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The Role of PSMA PET Parameters as Biomarkers for Response to PSMA-Targeted Radiopharmaceutical Therapy

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Prostate-specific membrane antigen (PSMA) PET is a well-established imaging tool for the evaluation of primary and recurrent prostate cancer (PCa). ^{177}Lu PSMA-targeted radiopharmaceutical therapy (RPT) enables direct delivery of β-radiation to PSMA-expressing PCa cells while minimizing damage to normal tissue. As PSMA RPT becomes more widely used, there is growing interest in evaluating the predictive and prognostic role of PSMA PET parameters to enable better patient selection and effectively monitor treatment response. The purpose of this paper is to review the role of PSMA PET parameters as biomarkers for PSMA RPT. Quantitative parameters on baseline PSMA PET can serve as prognostic biomarkers for overall survival and predictive biomarkers for prostate-specific antigen response. Alongside lesion-based assessments, changes in whole-body quantitative parameters from baseline to interim or end-of-treatment PSMA PET are prognostic for overall survival and progression-free survival in patients undergoing PSMA RPT. Changes in quantitative, whole-body PSMA PET parameters may better reflect changes in PCa following systemic therapy compared with individual lesion-based assessments. Further research is necessary in larger, prospective trials to characterize the role of PSMA PET parameters as prognostic biomarkers for progression-free survival and overall survival in metastatic castration-resistant PCa patients undergoing PSMA RPT.

Key Words: prostate cancer; theranostics; PSMA PET; radiopharmaceutical therapy; mCRPC

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Prostate cancer (PCa) is the most frequently diagnosed malignancy in developed countries and a leading cause of cancer death worldwide (*1*). The prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein that is significantly upregulated in PCa cells and serves as a target for molecular imaging and therapy (*2*). PSMA PET is a well-established tool for the evaluation of primary and recurrent PCa with superior diagnostic accuracy compared with conventional imaging (*3*,*4*). ^{177}Lu PSMA-targeted radiopharmaceutical therapy (RPT) enables direct delivery of β-radiation to PCa cells while minimizing damage to normal tissue. Results from the phase 3 VISION trial demonstrated that PSMA RPT prolonged overall survival (OS) in patients with metastatic castration-resistant PCa (mCRPC) who previously progressed on taxane-based chemotherapy and androgen receptor signaling inhibitors. These results paved the way to regulatory approval of this therapy in 2022 (*5*). The TheraP trial also demonstrated that PSMA RPT achieved similar OS, improved prostate-specific antigen (PSA) response rates, and reduced grade 3 or 4 adverse events compared with cabazitaxel in mCRPC patients, thus causing PSMA RPT to be proposed as a viable alternative to chemotherapy in the metastatic castration-resistant setting (*6*,*7*).

As PSMA RPT becomes more widely used, there is growing interest in evaluating the predictive and prognostic role of PSMA PET parameters to enable better patient selection and to effectively monitor treatment response. The purpose of this paper is to review the role of PSMA PET parameters as biomarkers for PSMA RPT. Pertinent literature is summarized in Table 1.

BASELINE PSMA PET VISUAL CRITERIA

In the VISION trial, ^{68}Ga-PSMA-11 PET/CT was used to determine the eligibility of mCRPC patients for PSMA RPT (*5*). Eligible patients had PSMA-positive mCRPC, defined as at least 1 PSMA-positive metastatic lesion (defined as uptake greater than that of the liver parenchyma in a lesion of any size in any organ system) and no PSMA-negative measurable lesions (>1 cm by CT) (*5*). Kuo et al. demonstrated moderate-to-substantial interreader agreement and substantial–to–almost perfect intrareader reproducibility for the assessment of ^{68}Ga-PSMA-11 PET/CT using VISION read criteria, whereas another multicenter cohort study found that patients who would have been screen failures based on VISION read criteria had a worse rate of more than 50% PSA decline, shorter PSA progression-free survival, and shorter OS (*8*,*9*). More recently, a retrospective analysis demonstrated that ^{18}F-DCFPyL has comparable biodistribution to ^{68}Ga-PSMA-11 and can serve as an alternative to ^{68}Ga-PSMA-11 for PSMA RPT patient selection (*10*).

