

Prognostic value of PSMA PET/CT in prostate cancer

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Abstract

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein expressed in the majority of prostate cancer (PCa). PSMA has an enzymatic function that makes metabolic substrates such as folate available for utilization by PCa cells. Intracellular folate availability drives aggressive tumor phenotype. PSMA expression is, therefore, a marker of aggressive tumor biology. The large extracellular domain of PSMA is available for targeting by diagnostic and therapeutic radionuclides, making it a suitable cellular epitope for theranostics. Positron emission tomography (PET) imaging of radiolabeled PSMA ligands has several prognostic utilities. In the pre-biopsy setting, intense PSMA avidity in a prostate lesion correlate well with clinically significant PCa (csPCa) on histology. When used for staging, PSMA PET imaging outperforms conventional imaging for the accurate staging of primary PCa, and findings on imaging predict post-treatment outcomes. The biggest contribution of PSMA PET imaging to PCa management is in the biochemical recurrence setting, where it has emerged as the most sensitive imaging modality for the localization of PCa recurrence by helping to guide salvage therapy. PSMA PET obtained for localizing the site of recurrence is prognostic, such that a higher lesion number predicts a less favorable outcome to salvage radiotherapy or surgical intervention. Systemic therapy is given to patients with advanced PCa with distant metastasis. PSMA PET is useful for predicting response to treatments with chemotherapy, first- and second-line androgen deprivation therapies, and PSMA-targeted radioligand therapy. Artificial intelligence (AI) using machine learning algorithms allows for the mining of information from clinical images not visible to the human eyes. AI applied to PSMA PET images, therefore, holds great promise for prognostication in PCa management.

Keywords: PSMA PET, Prostate cancer, Prognosis, Tumor biology, Artificial intelligence, PSMA PET volumetric indices

Introduction

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein with a large catalytic extracellular domain that allows for ligand binding (1,2). There is a low-level PSMA expression in different tissues in the body, including salivary glands, duodenal epithelial lining, and cells of the proximal convoluted tubules of the kidney (3). PSMA expression is low in normal and hyperplastic prostate glands (4). However, PSMA is over-expressed in prostate cancer (PCa) tissue (5). The level of its expression in PCa is higher in castration-resistant PCa compared to metastatic hormone-sensitive PCa, which in turn shows a higher level of PSMA expression compared with localized PCa. This differential PSMA expression in different phases of PCa progression suggests that its level of expression is proportional to the tumor aggressiveness and patient outcome (6). One of the catalytic roles of PSMA in PCa is conferred by its folate hydrolase 1 function, which cleaves folate off poly- γ -glutamated folate making folate available for cellular metabolism (7). High folate concentration is associated with increased tumor growth and invasiveness (8). Beyond its catalytic roles, PSMA also internalizes ligands bound to it, in this way helping to traffic folate into the cell (8). Intracellular folate activates major oncologic signaling pathways that modulate aggressive tumor phenotypes (9,10). For example, increased PSMA level is related to the modulation of mTOR transcription and the phosphorylation of 4EBP1, a downstream target in the mTOR signaling pathway (9). Similarly, PSMA expression increases the phosphorylation of Akt and its downstream targets, S6K and 4EBP1, while the inhibition of PSMA activity with 2-PMPA is associated with reduced phosphorylation of these molecular targets (9).

Imaging plays a vital role in the management of PCa. Molecular imaging has played critical roles in PCa management owing to the possibility of targeting different molecular targets and metabolic pathways in the tumor. Earlier molecular imaging probes targeting amino acid, fatty acid, and glucose metabolism in PCa show important limitations in their clinical applications. The first attempt at targeting PSMA for molecular imaging of PCa utilized a monoclonal antibody targeting the intracellular epitopes of PSMA with limited sensitivity and specificity for lesion detection (11). In the last decade, two molecular targets have been explored for the improved detection of PCa lesions, ^{18}F -fluciclovine targeting amino acid trapping by PCa (12-14) and PSMA ligands targeting the extracellular domain of PCA membrane-bound PSMA (15,16). Several small molecular ligands targeting PSMA have been synthesized and labeled with diagnostic and therapeutic radionuclides for imaging and therapy of prostate cancer. The list of the radioligand PSMA for imaging and therapy of prostate cancer is long and growing. The most successful radioligand in widespread clinical utilization across the world includes ^{68}Ga -PSMA-11, ^{18}F -DCFPyL, ^{18}F -PSMA-1007, ^{68}Ga -PSMA-I&T, and ^{18}F -rhPSMA-7.3 (17-20). Recently, the excellent performance of ^{68}Ga -PSMA-11, ^{18}F -DCFPyL, and ^{18}F -rhPSMA-7.3 for PET imaging of PCa have been reported in phase 3 clinical trials leading to their approval by the United States FDA (Federal Drug Administration) and other regulatory authorities for the initial staging and detection of recurrence of PCa (21-26).

Due to the central role that PCa cell membrane-expressed PSMA plays in tumor metabolism and progression, evidence supporting the prognostic information derivable from positron emission tomography (PET) imaging of PCa with radiolabeled PSMA ligands is increasingly being reported. In this review article, we will appraise the literature reporting the prognostic value of PSMA PET imaging in the different phases of PCa progression.

Prognostic value of PSMA PET in suspected prostate cancer

Men with suspected PCa based on clinical symptoms, clinical examination findings, and elevated serum prostate-specific antigen (PSA) undergo prostate biopsy for histological confirmation. Prostate biopsy, previously done blind, is now guided by imaging to improve the yield for disease detection. Transrectal ultrasound (TRUS)-guided biopsy has now been replaced by multiparametric magnetic resonance imaging (mpMRI)-guided biopsy of the prostate gland due to the lower sensitivity and specificity of the former (28,29). Primary PCa has varying aggressiveness, with tumor aggressiveness graded with the Gleason score or, more recently, the International Society of Urological Pathology (ISUP) grading system. ISUP grade group 1 PCa are indolent and are often treated with a surveillance or watchful waiting approach. The goal of image-guided prostate biopsy is, therefore, not only the accurate detection of PCa lesions but prevent unnecessary biopsy and over-diagnosis of ISUP grade group 1 lesions while improving the detection of clinically significant PCa (csPCa) defined as ISUP grade group 2 to 5 (Gleason score ≥ 7). PCa lesion assessed on mpMRI is graded using the Prostate Image-Reporting and Data System (PI-RADS), which assigned a score of 1 to 5 to lesions based on their likelihood of malignancy. The pooled prevalence of csPCa in lesions assigned PI-RADS score of ≥ 3 is 45% (30). The percentage of csPCa in lesions with PI-RADS scores 1 or 2, 3, 4, and 5 on mpMRI are 6%, 12%, 48%, and 72%, respectively (30). These data show that about half of all patients had unnecessary prostate biopsies based on mpMRI findings and a significant proportion of patients with csPCa are missed, indicating the need for improvement in detecting and predicting csPCa in men with suspected PCa.

