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Scientific Article

Prostate-Specific Membrane Antigen PET Response Associates with Metastasis-Free Survival After Stereotactic Ablative Radiation in Oligometastatic Prostate Cancer

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Purpose: Emerging data suggest that metastasis-directed therapy (MDT) improves outcomes in patients with oligometastatic castration-sensitive prostate cancer (omCSPC). Prostate-specific membrane antigen positron emission tomography (PSMA-PET) can detect occult metastatic disease, and PSMA response has been proposed as a biomarker for treatment response. Herein, we identify and validate a PSMA-PET biomarker for metastasis-free survival (MFS) following MDT in omCSPC.

Methods and Materials: We performed an international multi-institutional retrospective study of patients with omCSPC, defined as ≤3 lesions, treated with metastasis-directed stereotactic ablative radiation who underwent PSMA-PET/computed tomography (CT) before and after (median, 6.2 months; range, 2.4-10.9 months) treatment. Pre- and post-MDT PSMA-PET/CT maximum standardized uptake value (SUV_{max}) was measured for all lesions, and PSMA response was defined as the percent change in SUV_{max} of the least responsive lesion. PSMA response was both evaluated as a continuous variable and dichotomized into PSMA responders, with a complete/partial response (at least a 30% reduction in SUV_{max}), and PSMA nonresponders, with stable/progressive disease (less than a 30% reduction in SUV_{max}). PSMA response was correlated with conventional imaging-defined metastasis-free survival (MFS) via Kaplan-Meier and Cox regression analysis.

Results: A total of 131 patients with 261 treated metastases were included in the analysis, with a median follow-up of 29 months (IQR, 18.5-41.3 months). After stereotactic ablative radiation, 70.2% of patients were classified as PSMA responders. Multivariable analysis demonstrated that PSMA response as a continuous variable was associated with a significantly worse MFS (hazard ratio = 1.003; 95% CI, 1.001-1.006; $P = .016$). Patients classified as PSMA responders were found to have a significantly improved median MFS of 39.9 versus 12 months ($P = .001$) compared with PSMA nonresponders. Our study is limited as it is a retrospective review of a heterogenous population.

Conclusions: After stereotactic ablative radiation, PSMA-PET response appears to be a radiographic biomarker that correlates with MFS in omCSPC. This approach holds promise for guiding clinical management of omCSPC and should be validated in a prospective setting.

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Introduction

Globally, prostate cancer represents the third most common malignancy and is responsible for nearly 400,000 deaths annually.[1] Despite advances in technologies and treatment of both castration-sensitive and castration-resistant prostate cancer, metastatic disease remains largely incurable.[2-7] Although androgen deprivation therapy (ADT) is used to treat metastatic castration-sensitive prostate cancer (mCSPC), the majority of patients will eventually develop castration resistance, which is associated with higher rates of mortality.

Given this trajectory, there is significant interest in metastasis-directed therapy (MDT), used to improve outcomes by delaying progression and initiation of long-term systemic therapy. Several clinical trials have evaluated the role of MDT with stereotactic ablative radiation (SABR) in patients with limited metastatic disease, known as oligometastatic disease.[8-12] These trials have defined the oligometastatic state as no more than 3 to 5 metastases. For metachronous oligorecurrent mCSPC, the STOMP and ORIOLE trials demonstrated improved ADT-free and progression-free survival, respectively, with MDT, compared with observation.[13,14]

Importantly, numerical definitions of oligometastasis rely heavily upon the sensitivity of the imaging used.[15] With the advent of molecular imaging, the sensitivity of prostate cancer imaging has improved dramatically. Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein expressed on the surface of prostate cancer cells and is overexpressed by both local and metastatic prostate cancer.[16,17] PSMA-based positron emission tomography (PET) imaging has demonstrated high sensitivity and specificity in detecting occult metastatic disease,[18,19] and the PSMA response has been proposed as a potential biomarker for the response to systemic or local therapy.[20] Herein, we evaluated the post-SABR PSMA-PET response to MDT in patients with oligometastatic mCSPC (omCSPC) to assess the correlation between PSMA response and clinical outcomes.

Methods and Materials

Following institutional review board approval, we performed an international multi-institutional cohort study of men with newly diagnosed omCSPC treated with metastasis-directed SABR who underwent pre- and posttreatment PSMA-PET/computed tomography (CT). Patients included those treated at Johns Hopkins Hospital as part of the ORIOLE trial[14] (conventionally staged cohort) and those treated at Baskent University (PSMA-PET staged cohort).

