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# Treatment Response Evaluation in Prostate Cancer Using PSMA PET/CT

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**Learning Objectives:** On successful completion of this activity, participants should be able to describe (1) the common roles of PSMA PET for imaging of prostate cancer; (2) the use of PET as a therapy response evaluation tool; and (3) the PPP and RECIP criteria for PSMA-based response assessment in prostate cancer.

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In recent years, there has been a headlong rush into the use of prostate-specific membrane antigen (PSMA)–targeted PET for the staging and restaging of men with prostate cancer (PC). To date, there have been regulatory approvals for PSMA PET for purposes of initial staging, recurrence, and establishing eligibility for PSMA-targeted radiopharmaceutical therapy. Conventional imaging modalities, including bone scan and CT, are inadequate for identifying sites of PC in a variety of clinical scenarios. Further, current standardized response assessment approaches based on either conventional imaging or PET radiotracers that lack sensitivity for PC are inappropriate for response assessment in men with PC. There is currently no specific regulatory approval for the use of PSMA PET for response assessment. In the context of the use of PSMA-targeted radiopharmaceutical therapy and other cytotoxic therapeutic approaches, both the PSMA PET progression criteria and RECIP 1.0 have been shown to have value and to provide prognostic information. However, the role of those criteria is less clear for patients who are being treated with agents targeting the androgen signaling axis, given variable changes in PSMA expression. Ultimately, there may be key roles for machine learning and artificial intelligence in identifying imaging biomarkers based on changes in PSMA PET uptake during therapy.

**Key Words:** PSMA; prostate-specific membrane antigen; prostate cancer; radiopharmaceutical therapy; response assessment; PPP; RECIP

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Prostate cancer (PC) is the second leading cause of cancer-related deaths among men in the United States (*1*). According to the American Cancer Society's projections, 1,466,718 new cases of PC were anticipated worldwide for 2024 (*1*). The 5-y survival rate for patients with early, localized PC exceeds 99%; however, that rate plummets to 30% for patients with metastases (*2*). The treatment landscape of metastatic PC has evolved significantly over the past 2 decades. Multiple phase 3 trials have led to new drug approvals and rapid changes in the therapeutic armamentarium for PC (e.g., hormonal therapy, chemotherapy, radiopharmaceuticals, immunotherapy, and targeted therapies). Therapies initially developed in later stages of the disease (e.g., metastatic castration-resistant prostate cancer [mCRPC]) have started to move earlier in the PC trajectory, with new standards of care for metastatic castration-sensitive PC and non-mCRPC (*3*).

Overall, in oncology, determining response to therapy or defining disease progression is considered a pillar in the management of patients with cancer, especially when varying treatment options are available for the treating physician. In PC, conventional imaging using bone scans and CT has been the mainstay of radiographic follow-up in patients with PC (*4*).

The U.S. Food and Drug Administration (FDA) has approved the prostate-specific membrane antigen (PSMA)–targeted agents

$^{68}$Ga-PSMA-11, $^{18}$F-DCFPyL, and $^{18}$F-rhPSMA-7.3 for PET imaging (PSMA PET) for multiple indications (*5*). Current guidelines specifically recommend PSMA PET with those radiotracers in patients with PC and suspected metastases who are candidates for initial definitive therapy and who have suspected recurrence based on elevated prostate specific antigen (PSA) level to determine eligibility for treatment with PSMA-targeted radiopharmaceutical therapy such as $^{177}$Lu-PSMA-617 (*6*–*8*). PSMA PET has demonstrated higher detection accuracy in PC when compared with conventional imaging (*9*); however, its superiority for treatment response evaluation purposes has not been established to the best of our knowledge. Response evaluation methods have been developed for PSMA PET that distinguish partial response (PR), complete response (CR), progressive disease (PD), or stable disease (SD) (*10*–*12*). Evidence is emerging regarding the prognostic value of response categorization of metastatic disease using PSMA PET in patients with PC being treated with either androgen receptor pathway inhibitors (ARPIs) (*13*,*14*), taxane (*15*), or $^{177}$Lu-PSMA radiopharmaceutical therapy (*16*). Recent imaging guidelines recommend a baseline PSMA PET to be performed before the initiation of systemic therapies, and follow-up PSMA PET should be performed when the results are expected to change clinical management (*17*,*18*). An end-of-treatment scan at least 3 mo after systemic treatment has concluded.

An important topic discussed further in this article is the postulated flare phenomenon caused by increased PSMA expression after initiation of androgen-deprivation therapy (ADT) or ARPI in the castration-resistant population, whereas in hormone-sensitive disease, there may be decreased uptake which could underestimate disease burden (*19*). Further studies are needed to fully clarify the role of PSMA PET in response assessment during hormonal therapy in PC.

This article aims to discuss the present literature on the role of PSMA PET for treatment response evaluation for PC and provide guidance on its further development.

