SNMMI/ACNM Procedure Standard for Post-Treatment Imaging of ^{177}Lu-based Radiopharmaceuticals

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PREAMBLE

The Society of Nuclear Medicine and Molecular Imaging (SNMMI), founded in 1954 and headquartered in Reston, VA., is a nonprofit scientific and professional organization that promotes the science, technology, and practical application of nuclear medicine and molecular imaging. SNMMI strives to be a leader in unifying, advancing, and optimizing molecular imaging, with the ultimate goal of improving human health. With 13,000 members worldwide, SNMMI represents nuclear medicine and molecular imaging professionals, all of whom are committed to advancing the field. The American College of Nuclear Medicine (ACNM) is a professional organization providing education, training and advocacy for the most sought-after and trusted experts in nuclear medicine who deliver state-of-the-art and innovative care and service to our patients and referring physicians. The ACNM's mission is to foster the highest standards in Nuclear Medicine

consultation and service to referring physicians, hospitals, and the public, advance the science of Nuclear Medicine through a program of continuing professional development emphasizing high standards of Nuclear Medicine practice.

The SNMMI/ACNM periodically defines new standards for nuclear medicine practice to help advance the science of nuclear medicine and improve the quality of service to patients. Existing standards/guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

Each standard/guideline, representing a policy statement by the SNMMI/ACNM, has undergone a thorough consensus process in which it has been subjected to extensive review. The SNMMI/ACNM recognizes that the safe and effective use of diagnostic nuclear medicine imaging and therapy requires specific training, skills, and techniques, as described in each document.

The SNMMI and ACNM have written and approved these standards/guidelines to promote the use of high-quality nuclear medicine procedures. These standards/guidelines are intended to assist practitioners in providing appropriate care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, the SNMMI/ACNM cautions against the use of these standards/guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by medical professionals, taking into account the unique circumstances of each case. Thus, there is no implication that an approach differing from the standards/guidelines, standing alone, is below the standard of care. On the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the standards/guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology after publication of the standards/guidelines.

The practice of medicine involves not only the science but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these standards/guidelines will not ensure an accurate diagnosis or a successful outcome. All

that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these standards/guidelines is to assist practitioners in achieving this objective.

Introduction

Radiopharmaceutical therapies (RPTs) use radiolabeled molecules to target biomarkers preferentially expressed on tumor cell surfaces. Prior to therapy, molecular imaging with single-photon emitters, or now more commonly, positron emission tomography (PET) is used to assess whether the radiopharmaceutical demonstrates sufficient tumor localization to justify treatment. If present, the cells can be targeted with the same or slightly modified molecule radiolabeled with a therapeutic radionuclide (i.e., alpha or beta emitters). RPTs with ^{177}Lu-labeled compounds have shown clinical benefit in the treatment of neuroendocrine tumors (NETs) and metastatic castration-resistant prostate cancer (mCRPC), with Food and Drug Administration (FDA) approvals of ^{177}Lu-DOTATATE in 2018 and ^{177}Lu-PSMA-617 in 2022 [1,2].

NETs are a heterogeneous group of neoplasms classified based on their site of origin, degree of differentiation, proliferation index (Ki-67 index), and, more recently, genomic markers requiring differing treatment strategies [3]. ^{177}Lu-DOTATATE (Lutathera®, Novartis), also known as peptide receptor radionuclide therapy (PRRT), is a treatment option for NETs that express somatostatin receptors (SSTR). PRRT is typically given for four cycles, administered once every eight weeks. The National Comprehensive Cancer Network (NCCN) guidelines suggest imaging every 12 weeks (about 3 months) to 12 months for NETs, depending on tumor aggressiveness. However, there is no consensus on the timing of imaging for disease monitoring during PRRT [4]. In clinical practice, many centers do not perform imaging until the completion of PRRT while others perform restaging with CT or MRI at the halfway point (i.e., after two cycles). Additionally, guidelines do not recommend other methods to evaluate treatment response, including lab-based biomarkers such as chromogranin A [3,5].

^{177}Lu-PSMA-617 (Pluvicto®, lutetium Lu 177 vipivotide tetraxetan, Novartis) is a RPT for mCRPC. ^{177}Lu-PSMA-617 is administered for up to six cycles and is given once every six weeks. For response monitoring in mCRPC, Prostate Cancer Working Group 3 (PCWG3) recommends CT/MRI and bone scan every 8 weeks for the first 24 weeks after treatment initiation and then every 12 weeks thereafter [6]. Monitoring bone metastases, the most common metastatic disease site, poses challenges. CT has limitations in characterizing sclerotic lesions, which can be active versus treated disease. Bone scans show the osteoblastic activity of bone metastases, an indirect

measure of disease activity, also making it difficult to distinguish between active versus treated disease. Flare phenomenon, defined as a transient increase in osteoblastic activity of bone metastases after the start of effective therapy, is well defined in prostate cancer. A confirmatory scan 8-12 weeks after an initial scan can be used to confirm new lesions to avoid misclassification of flare as progressive disease. Like PRRT, there is no consensus on utilizing imaging for response monitoring during treatment with PSMA-targeted RPT, leading to a vast heterogeneity of imaging in clinical practice. Biochemical response assessment with serial PSA remains the most common method of response monitoring. However, PSA does not inform the disease distribution or its characteristics and can sometimes be discordant with the imaging or clinical response [7–9].

Pre-therapy PET imaging is standard before administering RPTs for both NETs and mCRPC to demonstrate the expression of biological targets [10–12]. In contrast to pre-therapy images, post-treatment ^{177}Lu imaging is not standardized or well-documented, but is increasingly used in clinical practice [13]. For both ^{177}Lu-DOTATATE and ^{177}Lu-PSMA-617, a post-treatment biomarker measurement that can assess antitumor activity tailored to their mechanism of action is highly desirable. In addition to beta-emissions for therapy, ^{177}Lu decay emits gamma rays (208 keV and 113 keV) that are suitable for imaging with single photon emission computed tomography (SPECT) / computed tomography (CT). The imaging properties of ^{177}Lu enable verification of delivery, along with detailed tracking of its distribution and retention over time, allowing for quantitative and dosimetry analysis. Additionally, serial post-treatment imaging can also be used for response monitoring that can impact patient management [14,15].

This procedure standard was developed through a collaborative effort by a group of clinicians and scientists to establish specific recommendations for post-treatment SPECT/CT in patients undergoing treatment with ^{177}Lu-labeled radiopharmaceuticals. The group reviewed existing evidence, identifying areas of strong consensus and aspects of post-treatment imaging that remain controversial or lack evidence. This document emphasizes the critical role of post-treatment ^{177}Lu SPECT/CT in providing both qualitative and quantitative response assessments, supporting its integration into routine clinical practice and serving as a foundation for more standardized procedural guidance. While the primary aim is not to define dosimetry-based personalization strategies, the routine acquisition of quantitative SPECT/CT lays the groundwork for a natural transition toward incorporating dosimetry calculations in future applications; an opportunity that is also briefly discussed in this document.

Imaging protocols for ^{177}Lu radiopharmaceuticals

Whether the goal is qualitative interpretation or quantitative assessment (including dosimetry), optimizing the SPECT/CT protocol is essential. This includes careful definition of energy windows and the use of an attenuation map via low-dose CT to ensure high-quality images for accurate interpretation. When clinically indicated, for example to support segmentation, higher-dose CT may also be considered. Table 1 outlines general starting-point recommendations for collimator and energy window settings, informed by SNMMI Medical Internal Radiation Dose (MIRD) committee guidance [16], early studies on modern 360º CZT systems [17], and the practical experience of the panel. The parameters shown serve as a foundation, with further optimization recommended based on individual system characteristics. These recommendations do not currently include dual-headed CZT systems, for which published guidance and panel experience remain limited; consultation with the manufacturer is advised to optimize acquisition and reconstruction protocols for these systems. To minimize variability and bias in the quantification of ^{177}Lu images, as well as to enable high-contrast lesion visualization, SPECT/CT is strongly preferred over whole body planar imaging. [18–20].