Inclusion criteria were patients with omCSPC, defined as ≤3 metastases on either conventional (CT/radionuclide bone scan) or PSMA-targeted (PET) molecular imaging. Patients with oligometastatic disease per conventional imaging but with polymetastatic disease per PET (range, 4-25 lesions) were eligible for inclusion, as patients in the ORIOLE trial were defined on conventional imaging but underwent pre-MDT PSMA-PET, to which investigators were blinded. Patients treated with concurrent ADT were also included in the analysis.

Before MDT, all patients received either ^{68}Ga-PSMA-HBED-CC or ^{18}F-DCFPyL-PSMA PET/CT. All patients underwent CT-based simulation with personalized immobilization specific to the metastasis location. Gross tumor volume and organs at risk (OARs) were identified by the treating physician. A variable planning target volume expansion of 2 to 5 mm was performed based on metastasis location. A SABR plan was generated with dose and fractionation based on tumor size and location, while maintaining normal tissue constraints to OARs per AAPM Task Group 101 recommendations.[21] Prescription doses ranged from 16 to 60 Gy in 1 to 5 fractions (1 patient was treated with hypofractionated radiation therapy in 15 fractions). Image guidance with cone beam CT was used to confirm patient set-up before treatment. A follow-up PSMA-PET/CT was performed to evaluate disease response after SABR. Following MDT, patients did not receive any systemic therapy until evidence of disease progression was observed (with the exception of the limited duration of concurrent ADT delivered with MDT). Available follow-up data from serial physical examinations, imaging, and prostate-specific antigen (PSA) measurements were obtained by chart review.

Summary statistics were calculated for patients and lesions. Each lesion was characterized as having a complete response (CR; no residual PSMA activity), partial response (PR; at least 30% reduction in SUV_{max}), stable disease (SD; <30% reduction or <20% increase in SUV_{max}), or progressive disease (PD; at least 20% increase in SUV_{max}). Discrete cutoff values were determined to reflect commonly used radiographic thresholds of response.[22] Multivariable binary logistic regression was used to identify clinical/treatment features associated with PSMA response (CR/PR). The primary outcome was metastasis-free survival (MFS) following SABR, stratified into PSMA responders (all lesions with CR/PR) versus PSMA nonresponders (at least 1 lesion with SD/PD); PSMA response was evaluated as a continuous variable for the worst responding lesion. MFS was defined as the time from MDT to development of new distant metastasis on conventional imaging, or death from any cause.[23] Given the clinical heterogeneity of the cohort, several subgroup analyses were also performed to evaluate PSMA response as a biomarker for MFS in more clinically homogenous groups, including those treated with and without concurrent ADT, metachronous and synchronous metastatic disease, conventional and PSMA staging, total and subtotal disease consolidation, and lymph node only and bone/visceral metastases. Our secondary outcomes included lesion local control (LLC) after MDT. Lesion local failure was defined as radiographic growth of a lesion on conventional imaging within the SABR-treated field in conjunction with a rising PSA level. Survival analyses were calculated with the Kaplan-Meier method and compared using a log-rank test. Multivariable Cox regression analysis was conducted for MFS. Variables included in the multivariable analysis were selected a priori based on characteristics known to be associated with prognosis.[14,24-26] Proportional hazards assumption was validated for PSMA response and the timing of the post-MDT PSMA-PET (Fig. E1). Interaction terms for PSMA response and covariates included in the multivariable Cox regression were calculated. All statistical analyses were conducted using IBM SPSS Statistics, version 27, and a 2-sided P value <0.05 was considered statistically significant.

Results

A total of 131 patients with 315 metastases (261 treated with MDT) were included in the analysis, with a median follow-up of 35.4 months (IQR, 21.3-49.9 months). Baseline demographic, clinical, and treatment characteristics at initial diagnosis (Table E1) and oligometastasis (Table 1) are reported. Characteristics of the conventionally staged and PSMA-PET-staged cohorts can be seen in Table E2. The majority of patients had metachronous disease (74.0%) and received MDT to all PSMA-positive lesions (87.8%). The characteristics of all 315 observed PSMA-positive lesions are summarized in Table E3. Among the 261 treated lesions, bone (52.5%) and lymph node (45.2%) metastases were most common. The median pre-MDT SUV_{max} for all lesions was 8.7 (IQR, 4.0-16.7) and was similar among metastasis locations (Table 1). Lymph node and bone lesions were both treated with a median biologically effective dose (α/β = 3) (BED_3) of 116.7 Gy (IQR: bone, 90-126; node, 90-124), while visceral metastases received a median BED_3 of 378 Gy (IQR, 234-419). A detailed list of radiation prescriptions used can be found in Supplemental Table E4.