## ROLE OF PSMA-TARGETED IMAGING IN PC

PSMA is a molecular target of great interest and importance in the imaging of PC. PSMA is a surface membrane glycoprotein that is highly expressed on PC cells (*20*). Although that antigen was discovered as early as 1993, it was as recent as December of 2020 that the first FDA-approved PSMA-targeted PET imaging radiotracer ($^{68}$Ga-PSMA-11) was cleared for clinical use in the United States. That development was contemporaneous to the ProPSMA trial and other studies showing that PSMA PET was superior to conventional imaging (CT and bone scan) for evaluating men with PC (*9*,*21*–*23*). Now multiple different PSMA agents are widely available, and there is a plethora of data correlating PSMA expression in PC with aggressive behavior, increased risk of progression, and development of castration resistance (*24*). Although other tissues do express PSMA (kidney, nervous system, small bowel, and salivary and lacrimal glands), they either do so to a lesser extent or represent tissues that are uncommonly involved with PC metastases. The result is a high-contrast form of imaging that is sensitive and specific and thus ideally suited for the evaluation of PC (*20*).

PSMA PET has been studied in multiple different clinical settings, with resulting data that support its role in the evaluation of PC at multiple time points in the disease trajectory, including, but not limited to, initial staging, recurrence, and mCRPC (*22*,*25*–*27*). Indeed, PSMA PET has demonstrated an increased detection rate compared with conventional imaging and, as a result, can lead to a change in management in a significant number of cases (*22*). Previously within the United States, efforts had been directed toward obtaining regulatory approval for these indications and with much success. However, as posttherapy PSMA PET examinations become more common, especially after the advent and FDA approval of PSMA-targeted radiotherapy, the focus in the scientific and clinical community has shifted to its potential roles in outcome prediction and response evaluation. One such example of the potential prognostic value of PSMA PET is demonstrated in a 2019 paper that showed that even a false-negative PSMA PET correlates with better disease-free survival than does a true-positive scan (*28*).

PSMA is expressed in normal prostate cells but is overexpressed in PC cells. In addition, PSMA shows coordinated expression with vascular endothelial growth factor receptor, a key driver of tumor-induced angiogenesis, suggesting PSMA as a potential indirect marker of neoangiogenesis in nonprostate solid tumors (*29*,*30*). This suggests that PSMA can be a dynamic biomarker with a strong prognostic value, as confirmed by some recent studies pointing to a correlation between a positive PSMA PET and the clinical outcome of the patient (*31*). The proPSMA study suggests a prognostic value of PSMA PET identifying metastatic disease early, thus influencing treatment decisions and potentially reducing the risk of recurrence (*32*). By improving accuracy in PC staging, PSMA PET could lead to better-tailored treatments and improved outcomes for patients at high risk of recurrence. PSMA PET has played a key role in stage migration of patients with metastatic disease in the hormone-sensitive setting, namely identifying high-volume patients eligible for ARPI (*33*,*34*) and more accurately delineating low-volume patients who may benefit from metastasis-directed therapy (*35*).

In the setting of PSMA-targeted therapeutic radiopharmaceuticals, PSMA PET is required to select patients for radiopharmaceutical therapy and, hence, to identify candidates who are most likely to respond to the therapy. In that context, an analysis of PSMA PET imaging parameters as predictive and prognostic biomarkers in the patient population of the TheraP study demonstrated that the $SUV_{mean}$ from PSMA PET was predictive of a higher likelihood of response to $^{177}$Lu-PSMA-617 therapy (*36*). Concordant results were observed from an exploratory secondary analysis of the VISION trial: it was found that baseline whole-body (WB) tumor $SUV_{mean}$ from PSMA PET was the strongest predictor of the efficacy of $^{177}$Lu-PSMA-617. Participants with higher tumor $SUV_{mean}$ levels showed greater improvements in radiographic progression-free survival (PFS) and overall survival (OS), but the benefit of the treatment was observed across all $SUV_{mean}$ quartiles (*37*).

Fewer studies have explored the use of PSMA PET to monitor treatment response to PSMA-targeted therapeutic radiopharmaceuticals. The LuPIN trial identified that an increase in the quantitative parameter total tumor volume (TTV) on posttreatment PSMA PET was a strong prognostic biomarker for early disease progression and shorter OS, regardless of PSA levels (*38*). Emerging evidence supports the use of PSMA PET as a prognostic biomarker, refining patient management and therapeutic response models. By accurately mapping metastatic burden and tumor heterogeneity, PSMA PET can provide insight into disease aggressiveness, aiding in the prediction of outcomes for patients with PC, both in the hormone-sensitive and castration-resistant settings.

## THERAPEUTIC RESPONSE EVALUATION IN PC

Objective response assessment criteria are needed to demonstrate the efficacy of a treatment. Although these criteria do not

always replace the physical exam and other less objective criteria completely, they often largely complement those approaches and sometimes replace them entirely. In PC, serial serum PSA levels have been traditionally used in response assessment. A rise in PSA in a patient with a history of treated PC is considered as an indicator of disease recurrence or progression. It should be noted that a single-time-point PSA measurement is sometimes not sufficient to draw a definitive conclusion, and repeat PSA measurements may be needed for more definitive conclusions (*39*). Another, more recently developed blood-based biomarker is circulating tumor DNA; whereas data are still being developed, they indicate that circulating tumor DNA at baseline can probably serve as a prognostic biomarker, and changes in the circulating tumor DNA after treatment can probably be used as an early predictor of both time to progression and survival (*40*).