Evidence is emerging to support the clinical utility of PSMA PET imaging for improved prediction of csPCa on prostate biopsy pathology (31). The PRIMARY trial is a prospective multicenter study that investigated the superiority of combined ^{68}Ga -PSMA-11 PET/CT plus mpMRI over mpMRI alone for predicting csPCa on histology (32). In a cohort 291 men, PSMA PET was positive in 211 men (73%), mpMRI was positive (PI-RADS 3-5) in 196 men (67%), and combined PSMA PET plus mpMRI positivity in 235 men (81%). csPCa was confirmed in 162 (56%) patients on histology. PSMA PET had a superior sensitivity for csPCa compared with mpMRI, and the combination of both had better sensitivity than either alone (sensitivity of 90%, 83%, and 97% for PSMA PET, mpMRI, and combined PSMA PET and mpMRI, respectively). The negative predictive value (NPV) showed a similar trend, 80%, 72%, and 91% for PSMA PET, mpMRI, and combined PSMA PET plus mpMRI, respectively. In contrast, there was no improvement in specificity when PSMA PET was added to mpMRI in the prediction of csPCa, 50%, 53%, and 40%, for PSMA PET, mpMRI, and PSMA PET plus mpMRI, respectively (32). A similar improved performance of PSMA PET and combined

PSMA PET plus mpMRI for csPCa had been previously reported by Eiber et al. in a smaller cohort of patients (33).

Maximum standardized uptake value (SUVmax) is a semi-quantitative metric with high intra- and inter-reader reproducibility. Varying criteria have been used to define PSMA PET positivity across studies contributing to the differences in the reported predictive ability of PSMA PET for csPCa on histology (34-36). The PRIMARY trial used a SUVmax cutoff of 4 to define PSMA PET positivity (32). In the prospective study of 99 patients by Margel et al., a SUVmax cutoff of 2.5 was used to define PSMA PET positivity (37). This lower SUVmax cutoff led an improved specificity of PSMA PET/MR compared with mpMRI alone (76% vs. 49%, $p < 0.001$) but not the sensitivity (88% for PSMA PET/MR vs. 92% for mpMRI, $p > 0.99$) and a similar NPV of 93% for each modality (37). Beyond the patient- and technical-related factors that may cause differences in SUVmax obtained from different scanners, the prevalence of csPCa in the study population is another important factor that may contribute to the variability in the performance of PSMA PET imaging (31). The NPV of PSMA PET will be improved when the study population has a low prevalence of csPCa but reduced when the study population has a high proportion of patients with csPCa. In line with the pathophysiologic role of PSMA in PCa, SUVmax of PSMA radioligand directly correlates with tumor grade (38,39). In a retrospective review of 200 patients, 162 of whom had csPCa, the median SUVmax of PCa lesion was 3.58 (Interquartile range, IQR: 2.74 – 5.60) (40). At different SUVmax thresholds of 3.0 to 5.0, PSMA PET showed decreasing sensitivity for detecting csPCa (ISUP grade group 2 - 5) of 84.6% (IQR: 78.1 – 89.9) at SUVmax threshold of 3.0 to 50.0% (IQR: 42.1 – 57.9) at SUVmax of 5.0. On the contrary, the specificity of PSMA PET for predicting csPCA improved from 21.1% (IQR: 9.6 – 37.3) at a SUVmax threshold of 3.0 to 92.1% (IQR: 78.6 – 98.3) at SUVmax threshold of 5.0. (40)

The prostate gland has traditionally been divided into three anatomic zones (peripheral, transitional, and central zones) with varying proportions of stromal and glandular elements in each zone. PCa most commonly arises from the peripheral zone. Using the data from the PRIMARY trial, Emmett et al., investigated the value of incorporating patterns of PSMA avidity and its location within the prostate gland (analogous to the PI-RADS) in predicting csPCa (41). They described a 5-point PRIMARY scoring system of 1 to 5. The proportion of csPCa confirmed on histology were 8.5% (4/47), 27% (15/55), 38% (11/29), 76% (89/117), and 100% (43/43) for PRIMARY scores 1, 2, 3, 4, and 5, respectively. The overall estimated area under the curve (accuracy) of the 5-point PRIMARY scoring system was 85% (95% CI: 81 - 89). Interestingly, the performance of this PSMA PET-based novel scoring system surpassed that of PI-RADS, which was 76% (95% CI: 71 - 81) for the PRIMARY trial cohort ($p = 0.003$) (41). This scoring is promising with the potential to standardize reporting of PSMA PET findings in the prostate gland and accurately predict the probability of csPCa. To achieve these objectives, more work is needed to validate these findings in a different and larger cohort of patients and its inter-rater consistency evaluated further.

A significant proportion of csPCa may still be missed despite prior mpMRI with transrectal/transperineal ultrasound targeting mpMRI-identified csPCa for biopsy (mpMRI/TRUS fusion biopsy). In one study of 100 consecutive patients, 16% of csPCa (ISUP grade group 2-5) identified on radical prostatectomy specimens were missed on mpMRI (42). To address the area of clinical need, a prospective study of 97 patients with suspected PCa but with contraindications to mpMRI or negative biopsy has investigated the performance of PSMA PET/TRUS fusion biopsy to detect PCa in this population (43). In the study, 64/97 (66%) of patients had positive PSMA PET findings and underwent PSMA PET/TRUS fusion biopsy. 23/64 (36%) of patients had histologically confirmed PCa with a Gleason score of 6 or higher. In 40 patients with 70 foci of focal avidity on PSMA PET, mpMRI prior to study enrollment were either negative or positive but with negative targeted biopsy. PCa (Gleason 7) were identified in four foci of PSMA avidity in patients with prior negative mpMRI and 14 foci among patients with prior positive mpMRI but a negative biopsy (Gleason 6 in 3 and Gleason 7 in 11). This study provided initial evidence supporting the performance of PSMA PET imaging for pre-biopsy identification of csPCa and targeted biopsy using PSMA PET/TRUS fusion technique in patients with contraindication to MRI or with prior non-diagnostic mpMRI despite high clinical suspicion for csPCa. To advance this further, the same group is investigating the comparative performance of PSMA PET/TRUS fusion biopsy versus mpMRI/TRUS fusion biopsy for identifying csPCa in men suspected of PCa but with a prior negative biopsy in the PROSPET-BX trial (44).