A post-PSMA PET scan was performed a median of 6.2 months (IQR, 4.6-8.7; range, 2.4-10.9) after MDT. The per lesion response rates after SABR were as follows: CR, 27.6%; PR, 51.7%; SD, 14.2%; and PD, 6.5%. In contrast, 90.7% of the 54 untreated lesions had SD/PD. Percent change from baseline SUV_{max} can be seen for treated and untreated lesions (Fig. 1). Multivariable logistic regression only identified that concurrent ADT was associated with an increased likelihood of lesion PSMA response (CR/PR) (OR = 3.04; 95% CI, 1.38-6.70; P = .006) (Table 2).

Table 1 Demographic, treatment, and lesion characteristics at time of oligometastasis

Oligometastatic characteristics	N = 131	Treated lesion characteristics	N = 261
Median age at oligomet (IQR)	66 (60.75-66)	**Location**	
Median PSA at oligomet (IQR)	4.5(1.9-11.8)	Node	118 (45.2%)
		Bone	137 (52.5%)
		Visceral	3 (1.1%)
		Prostate/Local recurrence	1 (0.4%)
Timing			
Metachronous	97 (74.0%)		
Synchronous/*de novo*	34 (25.2%)	**Median pre-MDT SUV_{max} (IQR)**	
		All Lesions	8.7 (4.0-16.7)
Staging imaging		Node	9.1(4.0-18.5)
Conventional (CT/Bone Scan)	35 (26.7%)	Bone	8.6 (4.2-15.7)
PSMA-PET	96 (73.3%)	Visceral	7.8 (6.2-10.2)
Number of PSMA lesions		**Median BED_3 Gy (IQR)**	
1	62 (47.3%)	All Lesions	116.7(90-126)
2	42 (32.1%)	Node	116.7 (90-124)
3	12 (9.2%)	Bone	116.7 (90-126)
≥ 4	15 (11.5%)	Visceral	378 (234-419)
Total PSMA consolidation		**PSMA SUV response**	
Yes	115 (87.8%)	Complete response	72 (27.6%)
No	16 (12.2%)	Partial response	135 (51.7%)
ADT with MDT		Stable disease	37 (14.2%)
Yes	86 (65.6%)	Progressive disease	17 (6.5%)
No	45 (34.4%)		
Median duration of ADT (IQR)	2 (1.0-3.75) mo.		
Mode of failure			
Long-term disease free	64 (48.9%)		
Oligoprogressor	32 (24.4%)		
Polyprogressor	35 (26.7%)		

Abbreviations: ADT = androgen deprivation therapy; MDT = metastasis-directed therapy; PSA = prostate-specific antigen; PSMA-PET = prostate-specific membrane antigen positron emisssion tomography; SUV = standardized uptake value.

Within the entire cohort, the 3-year LLC was 87%, and the median LLC was not reached. When stratified by lesional PSMA response, 3-year LLC rates were 92% versus 66% for PSMA responders and nonresponders, respectively (Fig. 2A). Per multivariable Cox regression, PSMA response, as a continuous variable, was associated with LLC (HR = 1.003; 95% CI, 1.001-1.006; P = .016) after accounting for BED_3 of SABR, lesion location, ADT, and pre-MDT SUV_{max} (Table 3).

Within the entire cohort, the 3-year MFS was 46%, and the median MFS was 35.4 months (95% CI, 23.6-47.2 months). When stratified by treatment response, the 3-year MFS was 51% versus 33% for PSMA responders and nonresponders, respectively (Fig. 2B). Similarly, the median MFS was significantly prolonged among PSMA responders versus nonresponders (39.9 vs 12 months, respectively; P = .001). Although death was considered an MFS event, only 2 patients died before developing a new, conventionally detected metastasis, neither of whom had PSMA progression nor died of prostate cancer. Given the heterogeneity of the cohort, which included patients with different staging imaging, timing of disease, use of ADT, and metastatic location, we evaluated whether PSMA response was associated with MFS within these subsets. PSMA response was significantly associated with MFS in patients treated with and without ADT (Fig. E2), in patients with metachronous disease (Fig. E3), in those staged with conventional and PSMA-PET imaging