The main advantage of imaging-based over biochemical tumor markers is their ability to localize tumor sites along with the ability to assess expression of the biomarker at each site (i.e., intrapatient heterogeneity) and to measure biomarker-expressing tumor volume. Knowing the location of the tumor can serve as a prognostic factor and help determine the optimal treatment approach (systemic vs. localized) and treatment goal and intensity (dosimetry) as well as the need of concomitant medication to combat side effects. In the case of PC, the presence of brain or mesenteric metastases might trigger the prophylactic administration of steroids. And if a patient has extensive bone involvement, closer attention to blood counts at the time of treatment helps determine whether the patient may not be a candidate for PSMA-targeted therapeutic radiopharmaceuticals altogether or if shorter-term check of blood counts are required.

Current versions of proposed standardized reporting frameworks for PSMA PET have begun to incorporate aspects of response assessment (*41*,*42*), although as efforts are made to harmonize the proposed systems, the results may prove cumbersome (*43*). Such efforts are in the early stages of development and will ultimately need to be added to various PET-viewing software packages.

The historical guideline-recommended imaging modalities for the detection of metastases in advanced PC and for the assessment of their response to treatment are $^{99m}$Tc-based bone scintigraphy (BS) for bone lesions and contrast-enhanced abdomen and pelvis CT or pelvis MRI for nodal, visceral, and bone lesions (*4*). However, all of those modalities have significant limitations for lesion detection and especially for response assessment.

BS has a sensitivity of 79%–88% and a specificity of 75%–82% for detecting bone lesions (*44*,*45*). The proportion of equivocal and false-negative findings on BS is problematic, with the latter probably being responsible for futile radical treatments (*46*), and a patient with widespread metastatic disease may be falsely identified as having oligometastatic disease (*35*). Evaluation of therapy response using BS also suffers limitations. A first important pitfall is the possible observation of a flare phenomenon in BS performed 8–12 wk after treatment initiation, consisting of the appearance of new osteoblastic foci on a first follow-up scan, which in reality represents a sign of favorable response to treatment. Such pseudoprogression cannot be distinguished from true disease progression without longer-term follow-up (*47*). The Prostate Cancer Working Group 3 (PCWG3) criteria suggest that all patients who have at least 2 new lesions at a first follow-up BS require a confirmatory BS after more than 6 wk of treatment continuation (*4*). BS progression is only confirmed if 2 or more new lesions are seen on the confirmatory BS (2 + 2 rule). Therefore, a change in treatment on the basis of progression can only occur after at least 14 wk of treatment (depending on the reassessment schedule).

Further, only the appearance of new lesions is considered, and an increase in the extent of preexisting lesions cannot be used as an objective criterion for BS progression, further limiting the value of BS in identifying disease progression. Moreover, diffuse metastatic bone disease on BS (i.e., a superscan), often observed in advanced PC, cannot be assessed for response because new disease cannot be distinguished on an already diffusely increased tracer uptake background. Lastly, BS assessment of response distinguishes only 2 categories (PD or non-PD) and cannot positively identify response because reduction and resolution of bone uptake takes a long time to occur, limiting the timeliness of readouts (*48*).

In contrast to its diagnostic performance in the assessment of visceral lesions, CT has limitations in the detection of node and bone lesions and in the assessment of their response to treatment. For nodes, CT only considers abnormal lymph nodes on the basis of size criteria and has both low sensitivity (42%) and limited low specificity (82%) (*49*). For the assessment of response to treatment, RECIST 1.1 and PCWG3 criteria only consider nodes larger than 15 mm in the short axis as pathologic and measurable (*4*,*50*). Nodules with a short axis larger than 10 mm but smaller than 15 mm are considered pathologic but nonmeasurable or a nontarget. For nodal and visceral lesions, RECIST 1.1 categorizes findings as CR, PR, SD, or PD. For bone, CT cannot detect lesions before significant osteolysis or sclerosis has occurred. RECIST considers bone lesions to be nonmeasurable, and their response to treatment cannot be assessed unless they have measurable extraosseous spread (*50*).

Although these multiple limitations argue against the use of BS and CT/MRI for response assessment, those methods are still commonly used because of their wide availability and use in many pivotal clinical trials (*51*). However, there is currently no evidence that disease staging and response stratification based on PSMA PET adds value for therapeutic decisions and, most importantly, for improving patient outcomes.

