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Journal

Journal of Nuclear Medicine

ISSN

0161-5505

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Publication Date

2026-10-29

DOI

10.2967/jnumed.126.272228

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Journal of Nuclear Medicine, published on October 29, 2026 as doi:10.2967/jnumed.126.272228

Patterns of Progression on Posttreatment Imaging During [^{177}Lu]Lu-PSMA Radiopharmaceutical Therapy

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We characterized patterns of treatment response and progression during [^{177}Lu]Lu-PSMA radiopharmaceutical therapy (RPT) using serial posttreatment SPECT/CT and prostate-specific membrane antigen (PSMA) PET imaging and evaluated cycle-by-cycle prostate-specific antigen (PSA)–imaging concordance. **Methods:** We retrospectively analyzed 361 patients from 2 academic centers who received at least 2 cycles of [^{177}Lu]Lu-PSMA RPT between May 2017 and March 2025. Posttreatment SPECT/CT scans were qualitatively evaluated to determine the site and pattern of response and progression, including PSMA low-avidity and PSMA-negative disease. Progression was defined by the appearance of new lesions or at least a 2-fold growth in preexisting lesions on SPECT/CT. PSA response was defined per Prostate Cancer Clinical Trials Working Group 3 criteria as at least a 50% decline from baseline. For cycle-by-cycle concordance analysis, PSA change was classified directionally as rising or falling relative to the prior cycle. In patients who paused or completed RPT after response, progression imaging was compared with the final on-treatment SPECT/CT scan. **Results:** Overall, 290 of 361 (80%) patients demonstrated a decrease in lesion size or number on posttreatment imaging. Of 312 patients with baseline bone disease, 81% demonstrated a response on posttreatment imaging. In total, 156 of 361 patients (43%) demonstrated progression during treatment. New osseous lesions developed in 132 patients, of whom 89 (67%) had PSMA low-avidity disease. At cycle 2, 64% of new lesions were osseous, increasing to at least 90% by cycles 4–6. PSMA-negative progression occurred in 22 patients (6%), predominantly in the liver (n = 11) and lymph nodes (n = 8), with 59% detected at cycle 2. Among 81 patients with imaging available at PSA progression after treatment completion or pause, 74 (91%) had imaging progression; of these, 69 (93%) demonstrated osseous and 13 (18%) nodal progression. PSA and imaging were discordant in 25%–43% of patients across cycles, with discordance increasing from cycle 2 to cycle 6. **Conclusion:** Progression during [^{177}Lu]Lu-PSMA RPT occurs most frequently in bone, with 67% of patients with new osseous lesions demonstrating a PSMA low-avidity disease component. PSMA-negative progression is uncommon and tends to emerge early. PSA–imaging discordance is frequent, underscoring the need for integrated imaging assessment throughout treatment.

Key Words: radionuclide therapy; SPECT/CT; ^{177}Lu-PSMA; prostate cancer; radioligand therapy; mCRPC

Received Feb. 10, 2026; revision accepted Sep. 17, 2026.
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Published online Oct. 29, 2026.
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J Nucl Med 2026; 00:1–7
DOI: 10.2967/jnumed.126.272228

In men with metastatic androgen pathway modulator–resistant prostate cancer (formerly metastatic castration-resistant prostate cancer) who have progressed after androgen receptor pathway inhibitors and taxane-based chemotherapy, [^{177}Lu]Lu-PSMA radiopharmaceutical therapy (RPT) has been shown to improve overall survival (OS) (*1*,*2*). However, a subset of patients fails to respond, and progression is common and has been observed as early as 6 wk (*3*–*6*). Progression identified on posttreatment imaging is impactful and has resulted in discontinuation of therapy in 12%–28% of patients (*3*,*7*–*9*). Another challenge in monitoring response to prostate-specific membrane antigen (PSMA) RPT is the discordance between prostate-specific antigen (PSA) levels and PSMA imaging, and in approximately one quarter of patients, imaging progression occurred before PSA progression (*3*,*10*).

As experience with [^{177}Lu]Lu-PSMA RPT evolves, diverse patterns of progression have been identified and have had an impact on future treatment options (*11*). Patients demonstrate heterogeneous responses, with some lesions responding whereas others progress, reflecting variable PSMA expression and tumor biology across metastatic sites. The efficacy of RPT requires PSMA expression, and the loss of PSMA expression is hypothesized as a cause of treatment failure (*12*–*14*).

The goals of this analysis were to characterize predominant patterns of disease response and progression on posttreatment SPECT/CT imaging during and after [^{177}Lu]Lu-PSMA RPT and to descriptively evaluate the agreement between PSA and imaging assessments across treatment cycles.