BASELINE PSMA PET WHOLE-BODY QUANTITATIVE PARAMETERS

Baseline Tumor Volume and SUV_{mean}

Multiple studies have evaluated the prognostic value of whole-body tumor volume on baseline PSMA PET in mCRPC patients undergoing PSMA RPT. Higher baseline whole-body PSMA tumor volume and PSMA 50% threshold of lesion SUV_{max} have previously been shown to be statistically significant negative prognosticators of OS in this patient population (*11*,*12*). These findings

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TABLE 1
Summary of Pertinent Literature

Topic	PMID	First author	Year published	Total patients (*n*)
VISION read criteria	37230533	Kuo	2023	125
	35273096	Hotta	2022	301
Tumor volume and PSMA TV50	32970216	Seifert	2021	110
	36302658	Kind	2023	70
SUV_{mean}	39162634	Kuo	2024	826
	38043558	Hofman	2024	200
Tumor–to–salivary gland ratio	36997329	Hotta	2023	237
HIT score	38637137	Swiha	2024	139
Nomograms to predict outcomes after PSMA RPT	34246328	Gafita	2021	270
	NA	Herrmann	2023	831
PSMA PET progression criteria	31806774	Fanti	2020	NA
	33789932	Michalski (*42*)	2021	46
RECIP 1.0	35422442	Gafita	2022	124
	37432081	Gafita	2023	124
Comparing different response criteria	35767071	Gafita	2022	124
Total lesion PSMA	37889298	Burgard (*54*)	2024	102
	38298510	Burgard (*56*)	2024	23
^{177}Lu-PSMA SPECT/CT parameters	36872949	Emmett	2023	125
	39117452	Yadav (*63*)	2024	122

PMID = PubMed identifier; TV50 = 50% threshold of lesion SUV_{max}; HIT = heterogeneity and intensity of tumors; NA = not applicable.

are also reflected in other studies that demonstrated that total osseous tumor volume derived from nuclear medicine bone scans is a negative prognosticator of OS in PCa patients (*13*).

On the other hand, higher SUV_{mean} on baseline PSMA PET is associated with higher absorbed doses of PSMA RPT and better reflects the overall avidity of PSMA expression than does SUV_{max} (*14*). A substudy of the VISION trial demonstrated that a higher SUV_{mean} on baseline ^{68}Ga-PSMA-11 PET imaging was associated with improved outcomes after treatment with ^{177}Lu-PSMA-617, whereas no association was found between SUV_{max} and OS (*15*). Importantly, this association was consistently demonstrated as baseline SUV_{mean} increased, and there was no cutoff to be used for binary patient selection. In the TheraP trial, high PSMA expression (defined as an SUV_{mean} of ≥10) on baseline PSMA PET was predictive of a higher likelihood of PSA response to PSMA RPT versus cabazitaxel (*6*,*7*). However, subsequent analyses from the TheraP trial demonstrated that PSMA SUV_{mean} was not predictive but prognostic for OS (*7*).

Since higher baseline tumor volume is associated with decreased OS whereas higher SUV_{mean} is associated with increased OS, there has also been growing interest in integrating both parameters into a single imaging biomarker. Seifert et al. demonstrated that total lesion quotient (tumor volume/SUV_{mean}) derived from baseline PSMA PET was an independent and superior prognosticator of OS compared with tumor volume (*11*). Further research is necessary to evaluate how tumor volume and SUV_{mean} should be weighted to optimize the prognostic value of baseline total lesion quotient.

NOTEWORTHY

- Quantitative parameters on baseline PSMA PET can serve as prognostic biomarkers for OS and predictive biomarkers for PSA response (*4*,*5*).
- Alongside lesion-based assessments, changes in whole-body quantitative parameters from baseline to interim or end-of-treatment PSMA PET are prognostic for OS and progression-free survival in patients undergoing PSMA RPT (*8*–*10*).
- Changes in quantitative, whole-body PSMA PET parameters may better reflect changes in PCa after systemic therapy than can individual lesion-based assessments (*9*,*10*).