## PET FOR RESPONSE EVALUATION

PERCIST is a response framework introduced in 2009 (*52*) using FDG PET/CT in different cancers. Briefly, the $SUV_{peak}$ of the most avid tumor corrected for lean body mass (SUL), within a 1-$cm^3$ volume, is measured in each scan (i.e., the $SUL_{peak}$ of the scan). It must also be more significantly avid than a background organ (usually liver), or the lesion is considered not measurable. Specifically, $SUL_{peak}$ greater than 1.5 times the mean plus 2 SD of the SUL of a 3-cm–diameter volume of interest in the liver, or twice the mean plus 2 SD in the thoracic aorta, can be considered measurable (*53*). A partial metabolic response is a reduction of at least 30% from baseline and at least 0.8 SUL. For stable metabolic disease, $SUL_{peak}$ changes must be within 30% of the baseline value. Progressive metabolic disease is defined as an increase of at least 30% and 0.8 SUL or the occurrence of new lesions, or there must be unequivocal progression in nontarget lesions (*53*). CR requires resolution of uptake within target lesions (to less than liver and similar to blood pool) and the absence of new lesions.

PERCIST was designed for FDG, so its applicability to PSMA is unclear (*54*). There are concerns about loss of PSMA expression by aggressive tumors creating false-positive responses by lowering PSMA uptake (*55*), which has been observed in a challenge trial with repeat $^{177}$Lu-PSMA-I&T (*56*) with rising PSA despite declining

PSMA uptake. A study of test–retest variability for $^{68}$Ga-PSMA-11 showed an excessive 50% variability (greater than the values that have been reported for $^{18}$F-DCFPyL (*57*,*58*)), but this was of $SUV_{max}$ rather than the $SUL_{peak}$ used in PERCIST, so its applicability is unclear (*59*). A 2021 European Association of Urology and European Association of Nuclear Medicine consensus statement suggested finding new detectability thresholds given the differences with FDG (*18*) and declined to endorse PERCIST for PSMA for the same reasons, preferring tumor volume where possible.

Nonetheless, PERCIST has been used without further modification with $^{68}$Ga-PSMA-11 to assess $^{177}$Lu-labeled theranostic PSMA agents (*60*,*61*), $^{225}$Ac-labeled theranostic agents (*62*), or external-beam radiation (*63*,*64*). There are also numerous modified PERCISTs, often using the PERCIST cutoffs of 30% with variables other than $SUL_{peak}$, sometimes not explicitly differentiating themselves from orthodox PERCIST. One study simply used body weight because of reproducibility concerns (*65*). A study of patients being treated with docetaxel used summed $SUV_{mean}$ of the 2 hottest lesions in each organ system instead (*66*) and was later cited in a renal cell PSMA study (*67*), a trial of $^{177}$Lu-PSMA-617 (*68*), and a recent study of rechallenge with $^{177}$Lu-PSMA-I&T (*56*). Equivalents to metabolic tumor volume and total lesion glycolysis with a variety of names have been used to assess $^{225}$Ac-PSMA-617 (*69*) and $^{177}$Lu-PSMA-I&T (*61*,*70*).

Despite any limitations, PERCIST may be better than RECIST for PSMA PET. A study of 88 patients with a mixture of treatments showed PERCIST (and European Organisation for Research and Treatment of Cancer criteria) detected more progression than RECIST 1.1 (*71*). PERCIST in 23 patients treated with $^{177}$Lu-labeled PSMA therapy (*72*) showed better agreement with biochemical response (*72*) than did RECIST. PERCIST (and other PET metrics) correlated with biochemical response, though not survival, in a study of 42 patients on a mixture of systemic therapies (*73*). A study of 72 patients receiving chemohormonal therapy showed better performance for PERCIST and the European Associating of Urologists and European Association of Nuclear Medicine criteria (which use total volume) than RECIST or findings on multiparametric MRI (*74*).

However, WB volumetric biomarkers may be more useful still. Thirty-nine patients with mCRPC who were treated with $^{177}$Lu-PSMA-617 showed poor agreement between PERCIST (or variant measures using $SUV_{max}$ or $SUV_{peak}$) and biochemical response or survival outcome, though the correlation was ultimately positive (*70*). Nineteen patients with mCRPC who were treated with $^{177}$Lu-PSMA-I&T showed metrics of PSMA-expressing tumor volume and overall expression (analogous to metabolic tumor volume and total lesion glycolysis) correlated better than PERCIST with patient survival (*61*) and were relatively stable on 2 different software platforms (*75*). Another study compared a modified PERCIST using metabolic tumor volume (therein described as TTV) to PSA response and OS in 55 patients with mCRPC who were treated with $^{177}$Lu-PSMA, showing better correlation than RECIST or $SUV_{mean}$ with OS and PSA changes (*70*). Another study of 51 patients treated with $^{177}$Lu-PSMA-617 showed total lesion PSMA divided by healthy liver tissue (again, a TLG analog) had better correlation with PFS and performance status (*68*) than the modified PERCIST, which used summed $SUV_{peak}$. Other metrics such as the percentage of bone volume affected by tumors (possibly incorporating level of uptake) have been suggested and may be more reproducible and faster (*63*).

