

PSMA PET Tumor-to-Salivary Gland Ratio to Predict Response to [¹⁷⁷Lu]PSMA Radioligand Therapy: An International Multicenter Retrospective Study

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Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy can improve the outcome of patients with advanced metastatic castration-resistant prostate cancer, but patients do not respond uniformly. We hypothesized that using the salivary glands as a reference organ can enable selective patient stratification. We aimed to establish a PSMA PET tumor-to-salivary gland ratio (PSG score) to predict outcomes after [¹⁷⁷Lu]PSMA. **Methods:** In total, 237 men with metastatic castration-resistant prostate cancer treated with [¹⁷⁷Lu]PSMA were included. A quantitative PSG (qPSG) score (SUV_{mean} ratio of whole-body tumor to parotid glands) was semiautomatically calculated on baseline [⁶⁸Ga]PSMA-11 PET images. Patients were divided into 3 groups: high (qPSG > 1.5), intermediate (qPSG = 0.5–1.5), and low (qPSG < 0.5) scores. Ten readers interpreted the 3-dimensional maximum-intensity-projection baseline [⁶⁸Ga]PSMA-11 PET images and classified patients into 3 groups based on visual PSG (vPSG) score: high (most of the lesions showed higher uptake than the parotid glands) intermediate (neither low nor high), and low (most of the lesions showed lower uptake than the parotid glands). Outcome data included a more than 50% prostate-specific antigen decline, prostate-specific antigen (PSA) progression-free survival, and overall survival (OS). **Results:** Of the 237 patients, the numbers in the high, intermediate, and low groups were 56 (23.6%), 163 (68.8%), and 18 (7.6%), respectively, for qPSG score and 106 (44.7%), 96 (40.5%), and 35 (14.8%), respectively, for vPSG score. The interreader reproducibility of the vPSG score was substantial (Fleiss weighted κ , 0.68). The more than 50% prostate-specific antigen decline was better in patients with a higher PSG score (high vs. intermediate vs. low, 69.6% vs. 38.7% vs. 16.7%, respectively, for qPSG [$P < 0.001$] and 63.2% vs 33.3% vs 16.1%, respectively, for vPSG [$P < 0.001$]). The median PSA progression-free survival of the high, intermediate, and low groups by qPSG score was 7.2, 4.0, and 1.9 mo ($P < 0.001$), respectively, by qPSG score and 6.7, 3.8, and 1.9 mo ($P < 0.001$),

respectively, by vPSG score. The median OS of the high, intermediate, and low groups was 15.0, 11.2, and 13.9 mo ($P = 0.017$), respectively, by qPSG score and 14.3, 9.6, and 12.9 mo ($P = 0.018$), respectively, by vPSG score. **Conclusion:** The PSG score was prognostic for PSA response and OS after [¹⁷⁷Lu]PSMA. The visual PSG score assessed on 3-dimensional maximum-intensity-projection PET images yielded substantial reproducibility and comparable prognostic value to the quantitative score.

Key Words: PSMA PET; [¹⁷⁷Lu]PSMA; radioligand therapy; visual criteria; parotid glands

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Patients with advanced metastatic castration-resistant prostate cancer (mCRPC) do not respond uniformly to [¹⁷⁷Lu]prostate-specific membrane antigen (PSMA) (1,2). Thus, identification of patients who will likely benefit from PSMA-targeted radioligand therapy remains an unmet clinical need.

High PSMA expression as assessed by PET and whole-body (WB) tumor SUV_{mean} is associated with better outcomes (3–7). PSMA PET should be used to select patients on the basis of tumor PSMA expression (8). However, the inclusion criteria based on baseline PSMA PET vary among major clinical trials and therapy centers across the world (Supplemental Table 1; supplemental materials are available at <http://jnm.snmjournals.org>) (1,2,6,9–17). The VISION trial applied qualitative (i.e., tumor uptake > liver uptake, assessed visually) thresholds (18). These criteria are relevant in identifying patients with absence of or low [⁶⁸Ga]PSMA-11 expression, and 13% (126/1003) of patients were screening failures (1). Men with screening failure according to the VISION PET criteria had worse short-term outcomes than those who were eligible (19). However, even after selection of patients by VISION PET criteria, many patients do not respond favorably to [¹⁷⁷Lu]PSMA, suggesting the need for further refinements of PSMA PET and other screening parameters.