Table 1: Suggested imaging protocol parameters to generate quantitative ^{177}Lu SPECT/CT images, a starting point for system-specific optimization.

	NaI Systems	**360º CZT Systems**
Collimator	Medium Energy	-
Anatomical coverage	Include critical organs and disease. Typically, 2 to 3 beds for eyes to thighs	Include critical organs and disease. Variable number of beds for eyes to thighs.
Include arms in FOV?	Yes	Yes
Matrix Size	128x128 256x256 (if counting rates allow)	Automatically determined using patient contour dimensions and voxel size.
Photopeak window	208 keV ± 10% [187.2 – 228.8] keV	208 keV ± 6% [195.5 – 220.5] keV
Lower scatter window	176.8 keV ± 5% [166.4 – 187.2] keV	185.1 keV ± 5% [175.8 – 194.3] keV

Upper scatter window	239.2 keV ± 5% [228.8 – 249.6] keV	-
Views	≥120	Continuous sweep mode (may correspond to ≥120 in conventional SPECT setups)
Duration per projection (assumes 2 head camera)	10 to 15 seconds	3-5 minutes per bed position.
Orbit	Non-circular	-
Mode	Continuous gantry rotation is preferable as more efficient for large number of projections	Rotational sweep mode
Reconstruction Parameters	OSEM algorithm, with attenuation correction and scatter correction, typically at least 8 subsets and 4 iterations. Include resolution recovery.	OSEM algorithm, with attenuation correction and scatter correction, 1 subset and 72 iterations. Include resolution recovery.

As noted, Table 1 provides general starting point recommendations. However, there is a growing trend toward the use of both the 208 keV and 113 keV photopeaks in multi-window acquisition protocols to improve image statistics. This dual photopeak approach can allow for reduced scan time, improved patient comfort, and potentially enhanced image quality. MIRD Pamphlet No. 26 [16] also acknowledges this strategy if the number of counts collected in the 208-keV window is considered insufficient. We encourage sites considering this approach to consult their camera manufacturer for guidance on appropriate acquisition settings and quantitative reconstruction workflows for dual-photopeak imaging.

Post-reconstruction filtering can be appropriate in both quantitative and qualitative imaging, depending on the context. In quantitative imaging, especially for dosimetry, light filtering (e.g., 3–4 mm Gaussian) is often used to suppress noise without substantially affecting resolution. For qualitative interpretation, stronger filtering (e.g., 6–8 mm Gaussian) is common to improve signal-to-noise and reduce the chance of false positives. If post-filtering is applied, the trade-off between resolution and noise should be considered based on the imaging goal.

To accurately convert SPECT-derived counts into activity, activity concentration, or standardized uptake values (SUV), the system's sensitivity must first be measured. Three widely accepted methods for this calibration are:

1. Planar point source method: A small, well-characterized ^{177}Lu point-like source of known activity, with minimal scatter and attenuation, is used and a planar acquisition is performed. Scatter correction using triple energy window (TEW) method (photopeak and scatter energy windows as specified in Table 1) should be applied to the acquired projection image. The total counts in the projection image are then summed, and the procedure is repeated for all camera heads and averaged.
2. SPECT cylinder method: A uniform cylindrical phantom containing a known concentration of ^{177}Lu, placed in a tissue-equivalent medium to generate scatter, is imaged using the same acquisition and reconstruction settings as those applied in patient studies. This approach addresses some of the limitations of point-source methods, particularly their inability to replicate the scatter and attenuation characteristics seen in clinical imaging. The average counts within multiple spherical volumes-of-interest (VOIs), ensuring they are positioned away from the cylinder edges to minimize partial-volume and edge effects, is determined.
3. National Institute of Standards and Technology (NIST) traceable source: A NIST-traceable medium-energy source (e.g., ^{75}Se or ^{57}Co) of known activity is used for system calibration as part of manufacturer's quantitative workflow [21]. The source is scanned under a standardized acquisition protocol, and quantitative reconstruction is performed. This process applies system-specific calibration factors, along with resolution recovery, scatter, and attenuation corrections, built into the reconstruction pipeline.

Since the activity of the source is known, the camera sensitivity (in units of cps/MBq) can be determined by dividing the measured counts by the product of the source activity and the total acquisition time (i.e., time per view × number of views).

By enabling accurate quantification, these calibrated images facilitate absorbed dose assessments in treated patients, which is further discussed in the dosimetry section of this document. Additionally, quantitative imaging allows for the generation of SUV images, which can be used for longitudinal assessments of tissue uptake, providing a valuable tool for monitoring treatment response over time. It should be noted that due to the limited spatial resolution of SPECT, partial volume effects may significantly impact quantitative accuracy, particularly in small lesions. Partial volume correction is strongly recommended to improve the accuracy of activity estimates, particularly for small lesions. A phantom with spheres of different sizes and known activity concentrations for each one can be incorporated as part of the calibration to establish a recovery curve for partial volume correction.

Clinical Utility of Post-treatment Imaging

The use of post-treatment ^{177}Lu imaging in clinical practice has expanded with the growing adoption of ^{177}Lu-based RPTs. A limited but increasing body of data supports this trend. This section highlights literature specific to NET and mCRPC.

In patients with NETs, post-treatment imaging can play a crucial role in monitoring tumor response to PRRT and can significantly influence clinical decision-making during treatment. In a retrospective analysis of 100 patients with well-differentiated NETs receiving PRRT, Yadav et al. reported that 24-hour post-treatment SPECT/CT changes patient management in 27%, with a higher impact observed in higher-grade tumors [14]. Some key applications and advantages of post-treatment SPECT/CT include:

- Establishing a baseline tumor burden: Post-treatment SPECT/CT after the first cycle of PRRT can serve as a new baseline for tumor burden assessment, particularly in more aggressively behaving tumors, when repeated SSTR-PET/CT imaging is impractical or when there is a long window between the baseline SSTR-PET/CT and the first PRRT cycle. This is supported by recent studies demonstrating the clinical value and reliability of early post-treatment imaging in assessing tumor response during therapy [14,22].
- Identifying new lesions or non-uniform response: Post-treatment SPECT/CT can detect new lesions despite ongoing PRRT, prompting clinicians to reassess and potentially modify therapy (Figure 1), such as discontinuing ineffective treatments early. However, in cases of non-uniform lesion response, a modified approach could involve continuing PRRT for responsive lesions while targeting oligometastatic progression with localized therapy. Post-treatment SPECT/CT imaging may be especially valuable for detecting SSTR-positive lesions occult on conventional anatomical imaging, such as osseous metastases [14,22,23].