## PSMA PET–SPECIFIC CRITERIA FOR RESPONSE EVALUATION IN PC

The PSMA PET progression (PPP) criteria were introduced as an initial effort to standardize the assessment of imaging-based response in metastatic PC using PSMA PET (*12*). The PPP criteria integrate biochemical and genetics data into the response assessment, which limits their use for calculation of imaging-based–only PFS. The PPP criteria derive progression as the appearance of at least 2 new lesions, which mirrors the PCWG3 criteria for progression on BS (Table 1) (*4*). It was shown retrospectively that progression on PSMA PET according to the modified PPP criteria after completion of $^{177}$Lu-PSMA-617 therapy was significantly associated with shorter OS (median OS, 7.0 vs. 29.0 mo) (*76*).

RECIP 1.0 was proposed as the first evidence-based standardized framework for response evaluation in PC using PSMA PET. Compared with PPP, which uses individual lesion measurements, RECIP 1.0 accounts for changes in TTV, capturing the entire extent of disease. That has clinical relevance, especially during treatment of advanced PC in which heterogeneous response by individual metastatic lesions is quite common, although it must be kept in mind that this heterogeneity might be of prognostic significance. RECIP 1.0 categorizes scans into CR, PR, SD, and PD on the basis of changes in PSMA-positive TTV and the appearance of new lesion(s) (Table 2). RECIP PD requires both the occurrence of new lesions and a minimum significant increase in tumor volume (>20% increase), whereas RECIP PR requires both the absence of new lesions and a substantial decrease (>30% reduction) of TTV. The appearance of new lesions and a concomitant decrease in TTV is classified as stable disease. In a retrospective, multicenter study of 124 patients, PR versus SD versus PD by RECIP 1.0 was associated with OS (median OS, 21.7, 13.1, and 8.3 mo, respectively) (*11*). RECIP 1.0 can be determined using 2 approaches, that is, visually by physicians (visual RECIP) or quantitatively using tumor segmentation software (quantitative RECIP) (*77*). Both visual and quantitative RECIP 1.0 achieved an excellent interreader agreement (83% and 92%, respectively). Agreement between visual and quantitative RECIP 1.0 was observed in 95% of cases, indicating that the 2 methods can be used interchangeably in both clinical trials and clinical routine. Although it was initially developed in patients with late-stage mCRPC, RECIP 1.0 was successfully validated in patients with early-stage PC with biochemical recurrence after definitive therapy (*78*), during the use of ARPI in early-stage mCRPC (*13*), and during $^{223}$Ra therapy (*79*). PROMISE V2 has proposed PPP criteria for response evaluation in early PC and RECIP 1.0 for late-stage mCRPC based on the

**TABLE 1**
Definition of PPP Criteria

| Progression criterion |
|---|
| Appearance of 2 or more new PSMA-positive distant lesions |
| Appearance of 1 new PSMA-positive lesion plus consistent clinical or laboratory data and recommended confirmation by biopsy or correlative imaging within 3 mo of PSMA PET |
| No new lesions, but increase by ≥30% in size or uptake plus consistent clinical or laboratory data and confirmation by biopsy or correlative imaging within 3 mo of PSMA PET |

**TABLE 2**
Definition of RECIP 1.0

| Definition | Criterion |
|---|---|
| New lesion | |
| Any new focal uptake of PSMA ligand | |
| Higher than surrounding background | |
| With tumor $SUV_{max}$ > blood-pool $SUV_{max}$ | |
| Not present on baseline scan (tumor $SUV_{max}$ < blood-pool $SUV_{max}$) | |
| With tumor uptake not attributable to physiologic uptake or pitfalls | |
| Any new malignant lesion detected on follow-up CT images independent of PSMA ligand uptake | |
| RECIP 1.0 classification | |
| RECIP CR | Absence of any PSMA ligand uptake on follow-up PET scan |
| RECIP PR | ≥30% decrease in TTV without appearance of new lesion(s) |
| RECIP PD | ≥20% increase in TTV with appearance of new lesion(s) |
| RECIP SD | Does not meet the criteria for CR, PR, or PD |

evidence available in 2023 (*41*). A case example of treatment response in PC using PSMA PET/CT evaluated by PPP and RECIP 1.0 is given in Figure 1.

## PSMA PET FOR RESPONSE EVALUATION DURING PSMA THERANOSTICS

On the basis of the positive results from the VISION trial (*80*), $^{177}$Lu-PSMA-617 was approved by the U.S. FDA in patients with mCRPC who progressed on ARPI and taxane-based chemotherapy. The prerequisite for being eligible for $^{177}$Lu-PSMA-617 is the presence of PSMA-positive lesions on the screening PSMA PET scan. An important question in the community is how to evaluate treatment response during PSMA-targeted therapeutic radiopharmaceuticals, especially considering that baseline PSMA PET imaging is available as a standard-of-care procedure.