MATERIALS AND METHODS

Study Population

We retrospectively analyzed 361 patients with metastatic androgen pathway modulator–resistant prostate cancer who received at least 2 cycles of [^{177}Lu]Lu-PSMA RPT at 2 centers (St Vincent's Hospital, Sydney, n = 269; University of California, San Francisco, n = 225) between May 2017 and March 2025. Patients received [^{177}Lu]Lu-PSMA-617 or PSMA-I&T at 7.4–8.0 GBq per cycle. Patients were excluded if they had single-cycle treatment, incomplete imaging, or insufficient data. Serum PSA was measured at each cycle. The Australian

center used a response-guided approach per Re-SPECT; the U.S. center followed Food and Drug Administration guidelines. Both institutional review boards approved with a consent waiver due to the retrospective design.

Qualitative Analysis of Posttreatment Imaging

Posttreatment SPECT/CT was performed after each treatment cycle; detailed acquisition parameters are provided in supplemental material (available at http://jnm.snmjournals.org). Posttreatment SPECT/CT was analyzed qualitatively using MIM Encore (version 7.3.5; MIM Software Inc.) enabling side-by-side comparison of sequential datasets. At each center, a nuclear medicine physician masked to PSA values interpreted images. Response was defined as a visual decrease in tumor burden (number and size) compared with the prior cycle; percentages reflect visual estimation, not quantitative segmentation. Progression was defined by the appearance of new lesions or growth in preexisting lesions compared with the immediately prior SPECT/CT scan. For preexisting lesions, a qualitative increase by at least 2-fold in the largest lesion diameter was used as the threshold for progression; this is a qualitative threshold chosen for clinical face-validity and is inherently subjective. For new lesions, both the number and the anatomic location were documented.

Visual analysis was performed according to the PROMISE version 2 framework (*15*). PSMA low-avidity disease was defined as new lesions demonstrating uptake above the level of the blood pool but at or below the physiologic liver uptake level. PSMA-negative disease was defined as new soft-tissue lesions on posttreatment SPECT with tracer uptake at or below the blood pool level. No formal quantitative thresholds were applied to distinguish PSMA low-avidity from high-avidity disease. Response in lymph nodes and hepatic lesions was defined as a qualitative decrease in size with or without a decrease in the PSMA avidity of lesions on SPECT/CT. Patient-level classification was based on the overall treatment course and categorized into 4 groups: response only (response at all evaluable cycles), progression only (progression at all evaluable cycles), mixed (any combination of response and progression across cycles, including patients with initial response followed by subsequent progression), and stable (no change across all cycles).

PSMA PET Imaging

Baseline PSMA imaging was performed a median of 49 d (interquartile range [IQR], 30–78 d) before treatment initiation. The acquisition followed institutional protocols using ^{68}Ga-PSMA-11 or ^{18}F-DCFPyL. In a subset of patients who paused or completed PSMA RPT after a response, PSMA PET was performed at PSA progression before any subsequent systemic treatment or at the discretion of the treating oncologist. The median interval between the last posttreatment SPECT/CT scan and the subsequent progression PET/CT scan was 159 d (IQR, 115.5–276.0 d).

Evaluation of Disease at Progression After Treatment Pause

In patients who paused or completed PSMA RPT after a response, posttreatment SPECT/CT from the final administered cycle was compared with either a subsequent PSMA PET/CT scan at PSA progression or the first posttreatment SPECT/CT scan from reinitiated therapy. Patients were included in this analysis only if no interval systemic therapy (e.g., chemotherapy) was administered between treatment pause and progression imaging.

PSA Response

PSA response was defined per the Prostate Cancer Clinical Trials Working Group 3 as at least a 50% decline (PSA50); progression was defined as at least a 25% rise from nadir with an absolute rise of at least 2 ng/mL (*16*). Cycle-by-cycle concordance was assessed by comparing PSA direction (rising or falling) with imaging assessment (response, stable, or progression). Concordance was agreement between PSA and imaging direction, and discordance was divergence.

PSA50 was calculated as an overall response rate across the treatment course; for cycle-by-cycle concordance analysis, PSA was assessed directionally as rising or falling relative to the immediately prior cycle.

Statistical Analysis

Kaplan–Meier survival curves were generated for progression-free survival (PFS) and OS, stratified by disease pattern group (response, mixed, or progression) defined by PSMA SPECT imaging findings across the overall treatment course. Log-rank tests were used to compare survival distributions across groups. Stable patients ($n = 17$) were excluded because of small lesion size. In the patients with evaluable osseous lesion ($n = 132$), PFS and OS were analyzed by PSMA-avid osseous lesion burden group (with vs. without low PSMA avidity). Quantitative variables used descriptive statistics, categoric variables used counts or percentages, and continuous variables used medians (with IQR) or means (with SD).