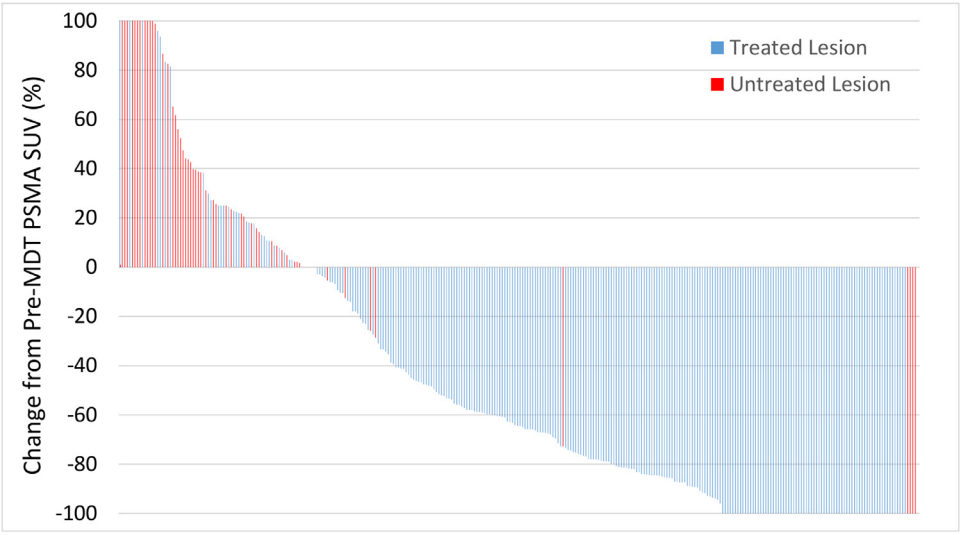

Figure 1 Waterfall plot demonstrating percent change of PSMA-PET SUV_{max} for both treated and untreated lesions.
Abbreviations: PSMA-PET = prostate-specific membrane antigen positron emission tomography.

Table 2 Binary logistic regression of characteristics predictive of SUV response (CR/PR) to MDT

	Multivariate	
Predictor of SUV response	**OR (95% CI)**	***P* value**
Lymph node (vs bone)	1.21 (0.56-2.62)	0.6
Pre-MDT SUV_{max} (continuous)	1.022 (0.99-1.05)	0.15
BED_3 (continous)	1.01 (0.99-1.02)	0.4
ADT with MDT	**3.04 (1.38-6.70)**	**0.006**

Abbreviations: BED_3 = biologically effective dose (α/β = 3); CR = complete response; MDT = metastasis-directed therapy; PR = partial response; SUV = standardized uptake value.

(Fig. E4), in patients with total PSMA consolidation (Fig. S5), and in patients with lymph node only and bone/visceral metastases (Fig. E6). Notably, PSMA response was only not significantly associated with MFS among patients with synchronous disease (only 2 PSMA nonresponders) and those with subtotal PSMA consolidation (only 1 PSMA responder). Per multivariable Cox regression, PSMA response, as a continuous variable, was associated with MFS (HR = 1.003; 95% CI, 1.001-1.004; $P < .001$) when accounting for total PSMA consolidation, disease timing, Gleason grade group, ADT, pre-MDT PSA, and staging imaging (Table 4). None of the covariates included in the multivariable Cox regression analysis, nor