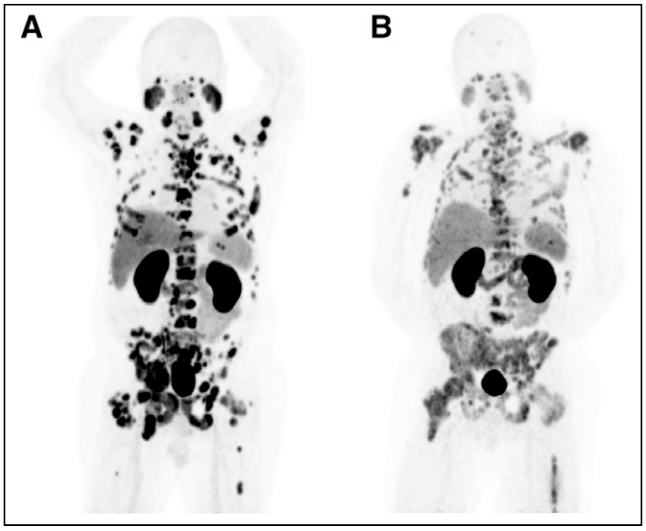


**FIGURE 1.** Case example of treatment response in metastatic PC using PSMA PET/CT. 72-y-old male with mCRPC previously treated with ARPIs and taxanes. Baseline $^{18}$F-DCFPyL PET/CT (A) from June 2022 showed diffuse skeleton involvement and pelvic lymph nodes. Follow-up $^{18}$F-DCFPyL PET/CT (B) from May 2023 after 6 cycles of $^{177}$Lu-PSMA-617 showed mixed response with majority of lesions decreasing in size and intensity, however, with occurrence of ≥2 new lesions (e.g., right femur and spine). Response classified as PD according to PPP criteria (≥2 new lesions) and SD according to RECIP 1.0 (≥1 new lesion without significant change in total tumor volume). Patient died 14.5 mo after $^{177}$Lu-PSMA-617 initiation.

According to the current Society of Nuclear Medicine and Molecular Imaging and European Association of Nuclear Medicine guidelines, interim PSMA PET scans should be conducted every 12 wk during PSMA-targeted therapeutic radiopharmaceutical administration to ensure optimal follow-up and treatment response assessment (*81*). However, the current FDA label does not include response assessment or monitoring, so such imaging is likely performed much less often in the United States relative to other regions such as Europe and Australia. Several retrospective studies have demonstrated the prognostic value of interim PSMA PET performed after 2 cycles of therapy (*11*,*76*,*77*). One report found the end-of-treatment PSMA PET after the last therapy cycle is associated with OS (*82*). Patients with RECIP PD had significantly shorter survival compared with those with RECIP non-PD (median OS, 10.9 mo vs. not reached; $P = 0.002$).

Posttherapy SPECT imaging using 1 of the γ-photopeaks from the $^{177}$Lu radionuclide has the potential to evolve as an imaging response biomarker for PSMA-targeted therapeutic radiopharmaceuticals, in addition to its value in dosimetry (*83*). SPECT at 24 h after $^{177}$Lu-PSMA administration represents a potentially cost-effective alternative to interim PSMA PET. $^{177}$Lu is a β-therapy that also emits 11% γ-rays, which can be used to derive WB tomographic images similar to PSMA PET. That allows image quantitation and evaluation after every treatment dose. Previous studies investigated the role of posttherapeutic SPECT for response evaluation during $^{177}$Lu-PSMA treatment. John et al. (*84*) demonstrated that TTV derived from SPECT after 2 cycles of $^{177}$Lu-PSMA-I&T in 96 patients with mCRPC is prognostic for PFS but not for OS. Song et al. (*85*) found that changes in tumor volume quantified on digital WB SPECT imaging performed 1–5 h after a second dose of $^{177}$Lu-PSMA-617 is prognostic for OS. In a multicenter retrospective

study, changes in TTV on SPECT after 2 cycles were associated with OS (hazard ratio, 0.28; $P < 0.001$) (*86*).

Nevertheless, attention should be paid particularly to new or progressive lesions at morphologic examination without PSMA uptake. PC metastases that have lost PSMA expression can be identified using a second imaging modality such as diagnostic CT or MRI or FDG PET (*81*). Emerging data support the broader use of WB MRI, including diffusion-weighted imaging sequences, for disease burden assessment and response monitoring, although its relative role in the standard of care for patients with advanced PC is yet to be fully defined (*87–90*). WB MRI can detect bone metastases with higher sensitivity than BS and CT and with a performance close to that of PSMA PET (*91*,*92*). In contrast to BS, WB MRI allows an accurate assessment and categorization of treatment response of bone, node, and visceral metastases in a RECIST-like fashion (PD, SD, but also PR and CR) using the Metastasis Reporting Data System for Prostate Cancer criteria (*93–95*). As it does not depend on the (persistent) expression of a tracer, WB MRI offers a good and consistent one-size-fits-all solution for patients, allowing assessment of bone, node, and visceral lesions, regardless of tracer expression (*96*). The technique is gaining acceptance because of reasonable acquisition times (<30 min) using the Dixon technique and deep learning image reconstruction (*90*,*94*). However, WB MRI can have limited applicability in patients with claustrophobia and cardiac devices, and some patients may still not tolerate the acquisition time.