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TABLE 1
Visual PSMA PET vPSG Score

PSMA expression	Finding of MIP image
High	Most of lesions show higher uptake than parotid glands
Intermediate	Neither low nor high
Low	Most of lesions show lower uptake than parotid glands

When assessing PSMA expression, 3 anteroposterior MIP images adjusted to 0–10, 0–20, and 0–30 SUV window range should be used. “Most of lesions” refers to 80% of extent (total area) of lesion (not number). If parotid glands show heterogeneous uptake, area showing lower uptake should be used as reference. When more than half of parotid glands are out of scan range, patient should not be evaluated with these criteria.

When measured quantitatively, [^{68}Ga]PSMA-11 uptake in the parotid glands exceeds liver uptake 2- to 3-fold (median SUV_{max} for liver vs. parotids, 9.7 vs. 21.3 (20)), which is close to the criteria used in the TheraP trial (lesion SUV_{max}, 20) (2). We hypothesized that use of the parotid glands rather than the liver as a reference organ would improve patient stratification for [^{177}Lu]PSMA. The aim of this study was to test a quantitative and visual PSMA PET tumor-to-salivary gland ratio (PSG score) to predict outcomes after [^{177}Lu]PSMA in a cohort of patients with mCRPC established retrospectively from multiple institutions.

MATERIALS AND METHODS

Study Design

This was a retrospective multicenter study using a published dataset ($n = 270$) (4,19). Images were visually analyzed by 10 masked central, independent readers. The informed consent requirement was waived by the UCLA institutional review board (waiver 19-000896).

Patients

Patients received [^{177}Lu]PSMA-617 or [^{177}Lu]PSMA-I&T between December 10, 2014, and July 19, 2019, in phase 2 clinical trials (NCT03042312 and ACTRN12615000912583) or via compassionate-use access programs (Supplemental Table 2). The [^{68}Ga]PSMA-11 PET/CT protocol is provided in the supplemental Materials and Methods (20) and in Supplemental Table 3. Treatment details are provided in the supplemental Materials and Methods (21–23). Patients were excluded from the current analysis if more than 50% of the parotid glands was outside the PET field of view (as described in the eligibility criteria in Supplemental Table 4).

Image Analysis

Quantitative PSG (qPSG) Score. We first assessed the WB tumor burden quantitatively using the [^{68}Ga]PSMA-11 PET qPSG score. Parotid glands and WB tumors were segmented semiautomatically on baseline [^{68}Ga]PSMA-11 PET images using qPSMA software (24). Output parameters included WB SUV_{mean}, the SUV_{max} of the lesion with the highest uptake (H-lesion), WB PSMA tumor volume, and bilateral parotid gland SUV_{mean}.

The ratio of WB tumor to parotid gland SUV_{mean} (qPSG = mean tumor WB SUV/mean parotid gland SUV_{mean}) was calculated. Patients were divided into 3 groups according to qPSG score: high (>1.5), intermediate (0.5–1.5), and low (<0.5). In addition, patients were grouped as high SUV versus low SUV to compare SUV-based criteria (2,6) with PSG scores (supplemental Materials and Methods).

Visual PSG (vPSG) Score. In a second step, we assessed the reproducibility and prognostic value of visual criteria using the parotid glands as an organ of reference (vPSG score). All readers were board-certified nuclear medicine physicians with more than 2 y of experience in PSMA PET interpretation. To assess whether the reader experience in treating patients with [^{177}Lu]PSMA therapy influences image scoring, both readers with extensive experience (>50 treatments; 5 readers) and readers with limited experience (≤ 50 treatments; 5 readers) were selected (Supplemental Table 5).