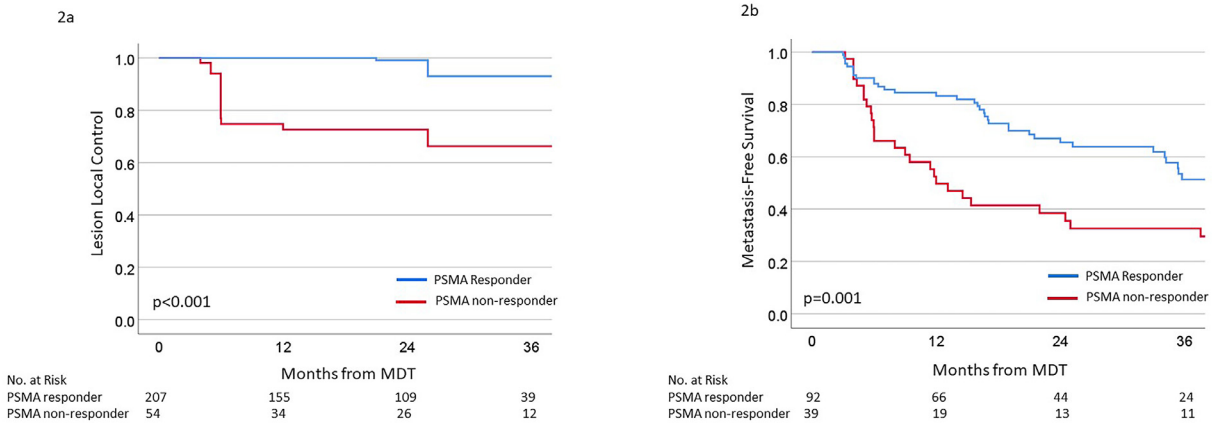

Figure 2 Kaplan-Meier survival curves of (A) lesion local control for treated lesions and (B) metastasis-free survival stratified by PSMA responders and nonresponders.
Abbreviations: PSMA = prostate-specific membrane antigen.

Table 3 Multivariable Cox regression analysis of variables associated with lesion local control for treated lesions

Clinical variable	HR (95% CI)	*P* value
PSMA response*	1.003 (1.001-1.006)	0.016
BED_3 (continuous)	0.97 (0.96-0.99)	0.005
Lymph node (vs bone)	1.44 (0.29-7.15)	0.7
Concurrent ADT (vs no ADT)	0.19 (0.03-1.07)	0.06
Pre-MDT SUV_{max} (continuous)	1.04 (1.01-1.06)	0.002

Abbreviations: ADT = androgen deprivation therapy; BED_3 = biologically effective dose (α/β = 3); MDT = metastasis-directed therapy; PSMA = prostate-specific membrane antigen; SUV = standardized uptake value.
*PSMA response defined as percent change in SUV_{max} after MDT, evaluated as a continuous variable.

the time from the end of MDT to post-MDT PSMA-PET, had a significant *P* value for the interaction with the PSMA response (Table E5).

Discussion

We report an association between post-MDT PSMA-PET response dynamics and important clinical outcomes. MDT induces a PSMA-PET response that is not observed in untreated metastases, and PSMA progression is associated with MFS, both as a continuous variable and a clinically valid dichotomization. Taken together, these findings suggest that PSMA-PET response may be an effective radiographic biomarker for distant control following MDT in omCSPC. The identification of a PSMA-PET response biomarker that correlates with MFS following MDT in omCSPC is of particular interest, as MFS has been shown to be a strong surrogate for overall survival in localized CSPC.[23] These findings allow for the early identification of patients (PSMA responders) who can remain off of any systemic therapy for a meaningful period of time, versus those that are likely to progress quickly (PSMA nonresponders) and potentially benefit from treatment intensification with early initiation of systemic therapy. Further work in elucidating which type and duration of systemic therapy for these rapidly progressing patients with omCSPC should be pursued.

Two previous studies compared MDT using PSMA- or choline-PET to identify lesions, and both found that PSMA-guided treatment improved ADT-free survival.[27,28] This improvement is likely due to the increased detection of occult metastatic disease with PSMA-PET and is consistent with our results of improved distant MFS with total PSMA-PET consolidation.[29] Additional reports with PSMA-PET-directed SBRT in both castration-sensitive and resistant oligometastatic prostate cancer have demonstrated similar 2-year local control rates ranging between 95% to 100%, but with a median PFS ranging from 12 to 41 months.[30-32] Glicksman et al.[33] reported that in a single-arm phase 2 trial of 37 patients with PSMA-PET-defined oligorecurrent prostate cancer (negative by conventional imaging) treated with MDT with either SABR or surgery, there was a biochemical response rate of 60%, and there was no biochemical evidence of disease in 22% of patients following MDT.