## PSMA PET FOR RESPONSE EVALUATION WITH NON-PSMA–TARGETED THERAPIES

Assessing chemotherapy response is essential for determining the management of metastatic hormone-sensitive PC and mCRPC. At present, therapy monitoring relies on the use of imaging combined with serum PSA levels (*4*). However, PSA can be unreliable as it provides an indirect estimation of the volume of disease, and new metastatic sites might appear even when PSA is decreasing. Several studies have reported discordance between serum PSA trends and PET imaging results (especially when PSA decreased while PET showed appearance of new lesions) (*97*). Interestingly, WB MRI–based studies reported the same observation (*98*). In addition, some specific sites of metastases in patients with mCRPC are associated with different OS: visceral metastases (especially lung and liver) are associated with increased mortality compared with bone metastases (*99*). But radiographic response assessments also have limitations. For example, RECIST 1.1 for sclerotic bone appearance on CT images, since it can have limited PSMA uptake, may represent treated sites of disease and often lack a soft-tissue component (*50*).

Although PSMA PET is primarily used for PSMA-targeted therapies, emerging data suggest its potential role in monitoring responses to cytotoxic agents including taxane-based chemotherapy (docetaxel and cabazitaxel). There are currently no specific validated response criteria for PSMA PET in this context. However, the cutoff of 30% change in TTV in PSMA-expressing disease, as established by the consensus statements on PSMA PET response assessment criteria (*18*), may have value. Those studies showed that a change in PSMA expression correlated closely with PSA trends, and that those criteria could be used as an independent predictive biomarker for OS (*15*). Other studies have used the same cutoff applied to the summed $SUV_{mean}$ (*66*).

However, the utility of end-of-treatment versus interim PSMA PET is still under investigation, and clear guidelines for timing remain to be established. Although evidence supporting the use of PSMA PET in evaluating chemotherapy response is growing, further research is needed to validate standardized protocols and optimize timing to maximize clinical utility.

The use of agents that target the androgen signaling axis creates specific challenges with PSMA PET for response assessment. In the preclinical setting, it has been observed that an interruption of the androgen signaling axis with agents such as androgen-deprivation therapy or second-generation antiandrogen drugs can drive increased expression of PSMA even while the tumor may be responding (*100*). Although concordant results were noted in an initial case of a patient starting androgen-deprivation therapy reported by Hope et al. (*101*), subsequent studies have demonstrated that the overall in vivo process is more complicated (*14*,*102*,*103*). Despite the complexity of the data, there are likely imaging biomarkers from serial PSMA PET scans that are associated with PFS and OS and of potential utility in patient prognostication (*14*). Further study is certainly needed to establish the role of PSMA PET for response assessment in the context of treatment with androgen-axis–targeted agents.

PSMA PET is being explored to evaluate responses to other systemic therapies, including poly(ADP-ribose) polymerase inhibitors (PARPi) and $^{223}$Ra. For PARPi, data on PSMA PET as a response biomarker are sparse, but early studies suggest it could play a role in evaluating the therapeutic effects of PARPi in metastatic PC, particularly when combined with other agents. The ongoing exploration of these systemic therapies with PSMA PET highlights the potential for more personalized, data-driven treatment adjustments based on real-time imaging results.

$^{223}$Ra-dichloride is an approved bone-targeting radiotracer for patients with mCRPC with bone metastases after 2 systemic therapy lines (*104*). However, since its approval, no imaging method has been firmly established to reliably monitor treatment response. Although there are emerging methods being tested, such as PSMA PET, none are yet considered the gold standard. A study has suggested a role in using PSMA PET response criteria (both RECIP 1.0 and PPP) in predicting OS after 3 cycles of $^{223}$Ra, but such an approach needs validation in larger studies (*79*).

## POTENTIAL ROLE OF PSMA PET IN TREATMENT RESPONSE FOR LOCAL THERAPIES

In cases of presumed early-stage PC localized to the gland (initially staged with PSMA PET) that were treated with primary radiation therapy, posttherapy PSMA PET demonstrated residual prostatic disease in 39% cases or new PD, including pelvic nodes and extrapelvic disease, in approximately 7% and 33% of cases, respectively (*105*). PSA before the PSMA PET scan was the only factor that correlated with PSMA-positive findings, with many patients demonstrating positive findings even in cases with extremely low PSA after therapy (>0.2 ng/mL, or velocity of >1 ng/mL/y) (*106*). Even more notable is the fact that patients with higher posttherapy PSA levels (>10 ng/mL) were more likely to demonstrate new distant disease at the time of repeat PSMA PET (*105*).

