Radiology

REVIEWS AND COMMENTARY • EDITORIAL

Quantitative Post-^{177}Lu-PSMA-617 SPECT/CT Analysis: Evidence for Adaptive Treatment Planning and Prognostication in Prostate Cancer

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Prostate cancer remains one of the most common malignancies in the United States, with approximately 12.5% of men diagnosed with prostate cancer during their lifetime, and it is the second leading cause of cancer-related death in the United States (1). Although variable, 10%–20% of patients develop metastatic castration-resistant prostate cancer within 5 years of diagnosis (2). Thus, it is imperative to have effective treatments for these patients.

One such treatment is the use of a radioligand that preferentially binds to prostate-specific membrane antigen (PSMA), which is preferentially overexpressed on prostate cancer cells. To establish the presence of PSMA-overexpressing disease, PET imaging is performed using one of several radioligands (3). Once PSMA-overexpressing disease has been confirmed, a therapeutic radioligand can be used for treatment. In current clinical practice, the radioligand of choice is lutetium 177 (^{177}Lu) PSMA-617, which has treatment effects related to emission of beta radiation, with secondary gamma radiation that can be used for imaging purposes. This therapy is administered in up to six cycles, given every 6 weeks. Based on the results of the VISION trial, the use of ^{177}Lu-PSMA-617 for treatment of metastatic castration-resistant prostate cancer has clear benefit, improving both overall survival (OS) and progression-free survival in this patient group (4).

Historically, ^{177}Lu-PSMA-617 was primarily reserved for patients with metastatic castration-resistant prostate cancer who were previously treated with taxane-based chemotherapy (primarily docetaxel or cabazitaxel). However, in the spring of 2025, the U.S. Food and Drug Administration approved the use of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer who have not previously received chemotherapy (5). An important element for monitoring disease status in patients receiving radioligand therapy is posttherapy whole-body imaging. Using the gamma radiation emission of ^{177}Lu-PSMA-617, SPECT/CT imaging can be performed to assess radioligand binding to sites of disease. Currently, to our knowledge, no unified standard exists for the frequency of posttherapy imaging, but there are strong arguments for its clinical utility (6).

The most important posttherapy imaging is the post–cycle 1 examination. This first examination has twofold utility. First, it represents the new baseline for the patient's disease, given that some interval of time has passed since the patient's previous PSMA PET examination. Second, it has technical significance in assessing whether the radioligand is appropriately bound to the area of the patient's disease. Beyond the first posttherapy scan, there is no definite standard practice for how many posttreatment imaging examinations to perform. There is a clear intuitive rationale for performing posttherapy imaging beyond the first posttherapy study to visualize whether there is decreased disease-associated activity suggesting positive treatment response. Additionally, continued posttherapy imaging allows for assessment of areas of nonresponse or areas of new activity suggesting disease progression.

From both a cost and logistical standpoint, using the activity of the already-administered ^{177}Lu-PSMA-617 for imaging is more prudent than midcycle PET imaging (6). In addition to visual analysis, areas of PSMA-overexpressing disease can be quantified. Areas of disease can be measured using total tumor volume (TTV) and intensity of activity (standardized uptake value). Patients who have higher volumes of disease at early-cycle posttherapy imaging have worse progression-free survival and OS (7). The evaluation of these posttherapy scans must also be considered within the context of the patient's serum prostate-specific antigen (PSA) level over the course of treatment. Typically, a down-trending PSA level over the course of treatment is a marker of positive treatment response, with PSA decrease associated with improved OS (8).

In this issue of *Radiology*, Ayati et al (9) present a secondary analysis of the ENZA-p clinical trial, using posttherapy

Author affiliation, funding, and conflicts of interest are listed at the end of this article.

See also the article by Ayati et al in this issue.

Radiology 2026; 319(1):e260836 • https://doi.org/10.1148/radiol.260836 • Content codes: GU NM CT

SPECT/CT imaging to evaluate early treatment response following ^{177}Lu-PSMA-617 therapy. The ENZA-p trial was a multicenter randomized phase 2 trial across 15 Australian sites. In the ENZA-p trial, participants were randomized to either a control group receiving enzalutamide daily or to an experimental group receiving enzalutamide plus two initial doses of ^{177}Lu-PSMA-617 at 2 and 8 weeks after commencing enzalutamide. A PSMA PET/CT examination was performed at 12 weeks. If there was residual persistent disease at that time, two additional doses of ^{177}Lu-PSMA-617 therapy were administered at 16 and 24 weeks. Ultimately, the trial demonstrated that the combination of ^{177}Lu-PSMA-617 and enzalutamide improved progression-free survival relative to enzalutamide alone (10).