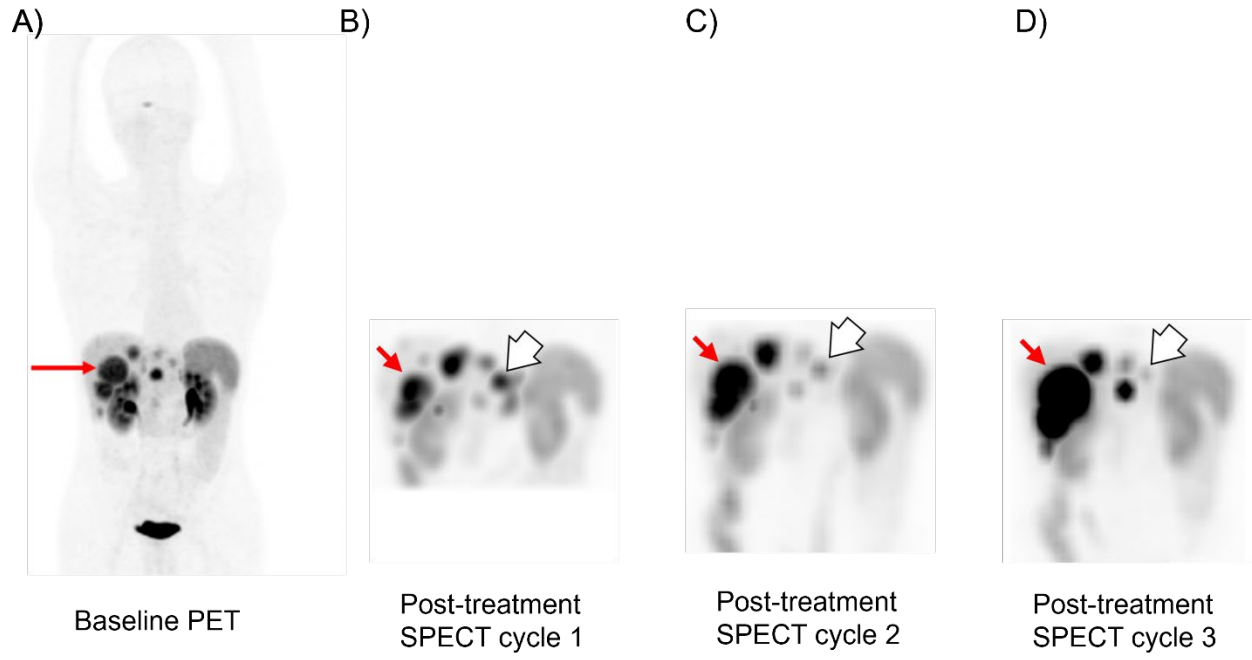

Figure 1: A patient with a grade 3 pancreatic neuroendocrine tumor. The red arrows demonstrate an increasing volume of liver disease as seen on A) the baseline maximum intensity projection (MIP) PET, and on serial post-treatment SPECT images collected at 24 hours post-injection and obtained at cycle 1 (B) cycle 2 (C) and cycle 3 (D) which resulted in stopping PRRT early. The white arrows highlight a lesion in the abdomen that shows decreasing uptake across cycles, consistent with treatment response.

- Altered biodistribution due to change in disease burden: Post-treatment SPECT/CT frequently demonstrates a substantial reduction (i.e., marked partial response) or even complete disappearance of tumor uptake (i.e., complete response), which serves as an early and favorable indication of therapeutic response (Figure 2). Clinicians can consider pausing PRRT in cases where there is little to no remaining SSTR-positive disease on post-treatment SPECT/CT, preserving remaining PRRT cycles for future use at the time of recurrence or progression. However, the impact of this strategy on long-term patient outcomes is unknown and requires further investigation [14,22]. Additionally, a subset of the "tumor sink effect", characterized by increased radiopharmaceutical uptake in normal organs over time [24], is not seen in all cases of response and depends on additional variables such as body weight and renal function.
- Detection of clinically relevant complications: The CT component of SPECT/CT imaging can identify clinically important conditions such as ascites and bowel or renal obstruction which may occur in patients with NETs. For instance, Aalbersberg et al. reported that the development of ascites during PRRT was associated with significantly worse outcomes, highlighting its prognostic significance and the need for routine review of the CT findings [22].

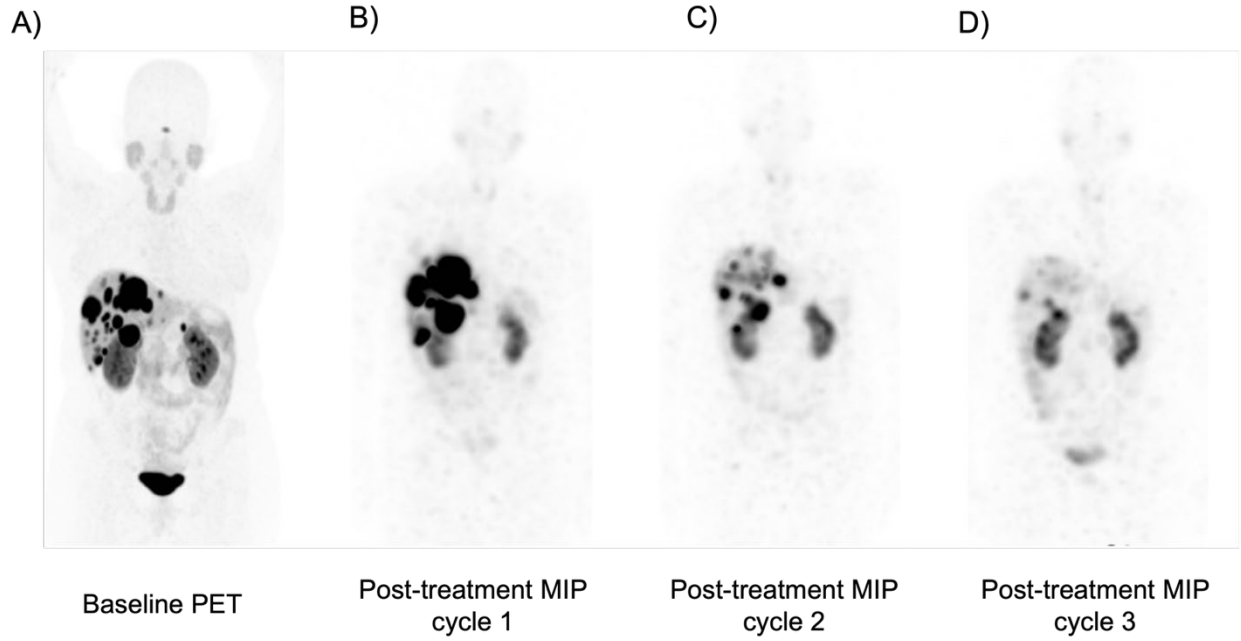

Figure 2: A patient with a grade 3 pancreatic neuroendocrine tumor received PRRT for multiple disease observed in the baseline PET (A). The maximum intensity projection (MIP) images from post-treatment SPECT collected at 24 hours post-injection and obtained after cycle 1 (B), cycle 2 (C) and cycle 3 (D) demonstrated marked response. Cycle 4 was withheld due to the much smaller tumor burden in the amount of disease seen in the liver at cycle 3.

Post-treatment imaging for patients with mCRPC treated with PSMA RPT provides critical clinical information, offering both qualitative and quantitative assessments of tumor and organ uptake, and can lead to management changes in up to 50% of patients [15]. Of those, almost 60% by detection of disease progression and 40% with marked response on post-treatment SPECT/CT. Although clinical assessments and serum biomarkers (e.g., PSA) are routinely employed, these measures may not always correlate directly with tumor volume or changes in disease extent and may be complementary to imaging findings [7,25,26]. Key advantages and clinical applications of post-treatment SPECT/CT include:

- Establishing a baseline for treatment response: Routine SPECT/CT imaging conducted immediately after the first therapy cycle can serve as a baseline for assessing therapeutic response, as continued disease progression can occur between pre-treatment PSMA PET/CT and treatment initiation (Figure 3). Although the SNMMI consensus statement allows baseline PSMA PET/CT imaging up to 3 months before initiation of therapy, interim disease progression during this window underscores the utility of post-treatment cycle 1 SPECT/CT as a more accurate starting point for response evaluation [27].