Although early imaging is crucial for early identification of metastatic disease, in patients with definitive radiation therapy, including brachytherapy and external-beam therapy, to the prostate gland, posttherapy imaging by PSMA PET should be optimally timed to minimize false positives due to local inflammation. One paper attempted to characterize pitfalls of postradiation therapy PSMA PET findings in patients with biochemical recurrence as defined by a PSA rise of more than 2 ng/mL above nadir after

definitive radiation. That study demonstrated that 77% of those patients had true recurrence, and that the false-positive rate was less than 10% (confirmed by pathology). The time since the last therapy in patients with false positives ranged from 1 to 20 y, but the majority of false-positive results were from indolent tumor remnants with treatment effects as seen in patients who were approximately 1 y out from therapy (*107*). This result may be due to the fact that radiation effects are long-lasting and may not affect cell death until the next cellular division, thus leaving detectable PSMA-expressing cells that are not viable. Indeed, complete histologic resolution after those therapies may take several years (*108*).

Currently, there are no substantial data to suggest what constitutes an ideal window for imaging with PSMA PET in a patient after radiation therapy, although the above-noted study suggests that PSMA PET has improved specificity when used at least 1 y out from therapy. It also warns against aggressive salvage therapy for a PSMA-positive finding in the gland less than 1 y from therapy, as those findings may represent a false positive. Such patients may benefit from repeat biopsy to assess the need for additional intervention. In observation studies, that patient group with residual indolent or posttreatment adenocarcinoma had similar outcomes as patients with negative biopsies (*109*,*110*). However, it could be argued that using PSMA PET within a 1-y posttherapy period still holds value in identifying early sites of extraprostatic recurrence that could be targeted with curable intent. There are currently no specific response assessment criteria that address lesions within the irradiated gland and how they might differ from extraprostatic lesions. One frequent question in daily practice is whether residual focal prostatic uptake with lower PSMA uptake than in the liver should be considered a sign of residual disease. Estimating residual intraprostatic tumor volume is not as easy as measuring an avid node. As such, response assessment of isolated intraprostatic recurrence is a topic that ideally could be assessed in future trials.

If indeed there is residual path-proven viable disease in the gland correlating to PSMA PET–positive findings, then there is literature supporting the feasibility and safety of PSMA PET avidity being used in planning for reirradiation in patients with locally recurrent PC. In this patient population, repeat gland radiation therapy resulted in complete PET response in 92% of patients (*111*). However, questions remain regarding the optimal manner by which to volumetrically delineate tumor within the prostate gland (*112*).

These findings together adjudicate the role of PSMA PET for use in the evaluation of recurrent disease in patients with low PSA and previously localized disease. By imaging with exquisitely sensitive PSMA PET tracers at lower PSA levels, we can identify early recurrent disease both inside and outside of the gland that would have gone undiagnosed by conventional methods and identify those patients who can potentially be cured by salvage therapies.

## REGULATORY AND REIMBURSEMENT LANDSCAPE

The processes for regulatory approval and reimbursement for PET radiotracers are very different in various countries. For example, in the United States, PET radiotracers must go through FDA approval to be clinically used. That approval process is initiated by a commercial or noncommercial (in-house radiopharmacy) manufacturer, based on data from a clinical trials. Hence, indications are clearly stated in the approval notice and package insert. Medicare may decide to pay for PET radiotracers or not, but if they pay, it is usually for the indications approved by the FDA. Private and public insurance carriers usually follow Medicare guidelines. In the past few years, Medicare has been paying only for 3 y for new imaging radiotracers, so-called pass-through status, and after that, the cost of the radiotracer is bundled into the reimbursement for image acquisition; however, that situation was at least temporarily rectified by recent new guidance from the Center for Medicare and Medicaid Services (*113*).

In Europe, the practice of radiopharmaceutical administration is regulated at a national level, and there are 3 main routes to get a radiopharmaceutical into the clinic for human use: marketing authorization, clinical trial, and the magistral approach (*114*). A marketing authorization is very expensive and takes years to obtain. A clinical trial is less expensive but takes at least a year. In contrast, the magistral approach is the least expensive and can take only a matter of months. A marketing authorization may be used for both established and new radiotracers. A clinical trial is mainly for novel tracers (first-in-human studies) and for new or additional uses of an already established tracer. The magistral approach is for known radiopharmaceuticals that have been previously tested in humans with available preclinical data. The payment for PET imaging agents and therapeutic radiotracers varies significantly among countries in Europe, and a complete discussion is beyond the scope of this article.

## CONCLUSION

The rapid adoption of PSMA-targeted diagnostic radiotracers has made it imperative that response assessment for men with PC be adapted to that new imaging modality. Although there are numerous approaches to objective imaging response, including RECIST, PCWG3, PERCIST, European Organisation for Research and Treatment of Cancer, PPP, and RECIP, there is not yet a unifying response assessment based on PSMA PET. In addition to an objective set of response criteria, it is also likely that careful assessment of PSMA PET data will uncover imaging biomarkers that will go beyond objective response and will instead provide prognostic information (*14*). Ultimately, it will likely require advanced imaging methodologies including machine learning and artificial intelligence to uncover those biomarkers (*115*–*117*).

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