Whole-Body Tumor-to-Background Visual Ratio

Although the VISION trial used the liver as the reference organ for screening PSMA PET/CT criteria, the PSMA uptake of the parotid gland is 2–3 times higher than that of the liver (*16*). Therefore, the use of the parotid gland as a reference organ can make screening criteria more stringent. A retrospective analysis of 237 men with mCRPC undergoing PSMA RPT stratified patients into 3 groups based on their SUV_{mean} ratio of whole-body tumor to parotid glands semiautomatically calculated on baseline PSMA PET using qPSMA software. This analysis found that patients with a high tumor–to–salivary gland ratio achieved a PSA decline of more than 50% at higher rates and had a longer median OS than did patients with an intermediate or low tumor–to–salivary

gland ratio (*17*). Classification of patients into 3 groups based on visual assessment of tumor–to–salivary gland ratio was also shown to have substantial interreader agreement and comparable prognostic value to the quantitative score, suggesting that a simple visual score derived from 3-dimensional maximal-intensity projection images could be used in a few seconds to exclude patients less likely to benefit from PSMA RPT (*17*).

The heterogeneity-and-intensity-of-tumors score, also developed as a visual alternative to quantitative SUV_{mean}, was also found to be comparable to quantitative SUV_{mean} for predicting survival outcomes after PSMA RPT, suggesting that it can serve as a surrogate for quantitative SUV_{mean} in clinical practice (*18*).

ADDITIONAL VALUE OF BASELINE ^{18}F-FDG PARAMETERS

Although ^{18}F-FDG PET is widely used to image multiple malignancies, it typically has a limited role in imaging early-stage PCa (*19*). However, ^{18}F-FDG PET may have a more prominent role in aggressive or late-stage mCRPC. Prior studies have shown that ^{18}F-FDG–positive/PSMA-negative lesions may be present in up to 33% of mCRPC patients undergoing PSMA RPT (*20–22*). The TheraP trial excluded patients with ^{18}F-FDG–positive/PSMA-negative lesions and had a higher screen failure rate, higher PSA response rates, and higher OS than was found in the VISION trial, suggesting that ^{18}F-FDG–positive/PSMA-negative lesions are negative prognosticators of OS in mCRPC patients undergoing PSMA RPT (*6*,*7*). Additionally, increased ^{18}F-FDG PET whole-body metabolic tumor volume was associated with lower response to PSMA RPT (*23*). These findings are also reflected in other studies that reported a longer median OS in patients without ^{18}F-FDG–positive/PSMA-negative lesions than in patients with ^{18}F-FDG–positive/PSMA-negative lesions (*22*,*24*,*25*).

Michalski et al. still offered PSMA RPT to patients with PSMA-negative metastases if most metastases were PSMA-positive, and these patients had longer OS than patients in the LuPSMA trial who were excluded for low PSMA expression or ^{18}F-FDG–positive/PSMA-negative lesions and were instead treated with the standard of care (*22*). A recently published report on the real-world experience of PSMA RPT after Food and Drug Administration approval found that patients who did not meet TheraP PSMA imaging criteria still benefited from therapy (*26*). Nevertheless, pretreatment ^{18}F-FDG PET may still be useful for further disease characterization in patients when PSMA-negative disease is suspected or there are signs of disease aggressiveness (*27*). Contrast-enhanced CT or MRI should also be performed in addition to PSMA PET imaging to identify potential sites of PSMA-negative disease, especially in patients with known liver metastases (*27*). Further research is necessary to characterize management strategies in patients based on molecular imaging phenotypes.