Prior to the widespread application of mpMRI for pre-biopsy prediction of csPCa, risk calculators that incorporate clinical information of the patients were used for risk stratification of patients (45). Newer risk calculators that include information available on mpMRI have been validated and are in common use to select patients for TRUS-targeted prostate biopsy (46,47). A novel risk calculator that incorporated pre-biopsy PSMA PET findings, mpMRI findings, and patients' clinical parameters has reported improvement of the novel MRI-PSMA risk calculator over the European Randomized Study of Screening for Prostate Cancer (ERSPC-MRI) risk calculator alone for predicting csPCa (48). In the cohort of patients, the novel MRI-PSMA calculator showed an AUC of 87.6% (95% CI: 75.5 – 86.9) for predicting csPCa compared with 80.5% (95% CI: 74.6 – 86.3) for ERSPC-MRI risk calculator ($p=0.001$). This novel risk calculator further validates the added utility of pre-biopsy PSMA PET imaging for predicting csPCa in men with suspected PCa.

Prognostic value of PSMA PET for initial staging of prostate cancer

Radical prostatectomy (RP) is offered to men with clinically localized PCa. Accurate pre-operative staging is vital to exclude patients with distant metastatic PCa from undergoing RP. Morphologic imaging modalities alone have not been accurate enough to exclude nodal or distant metastasis in patients with clinically localized PCa. The proPSMA study showed the superiority of ^{68}Ga -PSMA-11 PET/CT over combined CT and bone scan in the initial staging of patients with high-risk PCa (24). Despite its superiority over conventional imaging for PCa staging, with a true sensitivity (with histological validation) of only about 40% for detecting lymph node metastasis, the absence

of lymph node metastases on PSMA PET is insufficient to preclude lymph node dissection in patients (23,25). This limitation in the sensitivity of PSMA PET for the detection of lymph node metastasis is related to the low spatial resolution of clinical PET system for sub-centimeter nodes. Positive nodes on histology but negative on PSMA PET are significantly smaller (2 to 3 mm) than positive nodes on histology that are positive on PSMA PET/CT imaging (4 to 10 mm) (49). The risk of false negative PSMA PET is increased in patients with high-risk PCa. Patients with negative PSMA PET with an ISUP grade group 5 and mpMRI 5 have a high probability of lymph node metastasis on histology following extended pelvic lymph node dissection (ePLND) (50).

Society clinical guidelines recommend the use of nomograms for pre-operative prediction of lymph node metastasis in men with clinically localized PCa (51). Extended pelvic lymph node dissection (ePLND) is the gold standard procedure for lymph node staging. Due to the morbidity associated with the extensive tissue dissection at ePLND, only patients with >7% risk of nodal metastases based on novel predictive nomograms are recommended to undergo ePLND (51,52). With the widespread application of PSMA PET imaging for the pre-operative staging of PCa, further modifications have been made to the currently applied nomograms in routine clinical practice to improve their performance in avoiding unnecessary ePLND and improving the lymph node staging among patients with clinically localized PCa. Including PSMA PET positivity information in all the currently used predictive nomograms have been reported to show an improvement in the abilities of these risk tools in predicting patients with lymph node invasion at RP (53,54), thereby improving the pre-operative selection of the best candidates to undergo ePLND.

Overall, PSMA PET remains the most sensitive imaging modality for the pre-therapy whole-body staging of PCa (55). The value of PSMA PET for the initial staging of PCa lies in its ability to detect metastatic disease and reduce futile surgery (55-57). Based on the superiority of PSMA PET over conventional imaging, the National Comprehensive Cancer Network (NCCN) now recommends PSMA PET imaging for the initial staging of PCa without the need for patients to first undergo conventional imaging (58). Others have expressed uncertainty on the impact of the improved lesion detection rate by PSMA PET on the survival of patients in which treatment approach was altered based on the additional lesions seen on PSMA PET imaging (59). The mortality benefit of altering management decision based solely on additional lesions seen on PSMA PET remains unknown at this time. It is in view of this that the European Association of Urology, unlike the NCCN, is yet to recommend PSMA PET for the initial staging of patients with clinically localized PCa (51). A need, therefore, exists for studies investigating the survival benefit of changing management decisions based on additional lesions demonstrated on PSMA PET during the pre-operative staging of PCa.

Radical prostatectomy plus ePLND offer good long-term disease control for PCa. The institution of radical local prostate therapy in patients with disseminated disease is a cause of PSA persistence post treatment. PSA persistence is associated with a higher risk of clinical recurrence and cancer-specific mortality compared with patients who achieved complete biochemical

response post radical local therapy (60,61). Patients with positive nodes (miN1) on PSMA PET have significantly shorter time to biochemical failure compared with patients who have node-negative PSMA PET findings, suggesting that node positivity on PSMA PET/CT is predictive of poor treatment outcome in patients treated with RP plus ePLND (49,62-64). MiN1 status on PSMA PET may be a stronger predictor of PSA persistence than traditional risk factors, including the clinical T-stage, pre-RP PSA level, and tumor Gleason score (65). Beyond its ability to predict PSA persistence, miN1 disease status on PSMA PET is also predictive of biochemical progression-free survival (bPFS), with Odds ratio of 5.70 (95% CI: 3.61 - 9.00, $p < 0.001$) for bPFS in patients with two or more PSMA-avid nodes versus patients with miN0 disease (66). The number of PSMA-avid nodes also matters in patients with miN1 disease, with a shorter median bPFS in patients with two or more PSMA-avid nodes compared with those with one PSMA-avid node (4.1 vs 12.0 months) (66).