RESULTS

Patient Demographics and Baseline Characteristics

In total, 361 patients received at least 2 cycles of PSMA RPT (Fig. 1). Patient demographics and clinical characteristics are shown in Table 1. Of the 361 patients, 188 (52%) exhibited response only, and 54 (15.0%) showed progression only across all cycles; 102 patients (28%) exhibited a mixed pattern, with both responding and progressing lesions. Lastly, 17 patients (5%) remained stable throughout treatment.

The progression group, the mixed group, and the response group were strongly associated with both PFS and OS (Fig. 2). Patients classified as responders had a median PFS of 7.1 mo (95% CI, 6.5–7.9 mo) compared with 4.3 mo (95% CI, 3.6–4.9 mo) in the mixed group and 2.5 mo (95% CI, 2.0–3.0 mo) in the progression group ($P < 0.0001$). The median OS was 20.4 mo (95% CI, 16.0–28.1 mo) in the response group, 12.6 mo (95% CI, 10.2–13.8 mo) in the mixed group, and 7.5 mo (95% CI, 6.1–13.4 mo) in the progression group ($P < 0.0001$).

Of the 356 patients with evaluable PSA, 213 (60%) achieved PSA50, of whom 55 (15%) achieved a PSA with at least a 90% decline. Stable PSA (between a <50% decline and a <25% increase) was observed in 110 (31%) patients. PSA progression, defined per Prostate Cancer Clinical Trials Working Group 3 criteria as at least a 25% increase from nadir, occurred in 33 (9%) patients. Median PSA declined from 80.5 ng/mL (IQR, 18.6–249.5 ng/mL) at cycle 1 to a nadir of 19.3 ng/mL (IQR, 3.1–108.7 ng/mL).

Patterns of Response

Of 361 patients, 290 (80%) demonstrated at least 1 cycle with an imaging response, which includes both response-only patients ($n = 188$) and mixed-response patients ($n = 102$). Visual tumor response was seen in 46% (165/361) of patients at cycle 2 and in 68% (30/44) of those receiving cycle 6. The depth of response increased over time; the proportion of patients achieving a less than 50% reduction in tumor volume increased from 34% (121/361) at cycle 2 to 55% (24/44) at cycle 6. More than a 75% reduction was seen in 13% and 36% of patients at these respective time points. Fifty-nine of 361 (16%) patients were given treatment breaks based on a marked imaging and PSA response, of whom 19 of 59 (32%) stopped treatment after cycle 2.

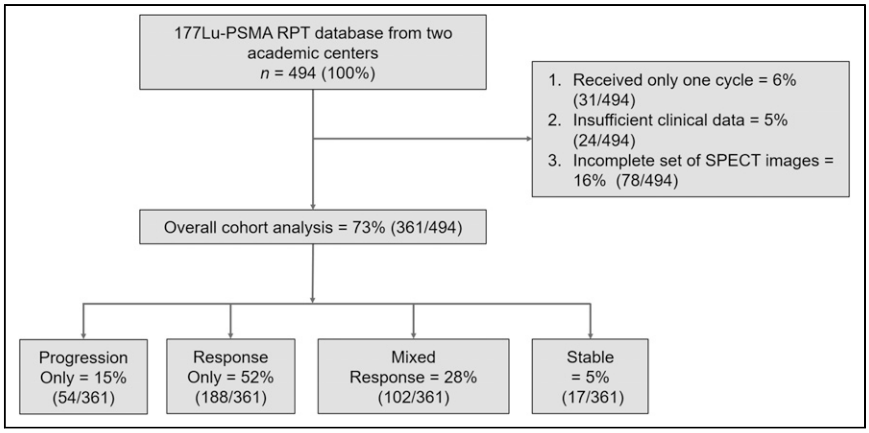


FIGURE 1. Patient flowchart.

Of the 312 patients with bone disease at baseline, 254 (81%) had a reduction in tumor volume and visual improvement in the number of lesions (Fig. 3). Of the 195 (54%) with lymph node disease, 119 (61%) responded. Of the 39 (11%) with liver metastases, 29 (74%) responded with reduction in the size of hepatic metastases.