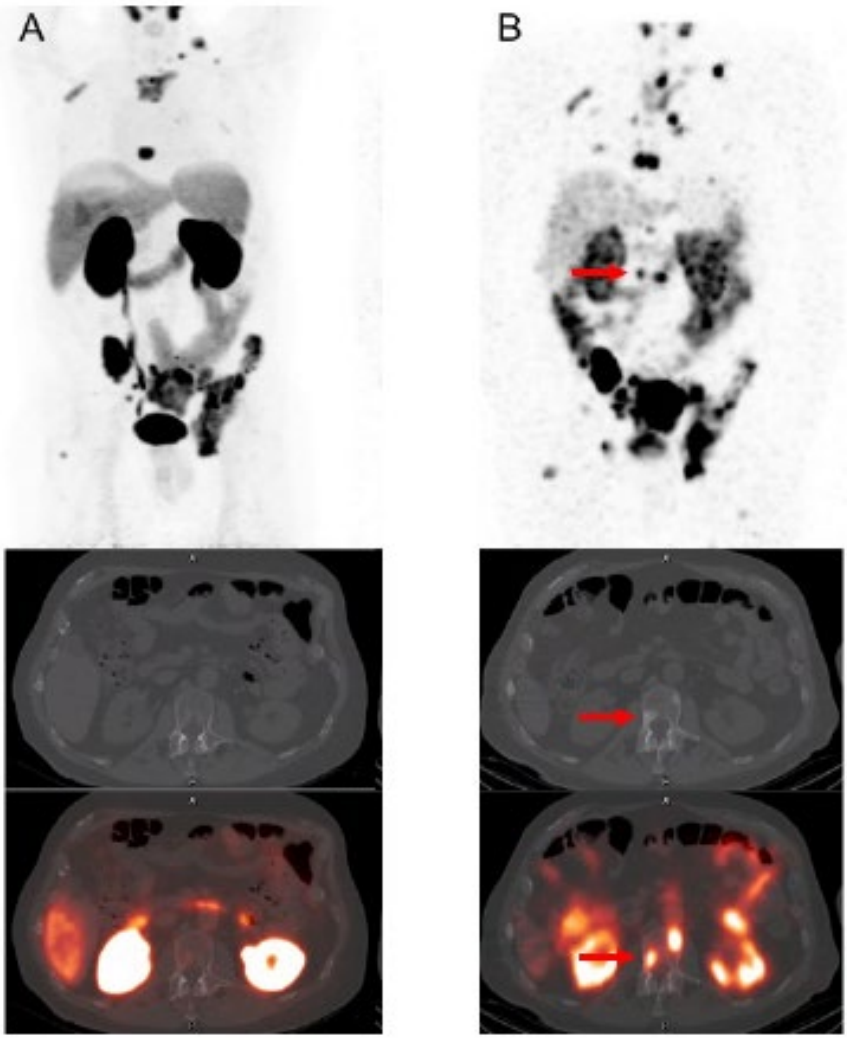

Figure 3: A) ^{68}Ga-PSMA-11 PET maximum intensity projection (MIP) shows multiple PSMA-avid osseous lesions. B) ^{177}Lu-PSMA-617 treatment started 2.5 months after PET. SPECT MIP, axial CT and fused axial SPECT/CT images acquired 24 hours after the first treatment cycle show multiple new PSMA-avid bone lesions. Representative transaxial CT and SPECT/CT show new sclerotic PSMA-avid lesions in the vertebral body (arrows).

Importantly, consistency in imaging timing across cycles is essential for reliable longitudinal comparisons. Figure 4 illustrates how varying imaging time points can lead to misinterpretation. with differences that could be mistakenly attributed to biological response.

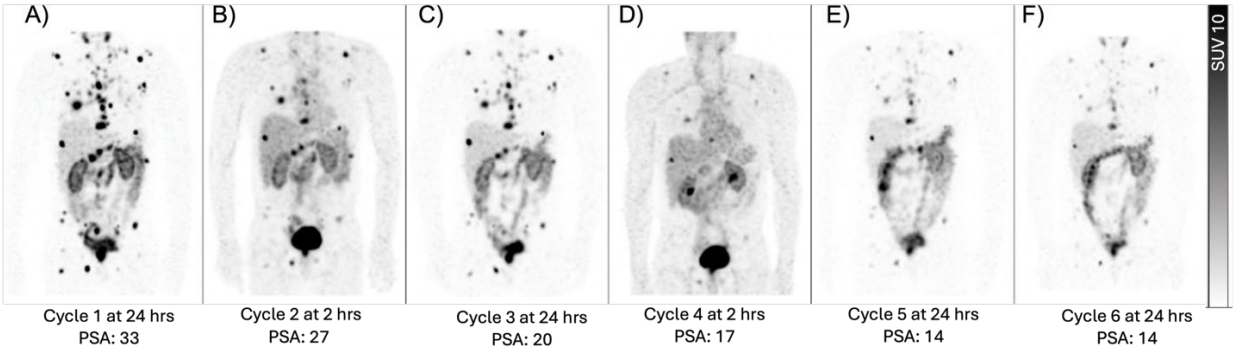

Figure 4: Post-treatment ^{177}Lu-PSMA SPECT images across multiple therapy cycles and time points. Panels A, C, E, and F show images acquired at 24 hours post-injection (cycles 1, 3, 5, 6), while panels B and D show images acquired at 2 hours post-injection (cycles 2 and 4). The difference in imaging time points (2 vs. 24 hours) leads to marked differences in lesion uptake, which can result in misinterpretation, particularly during response assessment. Images acquired at 2 hours (B, D) demonstrate lower lesion uptake and reduced apparent disease burden compared to their adjacent 24-hour counterparts (C, E), potentially leading to a false impression of disease progression or non-response. Note the higher blood pool activity visible in the earlier time point images.

- Detection of new lesions and non-uniform response: Post-treatment imaging can detect new metastatic lesions. The development of new lesions during therapy is associated with shorter biochemical progression-free survival and overall survival [9,25,28]. This detection can occur as early as after cycle two, potentially allowing timely adjustments to the treatment strategy. Importantly, post-treatment imaging offers an advantage for assessing metastatic disease that is occult or challenging to detect via conventional anatomical imaging or bone scintigraphy, especially bone metastases. This is particularly important in cases where biochemical markers, such as PSA, appear discordant with clinical progression or imaging findings (see Figure 5).