NOMOGRAMS TO PREDICT OUTCOME AFTER PSMA RPT

Prior studies have shown that increased C-reactive protein levels, increased levels of lactate dehydrogenase, a high fraction of PSMA-negative circulating tumor cells, amplifications in *FGFR1* and *CCNE1, CDK12* mutations, and *BRCA* gene or tumor suppressor mutations are associated with worse outcomes in men with mCRPC undergoing PSMA RPT (*28–33*). Gafita et al. developed screening nomograms that incorporate ^{68}Ga-PSMA-11 PET/CT variables and found that whole-body PSMA SUV_{mean} was strongly predictive of OS and PSA progression-free survival in mCRPC patients undergoing PSMA RPT (*34*). In a nomogram study using ^{18}F-rhPSMA 7.3 PET, whole-body PSMA SUV_{mean} parameters were similarly predictive of OS (*34*,*35*). In a post hoc analysis of the VISION trial aiming at building predictive models, ^{68}Ga-PSMA-11 whole-body SUV_{max} and PSMA-positive lesions in lymph nodes predicted OS (*36*). These studies suggest that PSMA PET parameters can add to existing nomograms derived from clinicopathologic variables and aid in patient selection for PSMA RPT both in clinical trial design and in individual clinical decision-making, although further prospective evaluation in larger cohorts is warranted. We also look forward to the results of future trials incorporating both PSMA PET parameters and biomarkers derived from liquid biopsy sampling to stratify responders and nonresponders to PSMA RPT.

PSMA PET IN RESPONSE EVALUATION

Standardized criteria for evaluating response to cancer treatment are crucial components of individual therapy planning and clinical trial design. The National Cancer Institute's radiographic RECIST 1.1 and the metabolic PERCIST 1.0 are currently used to assess therapy response across multiple oncologic diseases (*37*,*38*). In metastatic PCa, treatment response is typically evaluated using CT and bone scans according to Prostate Cancer Working Group Criteria 3 guidelines (*39*). However, prior studies have already shown that for PSMA PET response evaluation, molecular criteria outperform morphologic criteria for the detection of progressive disease (*40*). Therefore, there is growing interest in characterizing the role of PSMA PET in response assessment and understanding the significance of changes in tumor volume and uptake patterns after therapy initiation.

PSMA PET Progression Criteria

Fanti et al. developed PSMA PET progression criteria relying primarily on the appearance of new lesions (*41*). Michalski et al. demonstrated that progression on end-of-treatment PSMA PET using modified PSMA PET progression criteria was associated with shorter OS (*41*,*42*). Furthermore, in patients who had nonprogressive PSA values, progression by modified PSMA PET progression criteria was still associated with shorter OS (*42*). This analysis showed the added value of PSMA PET in assessing therapy response in patients who are not differentiated on the basis of conventional biomarkers, such as PSA.

RECIP 1.0

Gafita et al. studied a multicentric cohort of mCRPC patients undergoing PSMA RPT and used Response Evaluation Criteria in PSMA PET/CT (RECIP) 1.0 to stratify patients as having progressive disease, stable disease, or a partial response based on changes in whole-body tumor volume from baseline to interim PSMA PET and the appearance of new lesions on interim PSMA PET (*43*). In RECIP 1.0, patients with new lesions despite a reduction in overall tumor volume, suggesting a heterogeneous response by individual lesions, are classified as having stable disease (*43*). These patients had different survival outcomes from patients with progressive disease, who had new lesions in addition to an increase in tumor burden (*43*). Progression on interim PSMA PET after 2 cycles of PSMA RPT using RECIP 1.0 was prognostic for OS (*43*). RECIP 1.0 was also still prognostic for OS even when assessing only patients who did not have a PSA response or patients who did not experience PSA progression (*43*). RECIP 1.0 after 2 cycles of PSMA RPT is also prognostic for progression-free survival (*44*). Subsequent studies have reported on the accuracy of RECIP 1.0 determined by visual

reads or automated approaches (*45*,*46*). Since clinical implementation of qPSMA software is not expected soon, these approaches can be readily implemented in clinical practice. Machine learning models have also been developed for lesion detection and tracking. As an example, artificial intelligence–assisted TRAQinform IQ technology (AIQ Solutions) enables analyses based on per-lesion regions of interest at baseline and end-of-treatment PET as shown in Figure 1 (*47*). Large studies are needed to show that artificial intelligence–derived PSMA PET parameters can serve as effective surrogate endpoints that can replace conventional imaging for response assessment.