PET imaging allows for the quantification of the whole-body burden of disease. Metabolic tumor volume and total lesion glycolysis initially developed and validated for FDG PET imaging with prognostic value in different solid tumors are increasingly being investigated in oncologic imaging with other tracers such as radiolabeled PSMA (67-69). Zou and colleagues showed a strong correlation between PSMA PET-derived volumetric metrics using whole-body PSMA tumor volume (wbPSMA-TV) and whole-body total lesion PSMA (wbPSMA-TL) with the serum PSA and tumor Gleason score (70). Also, higher tumor burden was reported to be associated with shorter progression-free survival. The impact of PSMA PET-derived derived volumetric metric on patient survival has been further investigated in a large cohort of patients. Using data from PSMA PET imaging done for initial staging in 1348 patients, the PSMA PET-derived local tumor volume, metastatic lymph node volume, metastatic bone volume, and visceral metastatic tumor volume were all negatively associated with overall survival (71). This study confirms the prognostic role of tumor volume assessed on PSMA PET imaging on patients' overall survival (Fig 1). The investigation of the impact of PSMA PET on treatment outcome and patients' survival is a research area with profound impact to shape the future of the application of PSMA PET for guiding radical therapy of PCa, especially in Europe.

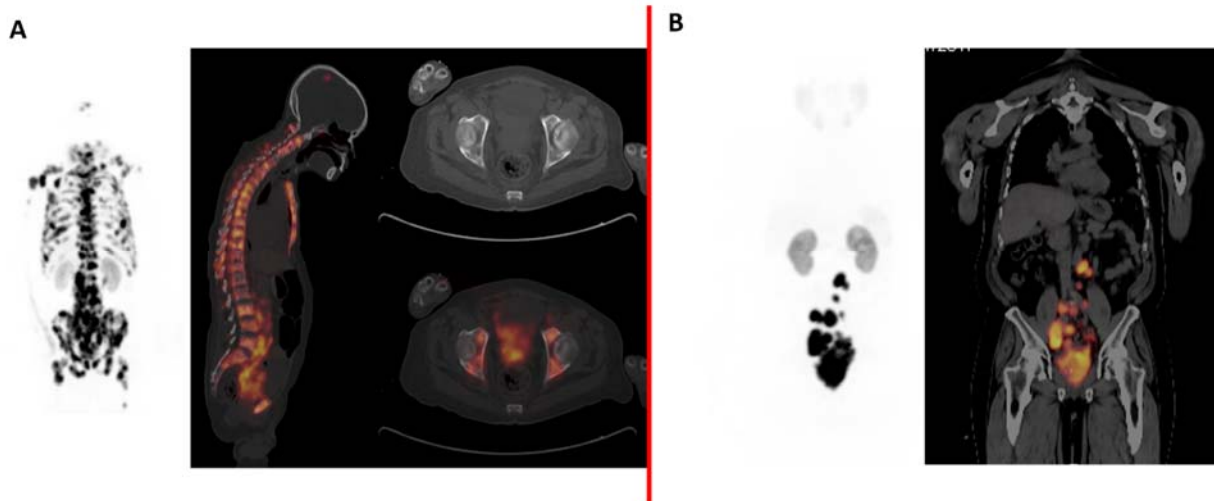


Figure 1: ^{68}Ga -PSMA-11 PET/CT imaging obtained for initial staging in two patients with newly diagnosed metastatic prostate cancer. Patient A had a Gleason score of 4+4 and a PSA level of 104.8 ng/mL at the time of PSMA PET imaging, which shows locally invasive disease with widespread nodal and skeletal metastatic disease. Patient B was diagnosed with a Gleason 3+4 disease and a PSA of 47.1 ng/mL at the time of PSMA PET imaging, which shows locally invasive disease and a relatively low volume of metastatic nodal disease. Based on the differential burden of disease, patient B has a higher likelihood of a favorable survival outcome post-treatment compared with patient A.

Prognostic value of PSMA PET for re-staging of prostate cancer

Following initial radical local therapy of PCa, a significant proportion of patients will eventually experience disease recurrence that manifests as rising PSA in the long-term during follow-up. The goal of treatment of patients experiencing biochemical recurrence of prostate cancer (BCR) is the prompt and accurate localization of the site of recurrence followed by salvage therapy, mostly radiotherapy (72,73). The institution of salvage therapy early, before serum PSA rises above 0.25 ng/mL, has survival benefit (74). At this level, PSMA PET imaging has a good positivity rate (75), with a performance superior to conventional imaging (76). PSMA PET imaging is, therefore, the recommended imaging modality for re-staging of PCa prior to salvage therapy (58,77,78).

PSMA PET localizes recurrence to the prostate bed, pelvic lymph nodes, or distant metastatic sites. The likelihood of PSMA PET positivity for localizing the site of recurrence increases with the serum PSA level. Different patterns of PSMA PET findings have prognostic implications on post salvage therapy bPFS and time to the occurrence of metastatic disease progression. Patients with a negative PSMA PET at the time of salvage radiotherapy (sRT) and receive radiation to the prostate bed have better odds of response to treatment and a more favorable 3-year bPFS (79,80). Metastasis-free survival (time to the appearance of M1 disease post sRT) and the time to attaining castration-resistant status are equally longer in patients with negative PSMA PET compared with those with positive localization of PCa recurrence on PSMA PET (81). A negative PSMA PET is likely to occur in patients with low PSA. At this time, the majority of PCa recurrence occurs in the prostate bed, with a higher likelihood of the intense urinary PSMA activity obscuring

its visualization on PET imaging. This explains the higher likelihood of response following sRT to the prostate bed in these patients despite negative PSMA PET imaging. A second reason may relate to the biological significance of PSMA avidity in PCa lesions. PSMA-avidity is a marker of aggressive disease. Hence, lesion without avidity on PSMA PET imaging may represent a more indolent disease with a more favorable outcome with or without treatment.

The presence of recurrence outside the prostate bed (PB) is an identified strong predictor of unfavorable response to sRT in patients treated for BCR of PCa, with PSMA PET finding outperforming serum PSA level in predicting 3-year bPFS (80). There is a higher chance of response to sRT therapy in patients with recurrence disease confined to the PB compared with patients who show nodal recurrence on PSMA (79). The presence of pelvic lymph node recurrence on PSMA PET increases the risk of developing metastatic disease after sRT (hazard ratio [HR]: 2.39; 95% CI: 1.3 - 3.6) (82). The proportion of patients with disease control at 3-years is higher when PSMA PET is negative or show recurrent disease confined to the PD (81%) than when PSMA PET imaging shows disease extension outside of the pelvis (80). Using the pattern of lesion recurrence demonstrated on PSMA PET imaging obtained for re-staging, different risk categories of patients with varying chances of response to treatment and post-treatment survival can be established. It remains to be seen how these different disease phenotypes seen on PSMA PET imaging at PCa recurrence will influence therapy approach, viz-a-viz adding androgen-deprivation therapy and other lines of systemic therapy to sRT, redefining the standard sRT field template, radiation boosting, among others.