Three-dimensional maximum-intensity-projection (MIP) baseline [^{68}Ga]PSMA-11 PET images adjusted to 3 different SUV window ranges (0–10, 0–20, and 0–30) were generated by a single lead investigator not involved in image analysis. Each reader was provided with the images (portable document format). Readers were asked to classify the patients into 3 groups (i.e., high, intermediate, and low) according to the vPSG score as described in Table 1. Representative images of each group are shown in Figure 1.

At more than 2 wk after the first reads, 50 cases were randomly selected for rereading to determine intrareader agreement. One lead investigator conducted the final analysis. A central majority rule (6 vs. 4) was applied in cases of disagreement to obtain the final reads. If disagreement persisted on intermediate versus high or on low versus intermediate (e.g., 5 vs. 5), the cases were classified as high or low, respectively, avoiding the intermediate category.

Clinical Outcomes

The clinical outcomes included a more than 50% prostate-specific antigen (PSA) decline (PSA50), PSA progression-free survival (PFS), and overall survival (OS). PSA50 was defined by a PSA decline of more than 50% compared with baseline at any time during the treatment (best response). PSA PFS was defined as the time from treatment initiation to PSA progression or death from any cause, as per the criteria of Prostate Cancer Clinical Trials Working Group 3 (25). OS was defined as time from treatment initiation to death of any cause.

Statistical Analysis

The R software package was used for statistical analysis. Two-tailed P values of less than 0.05 were considered significant. Clinical characteristics were compared among PSMA expression groups using the Mann–Whitney U and Fisher exact tests for continuous and

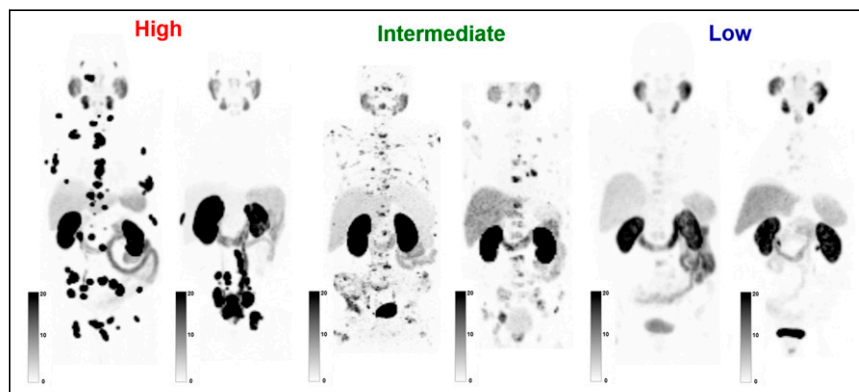


FIGURE 1. Representative MIP images of 6 patients classified as having high, intermediate, and low vPSG scores (MIP SUV range, 0–20).

categoric variables. The proportion of patients who had a PSA50 was assessed by the Fisher exact test, and the odds ratio from logistic regression was calculated. Kaplan–Meier analysis with the log-rank test and Cox hazard ratio regression was performed to evaluate survival outcomes. Multivariate Cox and logistic regression analyses were performed to test the PSG scores and previously reported prognostic factors for [¹⁷⁷Lu]PSMA (4). Intra- and interreader agreement was evaluated by weighted Fleiss κ -coefficients. Agreement between vPSG score (majority rule) and qPSG score was assessed by weighted Cohen κ -coefficients.

RESULTS

Patients

Between April 23, 2019, and January 13, 2020, 414 patients were retrospectively screened, and 177 men were excluded as specified in Supplemental Figure 1. Thus, 237 men were included in the final analysis. Seventy-five and 162 men were treated with [¹⁷⁷Lu]PSMA-617 and [¹⁷⁷Lu]PSMA-I&T, respectively. Table 2 depicts the clinical characteristics of the cohort. The median follow-up time was 21.2 mo (interquartile range, 14.1–30.6 mo).