Although RECIP 1.0 initially used interim PSMA PET, another retrospective analysis reported that progression on PSMA PET performed after the last cycle of PSMA RPT (end of treatment) using RECIP 1.0 was also prognostic for OS (*48*). Hartrampf et al. reported RECIP 1.0–based analysis with ^{18}F-PSMA-1007 and successfully differentiated patients with progressive disease versus nonprogressive disease (*49*). Other studies have shown that RECIP 1.0 is prognostic for OS in mCRPC patients treated with androgen receptor signaling inhibitors and in patients with biochemically recurrent PCa, suggesting that RECIP 1.0 can be applied to a wider variety of clinical settings (*50*,*51*).

A study compared the prognostic value and interreader reliability of 5 response assessment criteria (Prostate Cancer Working Group Criteria 3, RECIST, PERCIST, PSMA PET Progression, and RECIP) using baseline and interim PSMA PET and found that RECIP 1.0 identified the fewest patients with progressive disease and had the highest risk of death for progressive disease versus nonprogressive disease (*52*). By incorporating changes in total tumor burden in response evaluation, RECIP 1.0 may better reflect changes in metastatic PCa in men undergoing systemic treatment and help avoid premature treatment cessation (*52*).

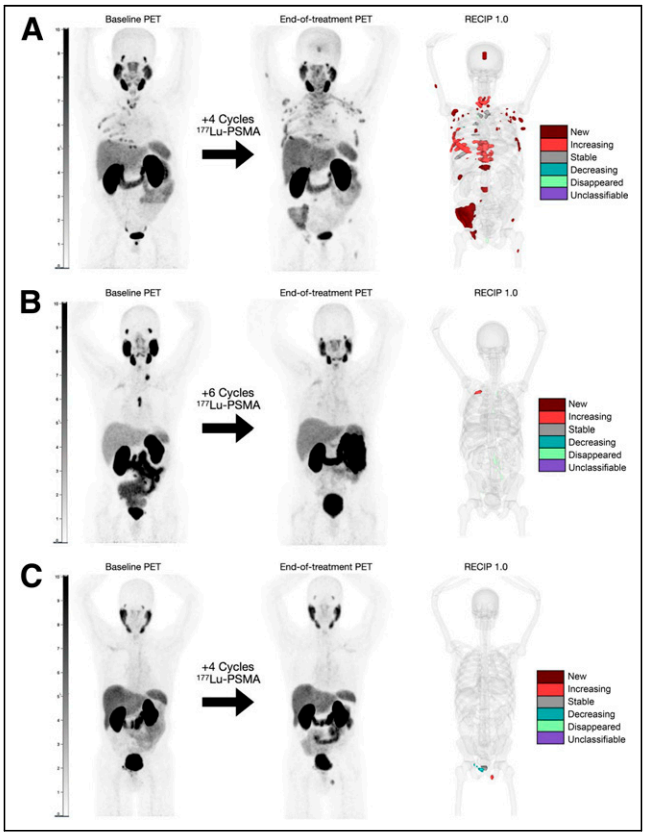

FIGURE 1. Classification by RECIP 1.0. with TRAQinform IQ technology, which was used to conduct lesion region-of-interest–based analyses at baseline and end-of-treatment PET. Regions of interest were matched across time points and categorized as new, increasing, stable, decreasing, or disappeared on basis of changes in total lesion PSMA. (A) A 67-y-old man with mCRPC treated with 4 cycles of PSMA RPT between baseline and end-of-treatment PSMA PET. Patient had new lesions, 512.7% increase in tumor volume, and 547.6% increase in PSA and was classified as having progressive disease based on RECIP 1.0. Patient had date of last follow-up of 6.3 mo from end-of-treatment PSMA PET. (B) A 73-y-old man with mCRPC treated with 6 cycles of PSMA RPT between baseline and end-of-treatment PSMA PET. Patient had no new lesions, 87.3% decrease in tumor volume, and 95.9% decrease in PSA and was classified as having partial response based on RECIP 1.0. Patient had date of last follow-up of 14.9 mo from end-of-treatment PSMA PET. (C) A 69-y-old man with mCRPC treated with 4 cycles of PSMA RPT between baseline and end-of-treatment PSMA PET. Patient had no new lesions, 3.3% increase in tumor volume, and 55.2% increase in PSA and was classified as having stable disease based on RECIP 1.0. Patient had OS of 44.3 mo from end-of-treatment PSMA PET.