Salvage lymph node dissection is a therapy option in men who experience nodal recurrence of PCa. For salvage lymph node dissection (sLND) to effectively eradicate disease, a sensitive imaging probe must be used for the pre-operative localization of the recurrent nodes. PSMA PET imaging, being the most sensitive imaging modality for lymph node metastasis is, therefore, a reasonable choice of imaging for pre-operative planning. In patients who had PSMA PET imaging followed by PSMA-targeted radio-guided sLND for nodal recurrence of PCa, a single lesion on PSMA PET was predictive of complete biochemical response to treatment (PSA <0.2 ng/mL) (HR: 0.57, 95% CI: 0.27 - 0.8, p=0.06) (83). In another study, tracer-avid retroperitoneal nodes (M1a disease) and the presence of three or more avid nodes on either PSMA PET or radiolabeled choline PET imaging were predictive of clinical recurrence after sLND for PCa recurrence (84). Put together, these studies show that the extent of recurrent PCa as demonstrated on PSMA PET imaging is prognostic for post-sLND treatment outcome in patients with PCa recurrence (83,84).

Prognostic value of PSMA PET in the treatment of metastatic prostate cancer

Salvage therapy for PCa recurrence aims to eradicate disease and delay the institution of systemic therapy. Eventually, disease progression occurs with PCa spread to distant sites in the lymph nodes, bones, and visceral organs. In the initial phase of the disease progression, metastatic prostate cancer is hormone-sensitive, requiring androgen for growth. PCa eventually becomes castration-resistant when tumor growth occurs independent of androgen drive. This phase of metastatic castration-resistant PCa (mCRPC) is the lethal phase of the disease. PSMA radioligand

therapy (PRLT) with ^{177}Lu -PSMA-617 was recently approved for the treatment of mCRPC following remarkable response and survival benefits demonstrated in several retrospective studies and landmark clinical trials (85-89). PSMA PET imaging is recommended prior to treatment with ^{177}Lu -PSMA-617 to demonstrate target expression (PSMA), a predictor of response to treatment (90,91). In recent years, many studies have been published reporting various parameters derivable from PSMA PET imaging obtained prior to or during PRLT with ^{177}Lu -PSMA-617 (92).

SUV is the most common PET-derived metric to quantify lesion radiotracer avidity. A higher SUV connotes higher expression of PSMA in the tumor with a potential for improved ^{177}Lu -PSMA-617 trapping and dose delivery to the tumor (93). SUVmax of the most intense lesion has not been shown to have significant prognostic importance in predicting PRLT outcome (94,95). SUVmax reflects the level of radiotracer uptake in the single most intense voxel in a given lesion (fig 2). This may limit its ability to predict the overall response to treatment when patients have multiple lesions with varying PSMA avidity. SUVmean averages radiotracer avidity in all voxels within a volume of interest (VOI). The prognostic significance of SUVmean of PCa lesion on PRLT outcome has been investigated by several groups. A retrospective study of 103 men with mCRPC who were treated with ^{177}Lu -PSMA I&T showed that SUVmean of lesions on the baseline PSMA-1007 PET imaging was predictive of PSA response (≥ 50 decline in serum PSA) at 8 weeks post-PRLT and overall survival (OS) (95). The impact of SUVmean on response to PRLT has been investigated in the TheraP cohort using a threshold SUVmean of ≥ 10 to define high PSMA expression (96). PSA response was more frequent in patients who had SUVmean of ≥ 10 (32 of 35 men, 91%) compared to men with SUVmean of < 10 (33 of 64 men, 52%). There was also an association between SUVmean of ≥ 10 and progression-free survival benefits (radiographic and biochemical) (96). Similar survival advantages (radiographic progression-free survival and OS) have been reported for the VISION cohort of patients who had high SUVmean of mCRPC lesions compared with those who did not (97). Nomograms have now been created that include tumor SUVmean, number of PSMA-avid metastatic lesions, and the sites of lesions on PSMA PET to predict PSA response, PSA progression-free survival, and overall survival in patients treated with ^{177}Lu -PSMA for mCRPC, establishing the integral role of PSMA PET imaging as a gatekeeper to selecting patients to undergo PRLT (98).