In this secondary analysis, Ayati et al (9) evaluated a total of 74 men from the experimental group of the clinical trial. Following both dose 1 and dose 2 of ^{177}Lu-PSMA-617 therapy, SPECT/CT examinations were performed covering the neck, chest, abdomen, and pelvis 24 hours (± 4 hours) after treatment administration. Following image acquisition, an experienced nuclear medicine physician used a semiautomated workflow to quantify mean standardized uptake value and TTV based on ^{177}Lu-PSMA-617 uptake. TTV complete response (CR) was defined as TTV less than 1 mL at dose 2.

Regarding visual analysis of posttherapy imaging, SPECT/CT images were evaluated by six nuclear medicine specialists for assessment of disease volume and appearance of new lesions (both PSMA-overexpressing and non-PSMA-overexpressing lesions). The nuclear medicine readers were blinded to clinical context and the imaging quantification. The readers participated in a calibration session before review of imaging. Qualitative CR was defined as a 90% or greater decrease in disease volume. Qualitative CR was assigned if at least two-thirds of the readers designated CR. Qualitative disease progression was designated if there were unequivocal new sites of disease or an obvious increased volume of disease. Deep PSA response was defined as a 90% or greater decline in PSA level (from pretreatment baseline) within 20 days following dose 2.

In the 74 participants, median OS was 31 months (95% CI: 25, 33), with a 2-year survival rate of 70% (95% CI: 58, 79). The median change in TTV was −57% (IQR, −89% to −38%), with only three of the 74 participants having an increase in TTV. Twelve of the participants had TTV CR. Among the participants with TTV CR, the 2-year survival rate was 83%, compared with 67% among participants without TTV CR. Regarding PSA response, 71 of 74 participants had both baseline PSA data before dose 1 and a repeat PSA measurement within 20 days after dose 2. Of these 71 participants, 45 experienced deep PSA response, with a median change in PSA level of −94% (IQR, −98% to −72%). Compared with the 83% (95% CI: 48, 96) 2-year survival rate in participants with TTV CR, participants without TTV CR but with a deep PSA response had a 2-year survival rate of 76% (95% CI: 58, 87). Participants who had neither TTV CR nor deep PSA response had a 2-year survival rate of 54% (95% CI: 33, 71). Regarding the visual analysis, nine of the 74 participants were considered to have qualitative CR. Only three of the participants had visual or quantitative evidence of progressive disease at dose 2.

Ultimately, these results suggest improved patient prognosis with positive volumetric TTV examinations, with a substantial subset of participants experiencing CR after only two doses. Given that these participants had no quantitative or qualitative evidence of disease after two doses, it is unclear whether uninterrupted continued treatments provide substantial benefit.

Although an early PSA response is an important marker for a more durable treatment response, it cannot be used in isolation, given the improved survival in participants who had both a deep PSA response and TTV CR compared with participants who had only a deep PSA response. As Ayati et al suggest, this difference is most likely secondary to some component of disease that is PSMA overexpressing but not PSA secretory. Thus, posttherapy imaging can help identify patients who need longer courses of therapy to reduce overall tumor volume.

The authors identify two important limitations of their study. First, only a small number of participants experienced disease progression during the study (4.1%), which limits the overall generalizability to a larger patient population with more aggressive tumors. Second, the semiautomated analysis used for the SPECT/CT imaging in this study involves both an upfront proprietary software cost as well as the cost of labor to both oversee and interpret the quantification data.

This article is important for the future of ^{177}Lu-PSMA-617 posttherapy imaging in that it provides a compelling argument to increase its overall use in general clinical practice and to go beyond the typical qualitative evaluation. With volumetric analysis, there can be greater diagnostic confidence that some patients with early treatment responses may be able to receive fewer than six doses at time of initial therapy, thus reducing overall toxicities as well as decreasing health care costs. Additionally, the quantitative evaluation ensures that patients with more slowly responding disease are not undertreated if they have an excellent PSA response but discordant TTV response. In the future, as the number of radioligand therapies increases and quantitative software continues to improve (particularly with artificial intelligence assistance), clinicians need to be aware of this information to best evaluate their patients from both a prognostic and treatment response perspective.

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Received March 20, 2026; revision requested March 30; revision received April 1; accepted April 6.

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Supplemental material: Supplemental material is available at *Radiology* online.

Funding: Authors declared no funding for this work.

Disclosures of conflicts of interest: Please see ICMJE form(s) for author conflicts of interest. These have been provided as supplemental materials.

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