Total Lesion PSMA

Other studies have evaluated the prognostic value of total lesion PSMA (whole-body tumor volume × SUV_{mean}), a biomarker similar to total lesion glycolysis in ^{18}F-FDG PET (*53*). In an analysis of 102 patients, changes in total lesion PSMA from baseline to interim PSMA PET after 2 cycles successfully classified patients as having partial response, stable disease, or progressive disease with unique survival outcomes, whereas the occurrence of new metastases in combination with changes in tumor burden did not yield a significant difference in OS between stable disease and progressive disease (*54*). Rosar et al. also demonstrated a 74% concordance between response assessments based on total lesion PSMA and those based on serum PSA. In multivariate analyses, molecular imaging response also remained an independent predictor of OS whereas biochemical response was no longer a significant predictor (*55*). More recently, Burgard et al. demonstrated that the relative change in the ratio between total lesion glycolysis derived from ^{18}F-FDG PET and total lesion PSMA derived from PSMA PET was prognostic for OS, establishing the utility of a biomarker derived from 2 different imaging modalities (*56*). We look forward to the results of prospective trials (NCT04833517) that will evaluate the outcomes and toxicities of PSMA RPT, as well as the prediction of treatment benefit using PSMA PET.

PSMA SPECT Tumor Volume as an Alternative to PSMA PET Tumor Volume

In addition to PSMA PET parameters, quantitative ^{177}Lu-PSMA SPECT/CT imaging can also provide lesion-based and whole-body tumor volume assessments (*57*). Prior studies have shown that changes in total tumor volume on ^{177}Lu-PSMA SPECT/CT can predict both OS and progression-free survival (*58*–*60*). These studies establish total tumor volume on ^{177}Lu-PSMA SPECT/CT as a biomarker that can provide valuable predictive information as early as 6 wk into treatment with PSMA RPT, which can help clinicians tailor treatment strategies appropriately. In addition to whole-body ^{177}Lu-PSMA SPECT/CT parameters, quantitative lesion-based responses (changes in the mean and maximum absorbed doses measured after cycles 1 and 2 of PSMA RPT) have also been shown to correlate with PSA response (*61*).

Another analysis combined PSA with visual analysis of ^{177}Lu-PSMA SPECT/CT after dose 2 of PSMA RPT to classify patients

as having partial response versus stable disease versus progressive disease and adjusted treatment intervals of PSMA RPT accordingly (*62*). Patients with partial response were given a break in treatment until a subsequent PSA rise, patients with stable disease were given 6-weekly treatments until 6 doses, and patients with progressive disease were recommended for an alternative treatment. This analysis found significant differences in OS and progression-free survival among the 3 groups and suggests that early response biomarkers derived from ^{177}Lu-PSMA SPECT/CT can be used to adjust dosing regimens of PSMA RPT in a more personalized manner (*62*). Another analysis of 122 patients who underwent PSMA RPT with subsequent SPECT/CT 24 h after treatment also found that 49% of patients experienced changes in management based on qualitative analysis of posttreatment SPECT/CT (*63*). These studies show that visual analysis of ^{177}Lu-PSMA SPECT/CT can serve as an effective surrogate for quantitative analysis to delineate progressors from responders in this patient population and impact subsequent management.

The phase 2 randomized clinical trial FLEX MRT (NCT06216249) is currently under way to determine the efficacy and the safety of a flexible and extended dosing schedule of PSMA RPT based on SPECT/CT response assessments obtained 24–48 h after injection of PSMA RPT.

CONCLUSION

Quantitative parameters on baseline PSMA PET can serve as prognostic biomarkers for OS and predictive biomarkers for PSA response. As PSMA RPT is moved earlier in the treatment of PCa, quantitative parameters may play an important role in helping treating clinicians select between a wider array of available therapeutic options. Both lesion-based assessments and changes in quantitative parameters on PSMA PET are prognostic for OS and suggest a role for PSMA PET in evaluating response to PSMA RPT. Changes in quantitative whole-body PSMA PET parameters may better reflect changes under systemic therapy than do individual lesion-based assessments.

DISCLOSURE

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