TABLE 1
Patient Demographics and Characteristics (n = 361)

Characteristic	Value
Age (y) at first RPT	64.9 (59.0–70.7)
Metastatic at diagnosis	95 (26.4)
Prior treatments	
Prostatectomy ± lymphadenectomy	106 (29.4)
Radiation therapy	227 (62.9)
Androgen deprivation treatment	317 (88)
Androgen receptor pathway inhibitor	345 (95.8)
Docetaxel	225 (62.3)
Cabazitaxel	82 (22.7)
Other life-prolonging treatment	95 (26.2)
Site of disease on baseline PSMA PET	
Prostate/prostatic fossa	112 (31)
Lymph nodes	195 (54)
Bone	312 (86.4)
Liver	39 (10.8)
Other viscera	20 (5.5)
Completed cycles during first set of RPT	
2 cycles	361 (100)
3 cycles	241 (66.8)
4 cycles	140 (38.8)
5 cycles	71 (19.7)
6 cycles	44 (12.2)

Continuous data are expressed as median, followed by IQR in parentheses. Qualitative data are expressed as number, followed by percentage in parentheses.

Patterns of Progression

Overall, 156 of 361 patients (43%) had progression on SPECT/CT in new lesions or existing lesions, irrespective of whether they showed a response. The first progression event occurred at cycle 2 in 27% of patients (96/361), at cycle 3 in 20% (31/241), at cycle 4 in 10% (16/140), at cycle 5 in 7% (11/71), and at cycle 6 in 0% (0/44).

Of the 361 patients, 132 (37%) developed new osseous lesions, 29 (8%) developed new nodal lesions, 20 (6%) developed new liver lesions, and 5 (1%) developed new lesions in other viscera (Fig. 3). Of the 132 patients with new osseous lesions, 89 (67%) developed osseous lesions with PSMA low-avidity components, often in combination with PSMA variable-avidity disease (Fig. 4). Of these 132 patients, neither PFS nor OS differed significantly by PSMA-avid bone lesion burden. Median PFS was 3.4 mo (95% CI, 2.8–4.6 mo) in the PSMA low-avidity bone group versus 4.5 mo (3.6–5.8 mo) in the non–PSMA low-avidity bone group (P = 0.55). Median OS was 12.7 mo (95% CI, 9.5–14.3 mo) versus 13.0 mo (95% CI, 10.6–15.9 mo), respectively (P = 0.82). By cycles 4–6, new lesions became rare and were almost entirely osseous (≥90%). Among patients developing new lesions, those with 5 or fewer consistently outnumbered those with more than 5, with more than 5 new lesions peaking at cycle 5 (9% of patients).

Growth in preexisting lesions occurred in 18%–28% of patients across cycles (Fig. 5, demonstrating progressive liver metastasis over cycles, and Fig. 6, demonstrating mixed response over cycles with progressing osseous lesions), peaking at cycle 2 (25%; 90/361 patients). Most patients with progression had more than 5 growing lesions per cycle (9%–18%), whereas 5%–14% had 5 or fewer growing lesions.

PSMA-Negative Progression

PSMA-negative disease progression occurred in 22 of 361 (6%) patients, and the locations were liver (11/22), lymph nodes (8/22), bone (4/22), and other viscera (2/22). The majority of PSMA-negative progression events occurred early in treatment, with 13 of 22 (59%) detected at cycle 2 and 6 of 22 (27%) at cycle 3. The majority were detected using CT (16/22, 78%), followed by ^{18}F-FDG PET/CT (3/22, 14%), PSMA PET/CT (2/22, 9%), and SPECT/CT (1/22, 5%). Stopping of further cycles because of PSMA-negative disease progression was noted in 21 of 22 patients. One patient continued treatment despite PSMA-negative progression, as liver-directed therapy with ^{90}Y radioembolization was performed after cycle 2, and cycle 3 was subsequently administered.

Patterns of Progression After [^{177}Lu]Lu-PSMA RPT

Of 361 patients, 81 had PSMA PET or SPECT/CT imaging available at the time of PSA progression after treatment pause or completion. Of these, 59 (73%) had paused treatment due to a marked response and subsequently reinitiated RPT at progression; 22 (27%) did not receive further PSMA RPT. Of the 59 patients who paused treatment because of a response, the mean treatment pause duration was 23 wk (range, 16–40 wk). Progression imaging consisted of PSMA PET in 44 of 81 patients (54%) and