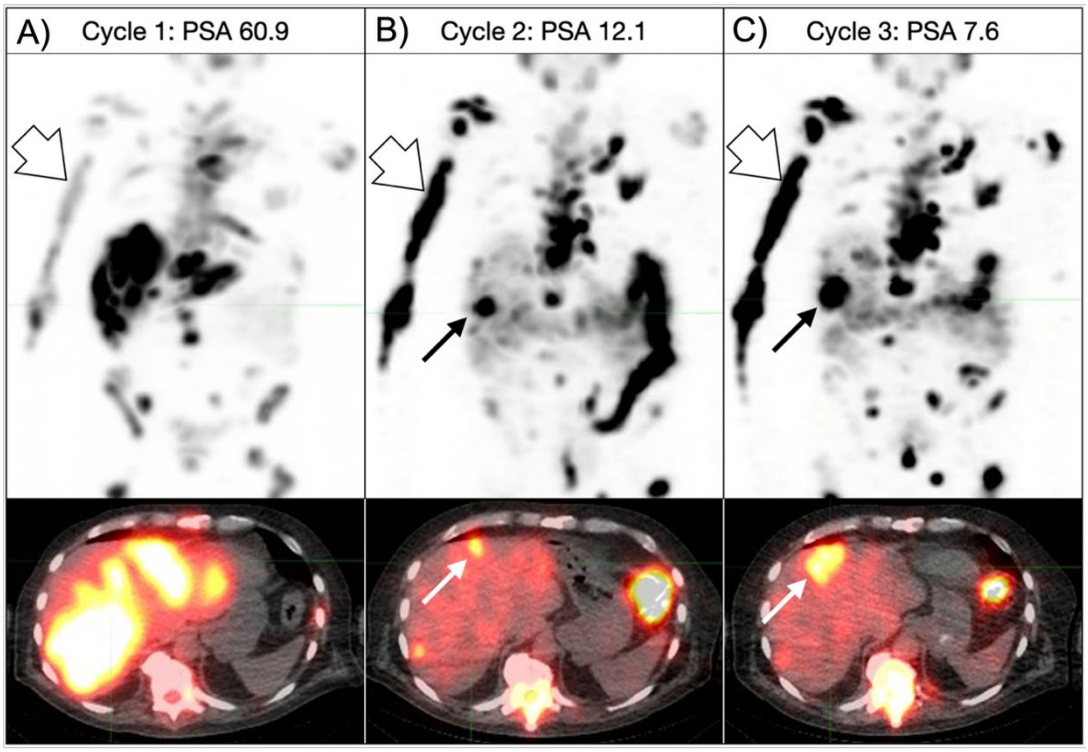

Figure 5: Post-treatment ^{177}Lu PSMA SPECT/CT images obtained at 96 hours post-injection demonstrating heterogeneous treatment response across three cycles of radioligand therapy. A) Post-treatment SPECT at cycle 1 shows widespread disease in the liver and bones (open arrow). B) after cycle 2, there is a marked response in hepatic lesions (black arrow), while osseous disease increases (open arrow), despite a substantial decline in PSA (from 60.9 to 12.1 ng/ml). C) By cycle 3, there is further progression in both liver and bone lesions (black and open arrows, respectively), even as PSA continues to decline (to 7.6 ng/ml). This example highlights the discordance between PSA trends and lesion-level response, reinforcing the added value of post-treatment imaging in capturing spatial heterogeneity in treatment response.

- Identification and management of marked therapeutic response: Post-treatment SPECT/CT may demonstrate a significant response to treatment. Such findings provide a clinical rationale to pause or defer subsequent therapy cycles until disease progression recurs [26,29,30]. In the TheraP trial, subsequent cycles were paused if uptake in all lesions fell to liver-level or below on 24 hour SPECT/CT, leading to deferred cycles in approximately 7% of the patients [30]. Further studies may need to explore the optimal threshold of decline in tumor burden, intensity of uptake or its combination with other markers such as biochemical response.
- Differentiation of cytopenia etiology: Emerging cytopenias during therapy pose a diagnostic challenge, as they could stem from progressive bone marrow metastases or treatment-related adverse events [31]. A decrease in disease burden on SPECT/CT supports a diagnosis of treatment-related cytopenia. Conversely, an increase in marrow

disease burden on SPECT/CT is suggestive of progressive disease, prompting a therapeutic strategy change.

- Incidental and clinically relevant CT findings: The CT component of SPECT/CT provides valuable supplementary information, aiding in detecting temporal changes in existing lesions, identifying new metastatic lesions, and revealing clinically relevant incidental findings. Even without contrast enhancement, careful evaluation and appropriate windowing of non-contrast CT images can detect new hypodense hepatic lesions, which may be PSMA-negative or low PSMA-expressing (Figure 6) [9]. Subsequent verification with contrast-enhanced CT or MRI is recommended. Additionally, the CT portion aids in recognizing treatment- or disease-related complications such as hydronephrosis or pathological fractures.

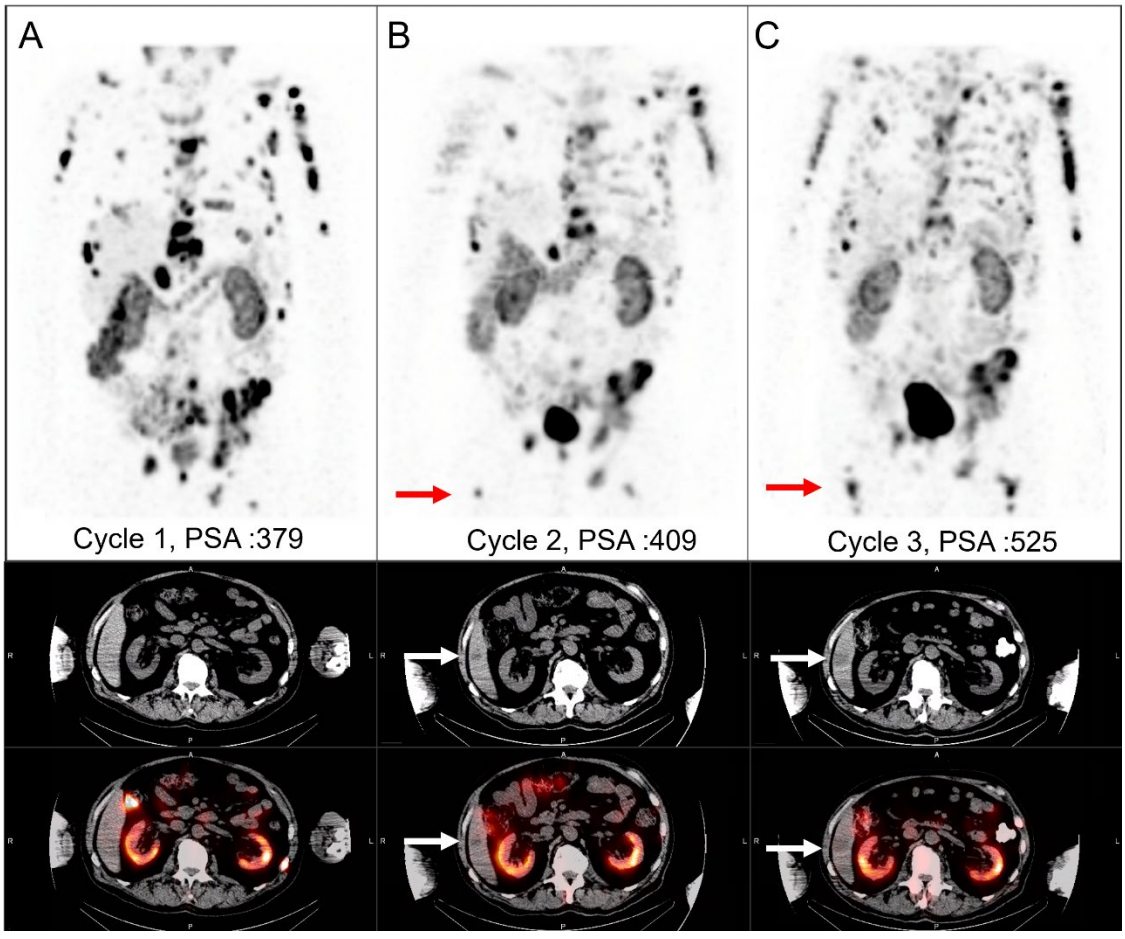

Figure 6: Serial ^{177}Lu-PSMA SPECT/CT images across treatment cycles take 24 hours post-injection. A) Maximum intensity projection (MIP) SPECT, CT and fused SPECT/CT images at cycle 1. B) At cycle 2, MIP SPECT shows a new PSMA-avid bone lesion in the right femur (red arrow), along with decreased uptake in some pre-existing lesions. CT and SPECT/CT reveal a new non-PSMA-avid hepatic lesion (white arrow). C) By cycle 3, MIP SPECT demonstrates multiple new PSMA-avid osseus metastases and increased uptake in existing lesions. CT and SPECT/CT show further enlargement of the non-PSMA-avid hepatic lesion and the appearance of additional new hepatic lesions (not shown). PSA levels (ng/ml) for each cycle are shown below the images

Potential to Reduce the Need for Interim PET/CT Imaging

As previously mentioned, imaging guidelines during RPT are not standardized for either NETs or mCRPC. Some centers do not perform imaging during RPT, while others may image in the interim or at other time points based on the overall clinical scenario. Conventional imaging (e.g., CT and MRI) or PET/CT may be used depending on which modality best visualized the disease at baseline. Post-treatment SPECT/CT is an alternative to PET/CT imaging during RPT, and it offers several advantages. First, the therapeutic radiopharmaceutical is imaged, negating the need for a separate radiopharmaceutical injection and limiting radiation exposure. Additionally, post-treatment SPECT/CT can be performed after each cycle, providing an up-to-date assessment of disease burden during treatment, which can impact management decisions after multiple cycles [7,8,14,15,25,26,32]. While PET/CT is commonly used at a single time point during therapy, post-treatment SPECT/CT allows for more frequent and less expensive imaging, potentially offering greater clinical value by enabling adaptive treatment decisions throughout the course of therapy.