PSG Score

Of the 237 patients, the numbers in the high-, intermediate-, and low-PSG groups were 56 (23.6%), 163 (68.8%), and 18 (7.6%), respectively, by qPSG score and 106 (44.7%), 96 (40.5%), and 35 (14.8%), respectively, by vPSG score (majority rule) (Supplemental Tables 6 and 7 show the clinical and PSMA PET characteristics of each qPSG and vPSG score group). There was no difference between the baseline clinical characteristics of any groups, except for the lower proportion of patients with prior docetaxel treatment in the low-qPSG group. The number of patients with PSMA PET nodal metastasis (N1) was lowest in the low groups both by qPSG score (33.3%) and by vPSG score (20.0%) ($P < 0.001$). The number of distant metastases (≥ 20) was lower in the low group (45.7%) than the intermediate (75.0%) and high (76.4%) groups by vPSG score ($P = 0.001$). WB tumor SUV_{mean} and PSMA tumor volume were highest in the high group, followed by the intermediate and low group, both by qPSG score and by vPSG score.

PSG Score and Clinical Outcome

Clinical outcomes for each of the 3 groups by vPSG and qPSG scores are summarized in Table 3. Comparisons between PSA PFS and OS in patients with a nonhigh PSG score (intermediate + low) versus a high PSG score (2 groups) are provided in Supplemental Figures 2 and 3, respectively. The PSA50, PSA PFS, and OS obtained by PSG scores and SUV-based criteria (high SUV vs. low SUV) are compared in the supplemental Materials and Methods.

PSA Response. A higher PSA50 was observed in the groups with a high PSG score than in those with an intermediate or low PSG score ($P < 0.001$) (PSA50 odds ratios for qPSG and vPSG scores are shown in Supplemental Tables 8 and 9). Both qPSG score and vPSG score were independent predictors of PSA50. Moreover, PSA50 in patients with a high PSG score was significantly better than in those with an H-lesion SUV_{max} of at least 20 (supplemental Materials and Methods).

PSA PFS. PSA PFS was longest in the groups with a high qPSG or vPSG score (Fig. 2). The corresponding hazard ratios are shown in Supplemental Tables 10 and 11, respectively.

OS. The longest OS was in the groups with a high qPSG or vPSG score (Fig. 3). The hazard ratios of the high groups were lower than those of the intermediate groups but were not significantly different from the low groups in univariate and multivariate analyses (Supplemental Tables 12 and 13). There was no difference

TABLE 2
Patient Characteristics and Clinical Outcome

Characteristic	Data
Total patients	237
Age (y)	72 (IQR, 66, 76)
PSA (ng/mL)	116.3 (IQR, 34.2, 388.1)
Initial NCCN risk group	
Low risk	9 (3.8%)
Intermediate risk	42 (17.7%)
High risk	92 (38.8%)
Metastatic	94 (39.7%)
Treatment history	
Previous docetaxel	190 (80.2%)
Second-line chemotherapy	86 (36.3%)
Androgen receptor signaling inhibitor	225 (94.9%)
Extent of disease on PSMA PET/CT	
Number of metastases ≥ 20	169 (71.3%)
Number of metastases < 20	68 (28.7%)
Sites of disease on PSMA PET/CT	
Pelvic nodal metastasis (N1)	113 (47.7%)
Distant nodal metastasis (M1a)	156 (65.8%)
Bone metastasis (M1b)	218 (92.0%)
Other organ metastasis (M1c)	72 (30.4%)
Cycles of [¹⁷⁷ Lu]PSMA received	
1	37 (15.6%)
2	64 (27.0%)
3	34 (14.3%)
4	78 (32.9%)
>4	24 (10.1%)
Injected activity per cycle (GBq)	7.4 (IQR, 7.4, 7.4)
OS (mo)	12.6 (95% CI, 11.0–14.2)
OS events	195 (82.3%)
PSA progression-free survival (mo)	4.6 (95% CI, 3.7–5.6)
PSA progression-free survival events	210 (88.6%)
PSA decline $\geq 50\%$	105 (44.3%)

IQR = interquartile range; NCCN = National Comprehensive Cancer Network.