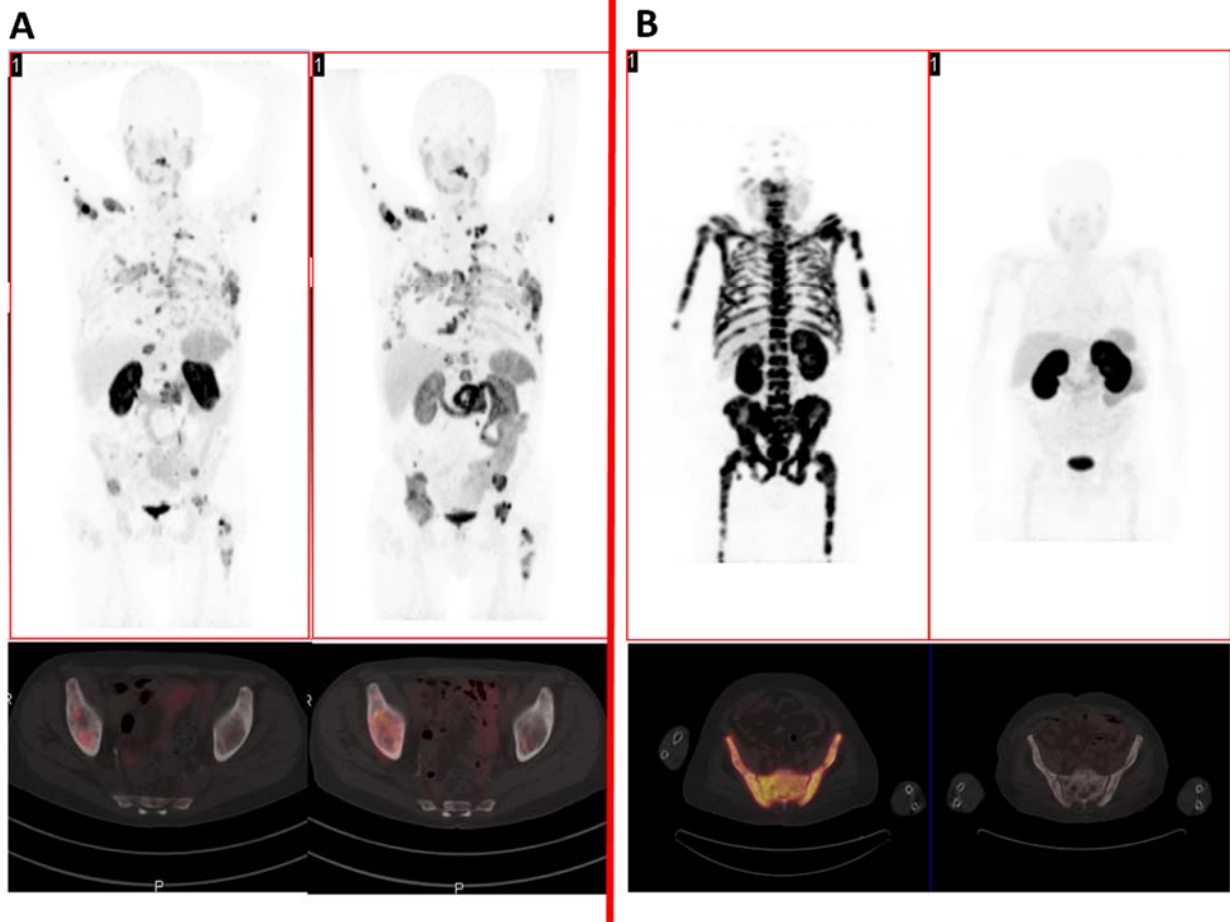


Figure 2: Pre- and post-treatment ^{68}Ga -PSMA PET/CT images of two patients who received PSMA-targeted radioligand therapy. Patient A had multiple skeletal metastases with low-grade PSMA avidity on the pre-therapy images (Right images). He showed poor response to treatment with PSA level doubling on treatment. Post-therapy images (Left images) show imaging findings consistent with disease progression (appearance of multiple new lesions). Patient B showed widespread skeletal metastases with intense PSMA avidity on the pre-therapy scan (Right images). There is complete molecular imaging response on post-treatment PSMA PET imaging (Left images). These two cases showcase the prognostic value of lesion avidity on pre-therapy PSMA PET imaging in predicting treatment outcome. Patient B with intense PSMA avidity demonstrated a more favorable response to treatment despite having a larger tumor burden than patient A.

Other PSMA PET-derived lesion quantification metrics have been investigated for their predictive roles in ^{177}Lu -PSMA PRLT. Whole-body quantification of PSMA-avid tumor volume, in theory, should outperform SUVmean in predicting response to PRLT. Results from the literature have however been inconsistent in supporting a prognostic value for wbPSMA-TL or wbPSMA-TV derived from baseline PSMA PET in mCRPC patients treated with ^{177}Lu -PSMA (95-97,99). There is a high level of variability in the SUV threshold set for computing these volumetric variables which may impact their consistency across studies. Also, the computation of wbPSMA-TL and wbPSMA-TV requires the drawing of VOI to encompass all PSMA-avid lesions. It is technically demanding

to accurately delineate all metastatic lesions and exclude foci of physiologic PSMA uptake. This may contribute to the lack of consistency in the predictive ability of these PSMA volumetric indices.

PSMA PET imaging may be used for molecular imaging-based response assessment during PRLT. Rosar and colleagues recently reported the prognostic significance of the change in the whole-body PSMA-avid tumor burden after two cycles of ^{177}Lu -PSMA compared with baseline volume of disease in mCRPC patients (100). Patients who achieved partial response based on PSMA PET imaging findings after two cycles of ^{177}Lu -PSMA had significantly longer OS compared with patients who had stable or progressive disease (24.6 months, 95% CI: 15.4 - 33.8 vs. 10.7 months, 95% CI: 0 – 21.8). In a multivariate analysis, lack of demonstrable response to PRLT on PSMA PET was an independent predictor of OS with a hazard ratio of 2.76 (95% CI: 1.45 - 5.26, $p=0.002$) (100).

Evidence is emerging supporting the application of Actinium-225 PSMA (^{225}Ac -PSMA) for targeted alpha therapy (TAT) of metastatic PCa (101). TAT exploits the highly energetic alpha particles released by ^{225}Ac for effective tumor killing. ^{225}Ac -PSMA induces longer or comparable duration of tumor control in relation to therapy agents applied prior to it (102). Its safety and efficacy have also been reported in many clinical scenarios, including in patients who experienced disease progression while on ^{177}Lu -PSMA (103), patients with extensive skeletal metastasis in whom response to ^{177}Lu -PSMA may be sub-optimal or induce severe bone marrow depression (104), and in patients with de novo hormone-sensitive metastatic PCa (105). Like PRLT with ^{177}Lu -PSMA, TAT with ^{225}Ac -PSMA is preceded with PSMA PET patient for optimum patient selection (101,106). However, there is a paucity in evidence to support the prognostic value of PSMA PET in TAT of PCa with ^{225}Ac -PSMA. In two separate works from Pretoria, Sathekge et al. Showed that patients who achieved a complete response to therapy on PSMA PET imaging obtained during or after ^{225}Ac -PSMA therapy achieved longer OS compared to patients who did not (107,108). There is a need to understudy the prognostic value of baseline PSMA PET imaging volumetric indices on response to TAT. While response to TAT is expected to be improved with lesion avidity for PSMA as demonstrated for ^{177}Lu -PSMA, there is an important difference in the kinetics of emitted particles between ^{177}Lu and ^{225}Ac that may result in significant differences. Alpha particles emitted by ^{225}Ac are very energetic but have a short pathlength in tissues. There is significant intra-lesion and inter-lesion heterogeneity in PSMA expression in PCa lesions (109). Therefore, a higher intensity of avidity and a more homogeneous expression of PSMA expression may be more important for effective tumor kill needed to achieve a survival benefit in patients treated with ^{225}Ac -PSMA compared with ^{177}Lu -PSMA.

^{177}Lu -PSMA is approved for the treatment of mCRPC in patients who have failed at least one line of novel androgen receptor signaling targeted therapies (enzalutamide or abiraterone) and/or taxane chemotherapy. PSMA expression is not required for the effectiveness of these therapies. PSMA expression is, however, a marker of PCa biology indicating that its level of expression may predict response to these conventional therapeutic agents. In a group of 44 men treated with

enzalutamide or abiraterone for mCRPC, the whole-body tumor volume on baseline PSMA PET scan quantified by wbPSMA-TV and wbPSMA-TL were significantly associated with response to therapy (110). Similarly, a higher reduction in wbPSMA-TV and wbPSMA-TL between baseline and post-treatment PSMA PET was significantly associated with a longer survival (110). Pan and colleagues have also investigated the impact of the heterogeneity of SUVmean between mCRPC lesions in patients treated with abiraterone (111). Patients whose lesions show a higher rate of SUVmean heterogeneity demonstrated significantly less response to treatment compared with patients with less heterogeneity. In the context of mCRPC disease, PSMA expression may be down-regulated, especially after several lines of therapy. This down-regulation of PSMA expression has been shown in patients treated with PSMA-targeted radionuclide therapy and is commonly associated with de-differentiation of tumor (112,113). At this stage of the disease, fluorodeoxyglucose (FDG) PET becomes the appropriate imaging modality for evaluating the extent of the disease.