These advantages of post-treatment SPECT/CT should be balanced with technical differences between PET and SPECT imaging. PET has higher spatial resolution than SPECT; therefore, smaller lesions may be more conspicuous on PET, and caution should be exercised when comparing across modalities. It is recommended that the baseline SPECT/CT (after therapy cycle 1) is used in comparison to SPECT/CT performed after subsequent RPT cycles, and comparisons to pre-RPT PET/CT should not be over-interpreted. SPECT/CT can also guide the need for further imaging with PET/CT, depending on additional clinical and laboratory data.

Value of Quantitative Imaging

Recent advances in SPECT reconstruction algorithms have increased interest in and availability of quantitative SPECT parameters. In NETs, two small studies demonstrated that obtaining SUV parameters from post-treatment imaging is feasible and that at 24 hours post-treatment, tumor SPECT and SSTR PET SUV values generally correlate [33,34]. In prostate cancer, preliminary studies suggest correlations between pre-treatment PSMA PET and post-treatment SPECT parameters [7,9]. However, SUV values from these two modalities are not directly comparable, and variability remains an issue [33]. The growing availability of quantitative SPECT software may allow further development of SPECT SUV as a useful imaging biomarker.

Well-calibrated SPECT/CT scanners are needed to ensure the quality of any quantitative data generated and applied to clinical care, and work is still required to understand clinical applicability.

Although several studies have shown that increased tumor volume at cycle 2 or 3 is associated with shorter progression-free survival, and stable or decrease in tumor volume was correlated with longer overall survival [7,25,35], routine clinical implementation of these quantitative measurements is still under evaluation. Tumor volume measurements remain time-consuming, require dedicated software, and depend on standardized methods before they can be widely adopted. However, recent developments in artificial intelligence (AI)-assisted segmentation show promise in addressing these challenges by automating tumor delineation and improving reproducibility and efficiency, which are expected to simplify implementation in the future [36–38]. Additionally, low PSMA-expressing or PSMA-negative disease, especially in the liver and bones, may not be captured in Total Tumor Volume (TTV), and attention to the CT component of SPECT/CT is required and dedicated contrast-enhanced CT/MRI should be obtained if the clinical scenario warrants.

Despite these challenges, the integration of post-treatment SPECT/CT imaging enables a more precise evaluation of response and fosters the development of its quantitative parameters as a reliable biomarker for clinical decision-making.

Dosimetry

To perform accurate dose assessments, it is essential to configure the imaging protocol based on the parameters outlined in Table 1. Valuable resources for dosimetry calculations include the MIRD Primer [39], the MIRD synopsis poster [40], and continuing education materials such as those by O'Donoghue et. al. [41]. In summary, serial quantitative imaging is used to track radiopharmaceutical biodistribution over time. Segmentation of tumors and organs at risk enables the generation a time-activity curves (TACs), which are often fitted to exponential functions [42] to determine the time-integrated activity (TIA); a measure of the total number of disintegrations within each region. The TIA in conjunction with precomputed S-values (for organ level dosimetry), voxel-kernels (for voxelized dosimetry), or Monte Carlo radiation transport simulations, is used to calculate the absorbed dose. At the organ level, the primary output is the mean absorbed dose, however, voxelized approaches can provide a more detailed characterization of dose distribution within a volume of interest (VOI). These include statistical measures such as mean, maximum, minimum, and median absorbed doses, along with dose-volume histograms. From these, additional clinically relevant metrics, such as D50 and D95 (which represent the absorbed dose

received by 50% and 95% of the target volume, respectively), and homogeneity index, can be derived to assess absorbed dose uniformity.

To more accurately model the biodistribution of the radiopharmaceutical, the TAC should ideally include multiple data points, with at least three time points measured within the first week post-injection [42]. However, repeated imaging may not always be clinically feasible due to logistical and patient-related constraints. It is crucial to acknowledge the limitations and document the uncertainty levels of using fewer time points, as this may impact the accuracy of pharmacokinetic modeling and dose estimation. To mitigate these logistical challenges, two approaches have been proposed to reduce the number of required SPECT acquisitions:

The single time point approach: This method simplifies dosimetry by estimating TIA from a single post-injection scan, reducing the burden of repeated imaging on patients and clinical workflows. Two common implementations of this approach include the Hänscheid [43] and the Madsen method [44].

The Hänscheid method assumes monoexponential clearance after a late imaging time point to extrapolate the TIA. It has shown acceptable accuracy for kidneys and tumors under controlled conditions. Specifically, Hänscheid et al. showed that single-time point imaging performed at approximately 96 hours post-injection provided reliable absorbed dose estimates for ^{177}Lu-DOTATATE therapy [43]. However, the accuracy of this approach may decline in patients with atypical kinetic behavior, such as those with impaired renal function or rapidly proliferating tumors exhibiting non-standard tracer dynamics.

The Madsen method uses a population-based reference time-activity curve that is scaled to the patient's single measured activity at any chosen imaging point. Because of this, it is less sensitive to the selection of the imaging time point. However, it relies on the assumption that the patient's kinetic profile matches that of the reference population, which may not hold in all cases. Differences in radiopharmaceutical uptake, clearance rates, and organ-specific retention times between patients, can lead to inaccuracies in dose estimates.

The hybrid prior information approach. This method involves collecting multiple time points during the first therapeutic cycle to establish patient-specific kinetics, which are then extrapolated to subsequent cycles using minimal sampling. Under normal circumstances, this approach can provide reasonable accuracy. However, if significant physiological changes occur during treatment, its accuracy may decline. For example, a study on individualized ^{177}Lu-DOTATATE therapy based on kidney dosimetry reported a gradual decline in renal function post-treatment, at a rate slightly higher than expected in the general population [45]. Notably, patients with

preexisting nephrotoxicity risk factors or moderately reduced glomerular filtration rates were at a greater risk of accelerated renal decline. Therefore, while the prior information approach offers a practical framework for reducing imaging requirements, individual patient factors, such as renal function, must be closely monitored to maintain accuracy in kinetic modeling throughout treatment.

Consequently, while the single time point approach is a valuable tool for streamlining dosimetry, its application should be guided by patient-specific factors. In clinical practice, combining single point methods with population-based studies and selectively incorporating multi-time point imaging in patients with non-standard kinetics may improve robustness and ensure more precise dose estimation.

Billing and coding

Post-treatment imaging and dosimetry are eligible for reimbursement through several AMA CPT® codes. Relevant codes for post-treatment imaging are summarized in Table 2, with detailed considerations relating to reimbursement for post-treatment imaging and dosimetry recently described by Graves et al [46]. Most centers utilize CPT 78832 for multi-bed SPECT/CT on one or more days post-treatment, however additional codes for whole body planar imaging (78802, 78804) and dosimetry (e.g. 77300, 77370, and 77295) are available for use as applicable.

Although the reimbursement examples provided reflect U.S. billing practices, the underlying principles supporting the use of post-treatment imaging, such as its role in guiding therapy decision and optimizing outcomes, are relevant in diverse global healthcare systems.

Table 2: Reimbursement codes that can be used for post-treatment imaging and dosimetry in ^{177}Lu RPTs.

