additionally, within the 37 enrolled patients, those managed with [68Ga]Ga-PSMA-11 PET/CT-guided MDT outnumbered those in the [18F]F-Fluorocholine group (26 versus 11). Consequently, larger and more balanced cohorts will be necessary to validate these observations in oligometastatic PCa. Second, the real-world retrospective nature resulted in the inclusion of both hormone-sensitive and CRPC cases. Once again, the restricted patient numbers precluded focused subgroup comparisons between these categories. Finally, it is recognized that ADT can substantially impair quality of life in PCa patients [6], whereas MDT offers the potential to defer systemic toxicities with acceptable tolerance [7-9]. It would therefore be valuable to assess whether the choice of guiding radiotracer ([18F]F-Fluorocholine versus [68Ga]Ga-PSMA-11) influences the ability to postpone ADT and maintain quality of life. Due to the retrospective design, this aspect could not be examined, underscoring the need for dedicated follow-up research.

Conclusion

In summary, these findings indicate that broadening detection of otherwise occult disease through next-generation imaging—effectively revealing more of the "submerged iceberg"—can positively influence oncological outcomes in oligometastatic PCa patients undergoing MDT. Nevertheless, further prospective randomized studies remain essential to substantiate the routine clinical integration of [68Ga]Ga-PSMA-11 PET/CT-guided MDT.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Cornford P, van den Bergh R, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer. Part II-2020 update: treatment of relapsing and metastatic prostate cancer. Eur Urol. 2021;79(2):263–82.
2. Chi KN, Agarwal N, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med. 2019;381(1):13–24.
3. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. N Engl J Med. 2019;381(2):121–31.
4. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med. 2017;377(4):352–60.
5. Smith MR, Hussain M, Saad F, Fizazi K, Sternberg CN, Crawford ED, et al. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Engl J Med. 2022;386(12):1132–42.

6. Tucci M, Leone G, Buttigliero C, Zichi C, di Stefano RF, Pignataro D, et al. Hormonal treatment and quality of life of prostate cancer patients: new evidence. Minerva Urol Nefrol. 2018;70(2):144–51.
7. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, de Bruycker A, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol. 2018;36(5):446–53.
8. Phillips R, Shi WY, Deek M, Radwan N, Lim SJ, Antonarakis ES, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. JAMA Oncol. 2020;6(5):650–9.
9. Deek MP, van der Eecken K, Sutera P, Deek RA, Fonteyne V, Mendes AA, et al. Long-term outcomes and genetic predictors of response to metastasis-directed therapy versus observation in oligometastatic prostate cancer: analysis of STOMP and ORIOLE trials. J Clin Oncol. 2022;40(29):3377–82.
10. Chiong E, Murphy DG, Akaza H, Buchan NC, Chung BH, Kanesvaran R, et al. Management of patients with advanced prostate cancer in the Asia Pacific region: 'real-world' consideration of results from the Advanced Prostate Cancer Consensus Conference (APCCC) 2017. BJU Int. 2019;123(1):22–34.
11. deSouza NM, Liu Y, Chiti A, Oprea-Lager D, Gebhart G, van Beers BE, et al. Strategies and technical challenges for imaging oligometastatic disease: recommendations from the European Organisation for Research and Treatment of Cancer imaging group. Eur J Cancer. 2018;91:153–63.
12. Fanti S, Minozzi S, Antoch G, Banks I, Briganti A, Carrio I, et al. Consensus on molecular imaging and theranostics in prostate cancer. Lancet Oncol. 2018;19(12):e696–708.
13. Cornford P, Bellmunt J, Bolla M, Briers E, de Santis M, Gross T, et al. Guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol. 2017;71(4):630–42.
14. EAU Guidelines [Internet]. Available from: http://uroweb.org/guidelines/compilations-of-all-guidelines/ [cited 2022 Oct 31].
15. Fendler WP, Eiber M, Beheshti M, Bomanji J, Ceci F, Cho S, et al. 68Ga-PSMA PET/CT: joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. Eur J Nucl Med Mol Imaging. 2017;44(6):1014–24.
16. Linee Guida dell'Associazione Italiana di Medicina Nucleare [Internet]. Available from: https://www.aimn.it/documenti/lineeguida/4_Imaging%20Oncologico%20con%2018F%20Colina.pdf [cited 2022 Dec 21].
17. Zilli T, Achard V, dal Pra A, Schmidt-Hegemann N, Jereczek-Fossa BA, Lancia A, et al. Recommendations for radiation therapy in oligometastatic prostate cancer: an ESTRO-ACROP Delphi consensus. Radiother Oncol. 2022;176:199–207.
18. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402–18.
19. Rao A, Vapiwala N, Schaeffer EM, Ryan CJ. Oligometastatic prostate cancer: a shrinking subset or an opportunity for cure? Am Soc Clin Oncol Educ Book. 2019;39:309–20.
20. Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. Radiother Oncol. 2020;148:157–66.
21. Gundem G, van Loo P, Kremeyer B, Alexandrov LB, Tubio J, Papaemmanuil E, et al. The evolutionary history of lethal metastatic prostate cancer. Nature. 2015;520(7547):353–7.
22. Fossati N, Suardi N, Gandaglia G, Bravi CA, Soligo M, Karnes RJ, et al. Identifying the optimal candidate for salvage lymph node dissection for nodal recurrence of prostate cancer: results from a large, multi-institutional analysis. Eur Urol. 2019;75(1):176–83.
23. Porres D, Pfister D, Thissen A, Kuru TH, Zugor V, Buettner R, et al. The role of salvage extended lymph node dissection in patients with rising PSA and PET/CT scan detected nodal recurrence of prostate cancer. Prostate Cancer Prostatic Dis. 2017;20(1):85–92.
24. Ning MS, Boyce-Fappiano D, Thaker NG. Oligometastatic disease in context of the radiation oncology alternative payment model: implications