Timing of posttreatment PSMA-PET imaging remains of critical importance. ADT initially increases PSMA expression in the short term through abrogation of androgen-related downregulation of *FOLH1* gene expression, leading to increased *FOLH1* transcription and subsequent

Table 4 Multivariable cox regression of variables associated with conventionally defined metastasis-free survival

Clinical variable	HR (95% CI)	*P* value
PSMA response*	1.003 (1.001-1.004)	<0.001
Total PSMA consolidation	0.59 (0.22-1.59)	0.29
Metachronous (vs synchronous)	3.35 (1.62-6.91)	0.001
Gleason grade group	1.13 (0.91-1.41)	0.28
Concurrent ADT (vs no ADT)	1.61 (0.37-6.70)	0.5
Pre-MDT PSA	1.003 (0.997-1.009)	0.3
Conventionally staged (vs PSMA staged)	0.52 (0.10-2.59)	0.4

Abbreviations: ADT = androgen deprivation therapy; MDT = metastasis-directed therapy; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.
*PSMA response defined as percent change in the SUV_{max} of the worst responding lesions, evaluated as a continuous variable.

increased PSMA expression.[34-36] This, however, is contrasted by a subsequent decrease in PSMA expression through tumor cell killing. Onal et al demonstrated a median decrease in PSMA-PET SUV_{max} of 66% following 3 months of ADT.[37] This decrease is likely due to the treatment effect of ADT reducing tumor mass, despite upregulation of PSMA on the remaining viable cells.[38] Given the above-noted time dependence of PSMA-PET avidity on ADT, post-SABR imaging should be performed at least 3 months following treatment, particularly if concurrent ADT was delivered, to avoid misclassifying patients with an ADT flare as having progressive lesions.

Surprisingly, within this study, concurrent ADT was not found to be significantly associated with MFS, despite it showing an increased likelihood of a PSMA response. This is likely due to the fact that patients with more aggressive disease characteristics are more likely to receive concurrent ADT. Given that the duration of the concurrent ADT was very short, it is possible that this short duration of ADT was able to overcome these more aggressive features and show an MFS benefit. Importantly, however, PSMA response was shown to be prognostic regardless of whether patients received concurrent ADT.

Although we demonstrated a correlation between SUV_{max} and clinical outcomes at the post-SABR time point, the optimal time for posttreatment imaging remains unknown, as the PSMA-PET response to MDT is seldom reported. Greco et al reported a single-institution phase 2 study evaluating the PET response following MDT in oligometastatic disease across multiple histologies. This study included 147 patients with prostate cancer (who underwent ^{68}Ga-PSMA PET) and demonstrated that a change in the PET SUV_{max} was associated with locoregional failure.[39] This study included a 3- and 6-month posttreatment PET, which showed similar results, though specific SUV_{max} changes over time were not reported. Sadestski et al reported a retrospective review of 12 patients (15 lesions) with bone metastases treated with SABR with pre- and posttreatment PSMA-PET. Posttreatment imaging was performed at a median of 17 months following treatment, and 93% of lesions demonstrated a complete SUV_{max} response. No lesion local failures were observed at a median follow-up of 26.5 months.[40] This report demonstrated a significantly higher complete SUV_{max} response rate than what we demonstrated here, which may be because of the earlier time point used for posttreatment imaging in our study. Notably, neither of these prior studies associated PET response with either MFS or overall survival, which is a major strength of the present study.

This study has several limitations. First, this was a retrospective review that included a heterogeneous cohort of patients. Although we attempted to control for the nuanced different clinical features apparent in our cohort, there may be confounding variables not accounted for. Second, post-MDT imaging was also performed at variable times (IQR, 4.6-8.8 months; range, 2.4-10.9), which may affect the degree of PSMA response observed. Although we have correlated outcomes with SUV_{max} percent change, this may not be the most biologically appropriate response assessment, as other markers of metabolic response, such as SUV_{mean} (which was not available for these cohorts) may serve as a more robust biomarker. Additionally, 2 different PSMA tracers were used in the cohort, which may have influenced our findings.[41] Another limitation is that detailed PSA kinetics were unavailable for the cohort, so the interaction between PSMA response and PSA kinetics could not be evaluated, which may provide an additional dimension for understanding the risk of disease progression. Finally, the ICE-CaP definition of MFS has been strongly correlated with overall survival within localized disease, and it is unknown if this association retains its significance in the oligometastatic setting. Despite these limitations, we have identified a novel radiographic biomarker of PSMA-PET change after SABR as a response indicator correlating with MFS.

Conclusion

In this multi-institutional, international patient series, PSMA-PET response in patients with omCSPC after MDT was associated with MFS. Pending prospective validation, our findings suggest that PSMA-PET should be considered for MDT targeting, evaluating treatment response, and guiding subsequent intervention. Future work is required to further refine our understanding of when post-SABR PSMA-PET imaging should be performed and how best to characterize the PSMA response.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101507.

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