Procedure	Reimbursement Code	FY2025 Medicare HOPPS Rate [47]
Single bed position SPECT/CT imaging	78830	$1,305.48
Multi-bed and/or multi-day SPECT/CT imaging	78832	$1,458.59
Single- or multi-bed SPECT imaging	78803 or 78831	$1,305.48
Whole body imaging on a single day	78802	$1,305.48
Whole body imaging on multiple days	78804	$1,305.48

Post-therapy dosimetry (basic radiation dosimetry calculations)	77300	$132.77
3D radiation treatment planning	77295	$1,368.26
Special medical physics consultation	77370	$132.77

In terms of healthcare financial burden, the cost of post-treatment imaging is minimal compared to the cost of the therapeutic radiopharmaceutical. Routine post-treatment SPECT/CT imaging would comprise only ~1-4% of the total cost of care throughout therapy, depending on local negotiated reimbursement rates (single- vs. multi-bed SPECT/CT). Therefore, post-treatment imaging provides added value in terms of informing subsequent patient management during therapy. Post-treatment SPECT/CT imaging is approximately one-third the cost per treatment cycle compared to mid-treatment diagnostic PET/CT. This difference is due in part to the lower reimbursement for the SPECT/CT technical component (HOPPS FY25t: $1,458.59) and the fact that no additional diagnostic radiopharmaceutical is required. In contrast, the use of PET/CT significantly increases the overall cost, as commonly used PET agents such as [^{18}F]DCFPyL($2,902), [^{64}Cu]DOTATATE: ($1,873), and [^{68}Ga]DOTATATE ($2,759) substantially contribute to the cost. This cost gap is often even greater with private payers, who typically reimburse at higher rates than Medicare.

Recommendations

Based on the comprehensive review of current practices, our expert panel recommends the following clinical actions to support the effective implementation of post-treatment imaging in ^{177}Lu-based radiopharmaceutical therapies. Table 3 provides a summary of these key recommendations, which are further elaborated in the text that follows.

Table 3: Summary of expert panel recommendations for post-treatment imaging with 177Lu-based radiopharmaceuticals.
1. Perform post-treatment imaging for all patients receiving ^{177}Lu-based RPTs. • For mCRPC, image after each cycle. • For NETs, at least every other cycle for lower grade tumors (grade 1) or every cycle for higher grade tumors (grade 3).
2. Use calibrated SPECT/CT systems suitable for quantitative imaging, even if quantitation is not performed at the time of study.

3. Single point imaging is acceptable in clinical practice, although multi-time point imaging is more accurate for dosimetry.
4. Acquire post-treatment SPECT/CT at ~24 hours for qualitative assessment. • Later time points (e.g., 48–72h) are preferred for dosimetry. • Earlier imaging (e.g., 4 h) may be considered when needed for logistical or clinical reasons. • Maintain consistent timing across cycles.
5. Ensure post-treatment SPECT/CT provides adequate anatomical coverage of critical organs and known sites of disease. • SPECT/CT should be used instead of planar imaging.
6. Consider using post-treatment SPECT/CT during therapy as an alternative to interim PET, as it provides accurate longitudinal assessment throughout the course of treatment.

1. *Perform post-treatment imaging for all patients receiving ^{177}Lu-based RPTs.*

Post-treatment imaging with 177Lu-based RPTs has gained increasing recognition as an essential tool for response assessment and clinical decision making [25,32,48]. While pre-treatment imaging is a well-established standard, post-treatment imaging protocols remain highly variable across institutions. Unlike biochemical markers, which may not accurately reflect tumor burden or lesion heterogeneity, post-treatment SPECT/CT allows direct visualization of radiopharmaceutical distribution. This enables the detection of new lesions, assessment of heterogeneous response, and identification of incidental findings or complications that may not be evident through laboratory data or clinical symptoms.

Routine post-treatment imaging facilitates longitudinal monitoring and informs critical treatment decisions such as continuation, modification, or early discontinuation of therapy. Thus, post-treatment imaging is essential for optimizing patient care. In clinical trials and real-world studies, post-treatment imaging has demonstrated its utility in changing management in up to 50% of patients receiving PSMA RPTs [15] and nearly 27% in patients receiving PRRT for NETs [14], underscoring its growing role in routine practice.

The panel strongly endorsed cycle-by-cycle post-treatment imaging for patients with mCRPC, given the frequent dynamic changes in disease at each cycle. Additionally, several studies have shown that new lesions identified on SPECT/CT during 177Lu-PSMA-617 therapy are associated with shorter progression-free and overall survival [9,25,28]. As disease

progression can occur between therapy cycles, even after pre-treatment imaging, routine SPECT/CT after each cycle enables early identification of treatment failure and supports timely adjustments to management strategies.

In NETs, imaging frequency is less clear, and the panel recommends tailoring frequency based on tumor grade. For aggressive grade 3 (G3) tumors, the panel recommends post-treatment SPECT/CT after every cycle to monitor response and detect progression. In contrast, for well-differentiated grade 1 (G1) tumors, imaging every other cycle was considered sufficient, balancing clinical utility with patient burden and resource use. Consensus for Grade 2 tumors was not reached given the heterogeneity of the clinical behavior; hence frequency of post-treatment SPECT/CT may need to be individualized based on the clinical factors, including Ki67, rate of growth, primary site, disease volume or its distribution [14].

This stratified approach reflects both the heterogeneity of disease biology and practical considerations in clinical care.

2. *Use calibrated SPECT/CT systems suitable for quantitative imaging, even if quantitation is not performed at the time of the study.*

   Calibrated SPECT/CT systems are essential for enabling quantitative imaging, which supports both clinical assessment and retrospective dosimetric analysis. Quantitative capabilities such as SUVs, dosimetry, and volumetric changes, provide objective tools to monitor treatment response. While thresholds for defining progression or response on post-treatment SPECT/CT remain under investigation, calibrated systems allow for consistent, reproducible imaging across treatment cycles and institutions, preserving the ability to perform retrospective analysis (e.g., in case of retreatment).

   Even if quantitative metrics are not immediately calculated, acquiring images on a system suitable for quantitation is recommended to enable future dosimetric or SUV-based assessments. This also supports research aimed at developing imaging biomarkers and understanding dose-response relationships.

   For response interpretation, panelists cautioned against relying solely on reduced uptake, which may not fully capture tumor dynamics. Instead, assessment should incorporate lesion morphology, volume changes, clinical progression, and biochemical markers. This highlights the value of integrating SPECT/CT with other clinical assessments to improve accuracy in response evaluation.

3. *Single point imaging is acceptable in clinical practice, although multi-time point imaging is more accurate for dosimetry.*

While multi-time point SPECT/CT imaging, ideally involving scans at three time points, allows for accurate modeling of radiopharmaceutical kinetics and absorbed dose estimates, it can be logistically challenging for both patients and clinics. In routine clinical settings, single time point imaging is often more practical and still provides clinical useful information, as discussed below in #4.

When timed appropriately, single scans can yield reasonably accurate dose estimates using population-based kinetic models (e.g., Madsen [44]) or simplified methods such as the Hänscheid approach [43,49–51]. A single-time-point approach reduces patient burden and resource demands while still enabling response assessment and, when needed, retrospective dosimetry. These simplified methods are especially important in centers where multi-time-point imaging is not feasible. Ultimately, patient-specific factors (such as renal function, tumor burden, or treatment changes) should guide whether simplified approaches are appropriate throughout therapy.

4. *Acquire post-treatment SPECT/CT at ~24 hours for qualitative assessment, with later points preferred for dosimetry, and earlier imaging (e.g. 4 hours) considered when needed for logistical or clinical reasons. Maintain consistent timing across cycles to enable reliable longitudinal assessments.*

The timing for post-treatment imaging time points was debated by the panel, reflecting two distinct goals: qualitative and quantitative assessment of tumor burden versus dosimetry. At present, qualitative post-treatment SPECT/CT has the greatest clinical impact, but the panel acknowledged that quantitative imaging holds promise for improving treatment planning and personalization [25,32,48]. A single-time-point SPECT/CT performed at ~24 hours post-injection allows for favorable tumor-to-background contrast and supports both qualitative interpretation and simplified quantification.