Qualitative data are number; continuous data are median.

in OS between patients with an H-lesion SUV_{max} of at least 20 and those with an H-lesion SUV_{max} of less than 20. In contrast, OS was longer in patients with a WB SUV_{mean} of at least 10 than in those with a WB SUV_{mean} of less than 10. OS did not significantly differ between patients with a high PSG score and patients with a WB SUV_{mean} of at least 10 (Supplemental Fig. 3).

TABLE 3
Outcomes of qPSG Score and vPSG Score for High, Intermediate, and Low Patients

Outcome	High	Intermediate	Low	P
qPSG score				
PSA decline $\geq$ 50% (<i>n</i>)	39/56 (69.6%)	63/163 (38.7%)	3/18 (16.7%)	<0.001
PSA PFS	7.2 (4.9–8.3)	4.0 (3.3–5.4)	1.9 (1.4–4.2)	<0.001
OS	15.0 (12.0–19.0)	11.2 (9.1–13.1)	13.9 (8.0–30.6)	0.017
vPSG score				
PSA decline $\geq$ 50% (<i>n</i>)	67/106 (63.2%)	32/96 (33.3%)	6/35 (17.1%)	<0.001
PSA PFS	6.7 (4.6–7.7)	3.8 (2.8–5.6)	1.9 (1.5–3.1)	<0.001
OS	14.3 (12.0–17.8)	9.6 (8.0–12.9)	12.9 (9.0–18.8)	0.018

Survival data are median, in months, followed by 95% CI in parentheses.

Agreement

Agreement between qPSG and vPSG scores was moderate (weighted Cohen κ , 0.60; 95% CI, 0.52–0.68). Complete agreement between qPSG and vPSG scores was seen in 160 (67.5%) of the 237 patients.

The inter- and intrareader reproducibility of the vPSG score for all readers (*n* = 10) showed substantial agreement (Fleiss weighted κ , 0.68; 95% CI, 0.63–0.73) or almost perfect agreement (Cohen weighted κ [mean], 0.83 ± 0.06), respectively (supplemental Materials and Methods). Agreement among readers with and without prior ^{177}Lu -PSMA experience is shown in Supplemental Table 14 and Supplemental Figure 4.

DISCUSSION

Quantitative (qPSG) and visual (vPSG) PET-derived scores for tumor ^{68}Ga PSMA-11 expression relative to parotid gland uptake predicted the PSA response and PSA PFS to ^{177}Lu PSMA of patients with mCRPC. The 3-dimensional MIP image-based vPSG score was substantially reproducible and did not require extensive experience with ^{177}Lu PSMA.

In the VISION study, the liver was used as the reference organ, and 87.4% of patients were eligible after ^{68}Ga PSMA-11 PET screening (1). PSMA tumor uptake equal to or greater than liver uptake appears to be the minimum target expression requirement for response to ^{177}Lu PSMA. The ^{68}Ga PSMA-11 uptake of the parotid

gland is 2–3 times higher than that of the liver (20). Therefore, use of the parotid gland as a reference organ would make the criteria more stringent and specific.

Only MIP images were used for visual analysis. MIP images display WB tumor PSMA expression and disease extent in a single image. However, vPSG score should be used in combination with cross-sectional image analysis to determine the presence of PSMA-negative lesions (1,18,19). The greatest value of the PSG score may be in its use to exclude patients less likely to benefit from ^{177}Lu PSMA—those with a low PSG score. Also, when available, ^{18}F FDG PET/CT may complement the PSG score and potentially improve prognostication. The presence of ^{18}F FDG-positive/PSMA-negative lesions was associated with poor response to ^{177}Lu PSMA (9,26–28). We propose that patients with a low PSG score be deprioritized from ^{177}Lu PSMA. PSMA PET-based exclusion criteria for ^{177}Lu PSMA may encompass patients with PSMA-negative lesions by CT or by FDG, patients with lesion uptake below liver uptake, and patients with a low vPSG score.