The prognostic value of PSMA PET has also been investigated in patients treated with taxane chemotherapy for mCRPC. In a total of 71 men treated with one or more lines of taxane chemotherapy, wbPSMA-TV ≥ 78.5 and wbPSMA-TL ≥ 278.8 were significantly associated with a shorter OS on univariate but not on multivariate analysis compared with men who had a lower total-body burden of disease (114). Other authors have also reported the prognostic significance of PSMA PET metrics in unselected population of patients treated with taxane chemotherapy or next-generation androgen signaling axis inhibitors (115,116). Among patients who had baseline PSMA PET imaging and subsequently received treatment for mCRPC with a first line agent (docetaxel or a next-generation androgen signaling axis inhibitor), wbPSMA-TL and wbPSMA-TV were significantly lower among patients who were alive at follow-up (22.2 and 192.4) versus patients who were dead (61.7 and 455.1, respectively) (116).

Prognostic value of PSMA PET for assessing aggressive tumor biology

Genetic mutations are a major driver for oncogenesis, including PCa. During cancer progression, additional somatic mutations are acquired to give the cancer cells a survival advantage with implications for aggressive tumor biology, resistance to treatment, and unfavorable disease outcomes. Molecular biomarkers of deleterious genetic mutations can be assayed from tumor biopsy specimens using services available from different commercial vendors such as Decipher. The Decipher scoring system quantifies the genetic mutation burden in a tumor and a higher score is predictive of aggressive tumor phenotype (117). In a study of 95 primary PCa tumors, PSMA expression was positively correlated with a higher Decipher genomic risk score (OR: 1.51, 95%CI: 1.45 - 1.56) (118). A positive linear correlation between PSMA expression and Decipher genomic risk score was reported ($r=0.19$, $p<0.001$). This study shows the potential for the use of PSMA PET imaging as a non-invasive surrogate marker of deleterious genetic cancer mutations in PCa patients. This potential of PSMA PET to identify lesions with genetic alterations has been investigated in a small number of patients. The study reported intense PSMA avidity in sites corresponding to the genomic index lesions, which were the lesions harboring higher

chromosomal copy number alterations (119). Acquired somatic mutations abound during cancer progression giving rise to tumor heterogeneity, especially common in advanced disease (fig 3). PSMA PET may, therefore, serve as a non-invasive tool for interrogating inter-lesion differences in disease phenotypes that are driven by differences in acquired somatic mutations.

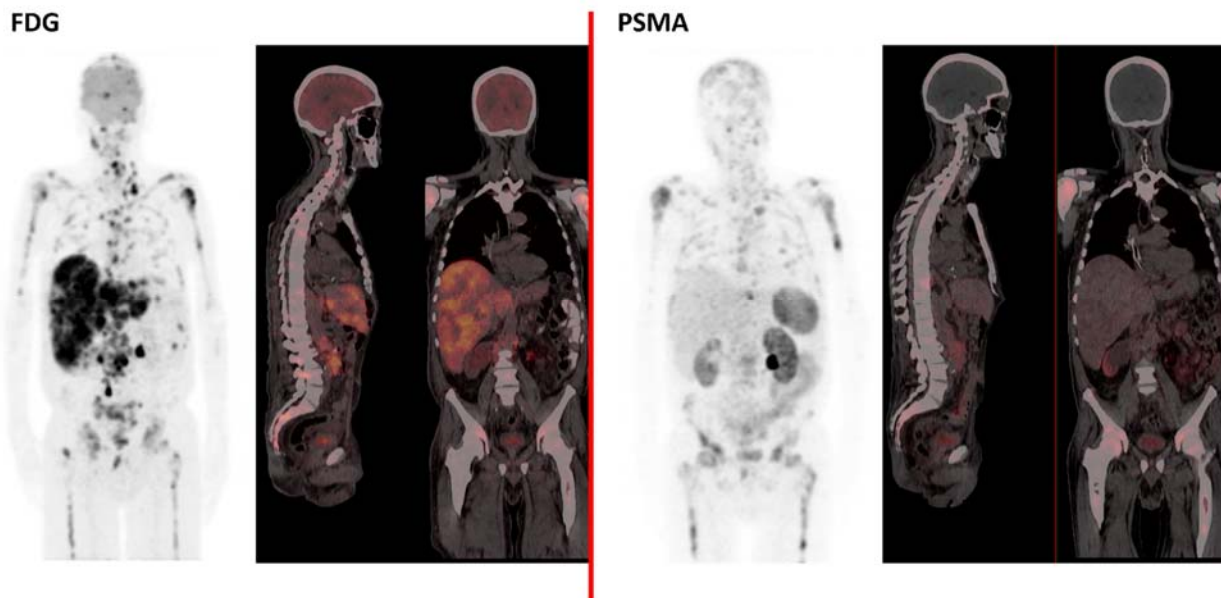


Figure 3: FDG PET and ^{68}Ga -PSMA PET imaging of a patient with multiple lines of prostate cancer therapies. Prior to receiving PSMA-targeted radioligand therapy, he had received treatment with docetaxel, abiraterone, and cabazitaxel. He developed biochemical (rise in serum PSA level) and clinical (worsening disease-related symptoms) evidence of disease progression while on PSMA-targeted radioligand therapy. ^{68}Ga -PSMA PET imaging shows declining tumor avidity despite evidence of disease progression by clinical and biochemical criteria. FDG PET imaging was obtained to evaluate for loss of PSMA expression in prostate cancer lesions. Images show extensive FDG-avid liver and skeletal metastases. PSMA PET imaging demonstrates avidity in fewer skeletal metastatic lesions. This case showcases tumor heterogeneity that may occur in advanced prostate cancer and the role of combined FDG PET and PSMA PET imaging for tumor delineation.