for local consolidative therapy. JCO Oncol Pract. 2021;17(12):773–6.
25. Treglia G, Pereira Mestre R, Ferrari M, Bosetti DG, Pascale M, Oikonomou E, et al. Radiolabelled choline versus PSMA PET/CT in prostate cancer restaging: a meta-analysis. Am J Nucl Med Mol Imaging. 2019;9(3):127–39.
26. Weber M, Hadaschik B, Ferdinandus J, Rahbar K, Bögemann M, Herrmann K, et al. Prostate-specific membrane antigen-based imaging of castration-resistant prostate cancer. Eur Urol Focus. 2021;7(2):279–87.
27. Staniszewska M, Fragoso Costa P, Eiber M, Klose JM, Wosniack J, Reis H, et al. Enzalutamide enhances PSMA expression of PSMA-low prostate cancer. Int J Mol Sci. 2021;22(14):7431.
28. Zukotynski KA, Emmenegger U, Hotte S, Kapoor A, Fu W, Blackford AL, et al. Prospective, single-arm trial evaluating changes in uptake patterns on prostate-specific membrane antigen-targeted 18F-DCFPyL PET/CT in patients with castration-resistant prostate cancer starting abiraterone or enzalutamide. J Nucl Med. 2021;62(10):1430–7.
29. 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(3):230–6.
30. Crawford ED, Koo PJ, Shore N, Slovin SF, Concepcion RS, Freedland SJ, et al. A clinician's guide to next generation imaging in patients with advanced prostate cancer (RADAR III). J Urol. 2019;201(4):682–92.
31. Lucchini R, Francolini G, Matrone F, Timon G, Franzese C, Marvaso G, et al. Attitudes, practices and perspectives on imaging strategies in prostate cancer: a national cross-sectional survey involving expert radiation oncologists on behalf of AIRO (Italian association of radiotherapy and clinical oncology) GU group. Med Oncol. 2021;39(1):3.
32. Sundahl N, Gillessen S, Sweeney C, Ost P. When what you see is not always what you get: raising the bar of evidence for new diagnostic imaging modalities. Eur Urol. 2021;79(5):565–7.
33. Jadvar H, Abreu AL, Ballas LK, Quinn DI. Oligometastatic prostate cancer: current status and future challenges. J Nucl Med. 2022;63(11):1628–35.