Three different SUV-scale windows were used for interpreting MIP images. A MIP image with a narrow window (SUV, 0–10) is useful to observe the distribution of lesions with low PSMA expression, and MIP images with a wider window (SUVs, 0–20 and 0–30) are helpful to compare lesion uptake with parotid gland uptake. Using MIP images enables rapid and reproducible evaluations, which can facilitate clinical implementation.

Agreement between qPSG score and vPSG score (majority rule) was moderate, because vPSG score is based on the extent (>80%) of lesions with uptake greater than that of the parotid gland, whereas qPSG score is independent of disease extent (based on SUV ratio only). Despite the methodologic difference, the outcomes of each group by qPSG and vPSG score were similar, suggesting that both criteria are valuable. qPSG score enables higher reproducibility as it is obtained semiautomatically; however, segmentation software is necessary.

Recently developed nomograms to predict outcome after ^{177}Lu PSMA require WB SUV_{mean} as a parameter (4). A classification using a WB SUV_{mean} of at least

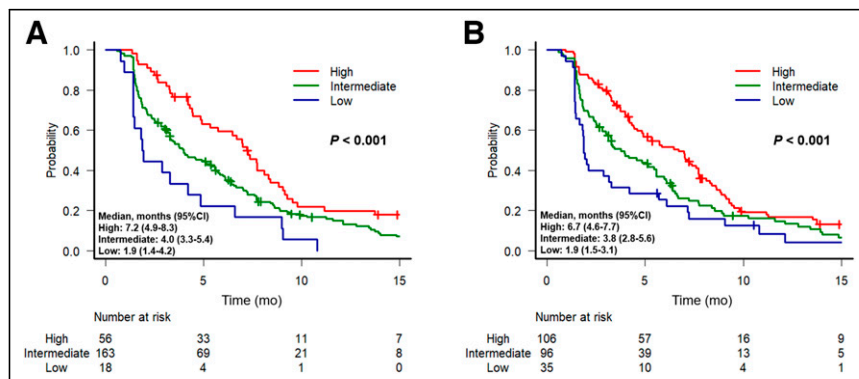


FIGURE 2. Kaplan-Meier curves for PSA PFS comparing groups with high, intermediate, and low PSMA expression classified by qPSG score (A) and vPSG score (B).

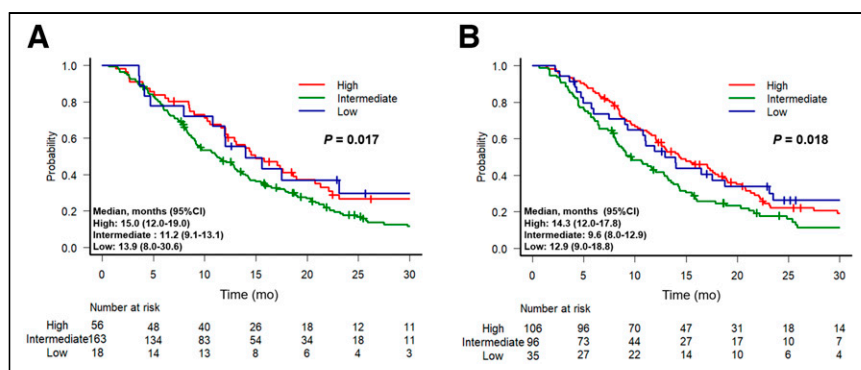


FIGURE 3. Kaplan-Meier curves for OS comparing groups with high, intermediate, and low PSMA expression classified by qPSG score (A) and vPSG score (B).