After two decades of decline in PCa incidence, the number of new PCa diagnoses is on the increase again (120), primarily due to new diagnoses of metastatic prostate cancer disease among Black men. PCa mortality is also two to four times higher for Black men compared to men of other races (120). In addition to socio-economic factors that predispose Black men to unfavorable outcomes of PCa treatment, men of African ancestry are known to be at increased risk of harboring deleterious genetic mutations with implications for aggressive disease phenotype and unfavorable treatment outcomes (121). The predictive role of PSMA PET in investigating the differences in disease phenotypes between Black and Caucasian men has been investigated in cohorts of South African men with PCa (122-124). In cohorts of patients who received PSMA PET imaging for the initial staging of PCa, there were no significant differences in the Gleason grade group distribution and the proportions of patients with lymph node and distant metastasis between the Caucasian and Black patients (122). In contrast, serum PSA levels

and SUVmax of the primary tumor were significantly higher among the Black men compared to their Caucasian counterparts (122,123). Gleason score normalized to the median SUVmax was 2.5 times higher in the Black patients compared with Caucasian patients with PCa (122). Despite a lack of significant differences in the Gleason grade group distribution between the two populations, Black men had significantly larger primary tumor volume than Caucasians (123). These findings provide molecular imaging-based evidence with PSMA PET to support the more aggressive tumor phenotypes among Black patients compared to Caucasians. In a cohort of patients who received PSMA PET imaging for the localization of PCa recurrence, no significant differences were found between Black and Caucasian patients with respect to disease characteristics (serum PSA and tumor Gleason score) and PSMA PET findings (PSMA PET positivity rate and miM1 disease rates) (124). More work is needed to further advance the role of PSMA PET imaging in interrogating the aggressive tumor biology among Black men in different settings.

Prognostic applications of artificial intelligence in PSMA PET imaging

There is a large and growing body of evidence reporting the potential prognostic utility of artificial intelligence (AI) applied to PSMA PET images in different settings among PCa patients (125). In patients with suspected PCa, radiomic models have been found useful in identifying csPCa (126). This application has the potential to improve the yield of identifying csPCa for targeted biopsy while reducing unnecessary biopsies of clinically insignificant lesions (127). It also has a potential application for guiding focal therapy of primary PCa (128). PSMA is expressed in about 90% of PCa lesions leaving a significant 10% of lesions that can be missed on PSMA PET imaging due to lack of significant PSMA expression. The capability of machine learning algorithm to identify PCa lesions in patients with negative PSMA PET imaging has been reported (129,130). This application may improve overall primary tumor detection rates, especially in the context of low or no PSMA expression. Despite its clear superiority for pelvic lymph nodes and distant metastatic detection above conventional imaging techniques, PSMA PET still underperforms in the detection of metastasis in small lymph nodes (<4mm). AI algorithm applied to the primary PCa lesion has the potential to predict the presence of lymph node invasion with acceptable accuracy (131,132). This may help improve the selection of patients who may benefit from ePLND with improved nodal staging while avoiding unnecessary ePLND and its associated morbidities in patients with a low risk for lymph node invasion. Patients with metastatic disease are treated with systemic therapy including ADT, chemotherapy, and ¹⁷⁷Lu-PSMA. Radiomic features extracted from pre-therapy PSMA PET have been found useful in predicting response to systemic therapy in patients with metastatic PCa (133,134).

AI applied to PSMA PET images holds a lot of promise for prognostication in PCa. There is, however, a lot of challenges that need to be surmounted to actualize these potentials. Many of the studies reporting favorable prognostic utility of AI in PCa management are single-institution small studies that use limited data set for training and validation of the AI models. This limits the external validity of the performance of these so-derived models. Machine learning algorithms

are very sensitive to errors, such that when these errors are not identified and corrected, they are propagated leading to inaccurate output function. The European Association recently published a position paper detailing some of the crucial problems with AI and providing recommendations for standardization (135).

Conclusion and future perspectives

PSMA PET imaging has revolutionized the management of PCa. Initial evidence establishing its superior sensitivity for lesion detection and impact on therapy decision have been followed by a growing body of evidence supporting its prognostic roles in different management settings of patients with PCa. In the pre-biopsy setting, PSMA PET is helpful in identifying the csPCa in patients with suspected PCa. In this way, it is useful in offering biopsy only to patients with high-risk lesions while reducing the number of invasive biopsy procedures in patients with low-risk, clinically non-significant disease. PSMA PET imaging has a limited sensitivity for the pre-operative staging of lymph node invasion of PCa. Despite this limitation, it still outperforms other imaging modalities for this indication and findings on staging PSMA PET are predictive of post-surgical treatment outcomes. Despite the initial disease control with local therapy with surgery or radiotherapy, the majority of patients eventually present with metastatic disease requiring therapy with systemic agents. PSMA PET performed in this setting has a good prognostic performance to predict individuals with the highest chance of response. In this sense, PSMA PET helps to discriminate between patients who will benefit from a given systemic therapy versus patients who may not, consequently helping to reduce futile treatment procedures and the attendant morbidities associated with such treatments.

In the future, continuing efforts are needed for clinical trials that will demonstrate the survival advantage of incorporating PSMA PET imaging into the decision-making process in the different stages of PCa management. More importantly, a phase 3 clinical trial is necessary to showcase the survival advantage of obtaining PSMA PET imaging for the initial pre-therapy staging of PCa and managing the patients based on PET imaging findings versus management decisions based on conventional imaging. This may be necessary for more widespread approval and application of PSMA PET/CT for this indication. Black men bear a greater burden of aggressive disease and respond less favorably to standard-of-care therapy options than patients of other races. Unfortunately, few or no Black men are included in most landmark trials establishing the survival advantage of PCa therapies, including PSMA-targeted radioligand therapy (88,89). Future studies should, therefore, make conscious efforts to include this high-risk patient population in a manner that allows pre-defined evaluation of therapy response in them versus men of other races. SUVmean has been consistently reported as a metric of prognostic significance in predicting response to PCa treatment, especially mCRPC response to ¹⁷⁷Lu-PSMA. Theoretically, it would be expected that volumetric indices such as wbPSMA-TL and wbPSMA-TV that take the whole-body tumor volume into account should outperform SUVmean as prognostic PET indices. This has not been the case in practice. This may be due to the lack of standardization in the methods for

quantifying these metrics. Different groups are reporting on the utility of AI algorithms for automatic lesion segmentation (136,137). This has the potential to improve the accuracy of quantifying these volumetric indices and improve their prognostic utility.

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