However, the accuracy of simplified single-time-point methods depends on how closely the imaging time aligns with the radiopharmaceutical's effective half-life. For example, the Hänscheid method suggests optimal timing when $0.75 < \text{imaging time} / T_{eff} < 2.5$, which may not always be satisfied with a 24-hour scan. The most accurate absorbed dose estimates to healthy organs are obtained with scans at ~48 hours post-injection for ^{177}Lu-PSMA-617 and ~72 hours for ^{177}Lu-DOTATATE [49–51]. Tumor dosimetry may benefit from even later acquisitions (e.g., 4 to 5 days post-injection) [43,45,48,49,52], but such protocols are often

impractical due to travel and scheduling limitations. In many clinical settings 24-hour SPECT/CT imaging offers a practical compromise.

Although imaging within the first 4 hours post-injection may be necessary for logistical or clinical reasons, it is generally considered less suited for both qualitative interpretation and dosimetric review due to higher blood pool activity and incomplete radiopharmaceutical kinetics. Nevertheless, early same-day post-treatment imaging (e.g., 4 hours) still generates images that help direct therapy and useful for treatment response assessment [48].

Regardless of the chosen time point, the panel strongly emphasized the importance of consistent timing across all treatment cycles. Standardizing post-treatment SPECT/CT time points enables reliable longitudinal comparison for both qualitative and quantitative evaluation. Variability in timing can alter lesion contrast and lead to misinterpretation of disease progression or response.

5. *Ensure post-treatment SPECT/CT provides adequate anatomical coverage of critical organs and known sites of disease.*

Adequate anatomic coverage is essential for both qualitative assessment (e.g., detection of new lesions) and quantitative analysis (e.g., dosimetry for organs at risk). By acquiring volumetric SPECT/CT across multiple bed positions, better lesion localization, improved response monitoring, and more accurate dosimetry can be achieved.

The panel recommended acquiring SPECT/CT images that allow coverage from the base of the skull to the mid-thigh, encompassing key regions such as the liver, kidneys, spine, and common sites of metastatic disease. Kidneys should be consistently included within the field of view to support dosimetry assessments. That coverage is typically achieved with 2 or 3 bed positions on NaI SPECT/CT systems.

The CT component of the SPECT/CT should also be routinely reviewed during therapy to detect anatomical changes or emerging lesions, particularly in the liver. Diagnostic CT should be obtained as clinically indicated to further characterize equivocal or low-PSMA-expressing lesions.

There was unanimous agreement that SPECT/CT should be routinely used instead of planar imaging due to its superior qualitative and quantitative accuracy and its ability to support three-dimensional response assessment. Planar imaging, in contrast, is limited by its lack of depth information and inability to perform reliable quantitative analysis, making it insufficient for modern post-treatment evaluations.

6. *Consider using post-treatment SPECT/CT during therapy as an alternative to interim PET, as it provides accurate longitudinal assessment through the course of treatment.*

The panel concluded that in many clinical scenarios, especially during therapy, SPECT/CT is a viable and valuable alternative to interim PET/CT. SPECT/CT imaging following ^{177}Lu-based RPT provides valuable clinical information that can, in many cases, substitute for PET during the treatment course. While PET offers superior spatial resolution and lesion detectability, post-treatment SPECT/CT has the distinct advantage of visualizing the therapeutic radiopharmaceutical itself, eliminating the need for a separate injection and reducing both radiation exposure and cost. This is also particularly important in settings where PET/CT is not readily available or when repeated PET/CT scans may not be practical. Furthermore, SPECT/CT supports both qualitative review and quantitative analysis when performed on a calibrated system. Importantly, post-treatment imaging can be performed after each cycle, while the use of PET/CT after each cycle would not be operationally supported. This provides opportunity for real-time decision making and optimization of management strategies during the course of treatment.

Future Directions

Post-treatment imaging is crucial to realizing the full potential of theranostics by enabling personalized, dosimetry-based treatment planning. Measuring absorbed dose in both tumors and normal organs is key to optimizing therapeutic efficacy while minimizing toxicity. As the field advances, several areas of research and clinical development have emerged as priorities.

A critical focus is the establishment of reliable dose-response relationships and normal tissue complication thresholds. Correlating absorbed dose with tumor response is essential for guiding dose escalation strategies or extended-cycle therapy in patients who may benefit from intensified treatment. At the same time, improving our understanding of dose limits for organs at risk is necessary to reduce treatment-related toxicity and enable safer, individualized administered activities. While thresholds for normal tissue toxicity in RPTs are often extrapolated from external beam radiation therapy, important differences in dose rate, radiation type, and fractionation, limit the direct applicability of these benchmarks. To date, normal tissue dose limits remain poorly defined in the context of RPTs.

Bone marrow dosimetry remains a topic of interest and ongoing debate. While it has the potential to inform treatment decisions, challenges related to methodological complexity and uncertain clinical impact have hindered routine implementation. Longitudinal studies are needed

to clarify whether routine assessment of marrow dose can improve clinical outcomes. Kidney dosimetry was also discussed, particularly for patients with moderate renal impairment (e.g., eGFR < 50 ml/min/1.73 m²). Although some panelists supported dosimetry-driven adjustments to reduce the risk of renal toxicity, others favored continued reliance on clinical monitoring alone, citing the lack of validated renal dose thresholds. These discussions further highlight the need for high-quality evidence to support individualized dosimetry in routine practice.

To improve access to image-based dosimetry, validation of single time point dosimetry models has also emerged as a priority. The models presented earlier in this document from Hänscheid and Madsen, offer more practical alternatives to multi-time point imaging by reducing patient and clinic burden while maintaining acceptable accuracy. Determining optimal imaging time points and schedules will also be essential to balance clinical utility with resource efficiency.

In parallel, technological advances aimed at enabling faster acquisitions are gaining traction. For example, ultra-fast CZT-based SPECT protocols targeting 1 to 3 minutes per bed [53], and the use of artificial intelligence to enable high-quality image reconstruction from reduced projections [54], may make dosimetry acquisitions more practical and better suited for routine clinical workflows.

At the same time, developing standardized response criteria for interpreting post-treatment imaging, incorporating both qualitative and quantitative metrics, remains a critical unmet need. Variability in imaging protocols, interpretation, and reporting across centers continues to limit broader adoption of post-treatment imaging for response monitoring. Efforts to establish standardized reporting frameworks (like RECIST or PERCIST) would improve communication among clinicians, support multi-center harmonization, and facilitate consistent assessment of treatment response. Future prospective clinical trials should incorporate post-treatment SPECT/CT imaging alongside these standardized response criteria to validate their utility and support integration into routine clinical practice.

Importantly, prior studies have shown significant interpatient variability in absorbed dose to tumors and normal tissues when fixed activity regimes are used [55,56], and some evidence suggests improved tumor response with higher absorbed doses [57–61]. In addition to the clinical advantages and recommendations outlined throughout this document, these considerations further underscore the importance of consistently collecting post-treatment SPECT/CT, particularly for image-based dosimetry, as a foundation for future personalized treatment

strategies. Such data will be critical for refining dose thresholds, validating predictive models, and advancing the theranostics paradigm while maintaining acceptable toxicity profiles.

Conclusion

This procedure standard highlights both established best practices and areas requiring further investigation in post-treatment imaging for ^{177}Lu-based RPTs. While routine SPECT/CT and quantitative imaging are widely supported, debate remains on the ideal frequency, methodology, and clinical application of dosimetry. Despite these uncertainties, post-treatment imaging is essential for optimizing patient care, enabling response assessment, early detection of progression, and dose personalization. Beyond clinical benefits, systematic data collection through post-treatment imaging is crucial for refining dose-response relationships, normal tissue toxicity thresholds, and future treatment strategies. As RPTs move earlier in the disease course and expand into retreatment and combination therapies, these insights will enhance personalization, improve outcomes, and guide the next generation of clinical standards.

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