10 identified treatment responders in the VISION and TheraP cohorts (6). In our cohort, both qPSG score and vPSG score had similar prognostic value to a WB SUV_{mean} of at least 10. The qPSG score is based on an SUV ratio (WB tumor to parotid glands) rather than a fixed SUV threshold to reduce some inherent variability in SUV measurements across patients, scanners, and reconstruction algorithms (29). The need for tumor segmentation software precludes current clinical use of quantitative parameters such as WB tumor volume/SUV_{mean}. There are multiple WB segmentation tools under clinical development (24,30–33), but none are yet validated and widely available.

We propose a simple visual score to derive prognostic information from the screening 3-dimensional MIP [⁶⁸Ga]PSMA-11 PET images. In contrast, a binary SUV_{max} classification (H-lesion SUV_{max} ≥ 20 vs. < 20) was not prognostic of patient OS, because H-lesion SUV_{max} does not account for disease heterogeneity, a key determinant of treatment response to [¹⁷⁷Lu]PSMA (3,12). The 3-dimensional MIP-based vPSG score can be implemented quickly and at no cost in the clinic after further validation. Integration of the vPSG score in the [¹⁷⁷Lu]PSMA nomogram approach (4) may improve its accuracy and further support clinical adoption.

We divided patients into 3 rather than 2 groups. The rationale was to capture, in the intermediate group, patients with heterogeneous PSMA expression. This grouping predicted PSA responses well. However, the group with an intermediate PSG score tended to show worse OS than the group with a low PSG score. Possible explanations include the small population, partial-volume effects, less advanced disease stage, and lower tumor burden in the low group. As such, the 3-group PSG score is more suitable as a biomarker for PSA response than for OS.

Limitations of this study include the lack of independent PSG score validation and the retrospective design. Moreover, the cohort did not include patients who were excluded from [¹⁷⁷Lu]PSMA by the local treating sites. Thus, patients with low PSMA expression may be underrepresented. Also, the PSG score was tested only with [⁶⁸Ga]PSMA-11 PET, and its efficacy with other PSMA-targeted PET tracers (e.g., [¹⁸F]DCFPyL) is unknown. Considering similar normal-organ and tumor biodistribution patterns between [⁶⁸Ga]PSMA-11 and [¹⁸F]DCFPyL (34), we anticipate that the PSG score may be applicable to [¹⁸F]DCFPyL PET as well. Nevertheless, confirmatory studies have yet to be conducted. Finally, our criteria focus on only PSMA expression. Although high PSMA expression

increases the likelihood of sufficient delivery of radiopharmaceutical to tumor, various factors (e.g., administered and absorbed dose, genomic DNA repair mechanism, radiosensitivity, and other biologic tumor characteristics) are associated with radioreistance (35). More comprehensive inclusion criteria may be necessary to refine patient selection.

CONCLUSION

This study proposes a PSG score derived from pretherapeutic [⁶⁸Ga]PSMA-11 PET as a novel predictive and prognostic biomarker for response to [¹⁷⁷Lu]PSMA. After further clinical validation, this score, together

with other cross-sectional or metabolic imaging, may improve patient selection.

DISCLOSURE

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No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: Can the PSMA PET criteria using salivary glands as a reference organ (i.e., PSG score) optimize stratification of patients with mCRPC based on the response to [^{177}Lu]PSMA?

PERTINENT FINDINGS: WB tumor uptake was compared with salivary gland uptake visually and quantitatively on baseline [^{68}Ga]PSMA-11 PET images, and patients were classified into groups with high, intermediate, and low PSMA expression. Patients with high expression classified visually and by qPSG score showed a significantly better PSA response and OS after [^{177}Lu]PSMA.

IMPLICATIONS FOR PATIENT CARE: The PSG score can be a valuable biomarker for response to [^{177}Lu]PSMA and may assist in individual clinical decision making and future clinical trial design.

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