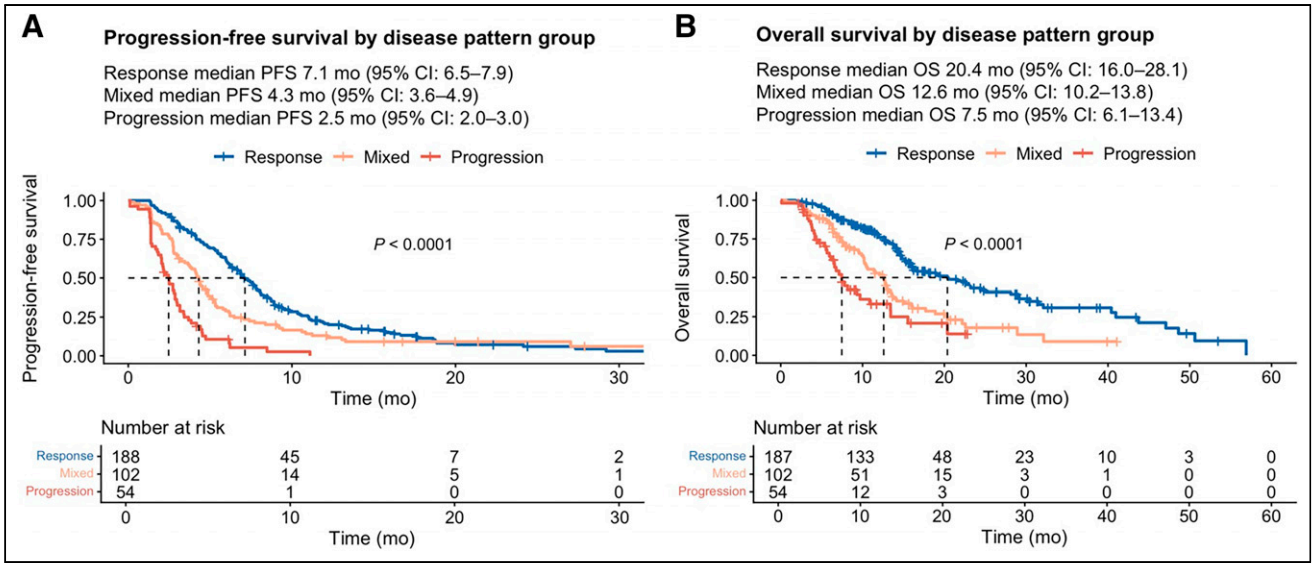


FIGURE 2. PFS and OS by disease pattern group. Kaplan–Meier curves for PFS (A) and OS (B) are stratified by imaging-defined disease pattern across PSMA RLT treatment course: response (n = 188), mixed (n = 102), and progression (n = 54). Of 361 patients, 17 classified as stable were excluded from Kaplan–Meier analyses because of small group size.

posttreatment SPECT/CT from the first reinitiation cycle in 37 of 81 patients (46%).

Of the 81 patients, 7 (9%) showed no imaging progression. Among the 74 patients (91%) with imaging progression, all developed new lesions: 39 (53%) with less than 5 lesions and 35 (47%) with more than 5 lesions. Osseous progression was most common, occurring in 69 of 74 patients (93%), whereas nodal progression occurred in 13 of 74 (18%). New lesions in prostate, liver, and other viscera were uncommon. Additionally, 58 of 74 patients (78%) demonstrated growth in preexisting lesions.

Response on Imaging Versus PSA

Concordance between PSA and imaging declined over treatment cycles, from 74.6% (261/351) at cycle 2 to 56.8% (25/44) at cycle 6. Of the 361 patients, 163 (45.2%) showed discordance at at least 1 cycle, whereas 198 (55%) maintained concordance throughout treatment. Within concordant cases, 77.0% demonstrated a simultaneous response and 23% showed simultaneous progression (Supplemental Table 1). Among discordant cases, 40% demonstrated PSA progression with an imaging response, 26% showed imaging progression with a PSA response, and 34% displayed mixed patterns with one modality stable whereas the other showed response or progression. Patients with a concordant response at cycle 2 (n = 197) tended to continue responding, with 73% showing a continued response at cycle 3 and 15% completing all 6 cycles. In discordant cases at cycle 2, the median PSA increase for patients with PSA progression despite an imaging response was 30.3% (IQR, 11.7%–65.6%), whereas the median PSA decrease for patients with imaging progression despite a PSA response was 32.3% (IQR, 17.4%–50.9%). In contrast, among patients with concordant progression at cycle 2 (n = 64), 83% were discontinued by cycle 3.

DISCUSSION

In this large, multicenter retrospective series, we demonstrated that progression most commonly occurs in the bones, with nodal progression being relatively uncommon. In 67% of patients, a PSMA low-avidity osseous progression developed, a pattern more prevalent than previously recognized. In contrast, PSMA-negative progression was uncommon (6%), occurring early and predominantly in the liver.

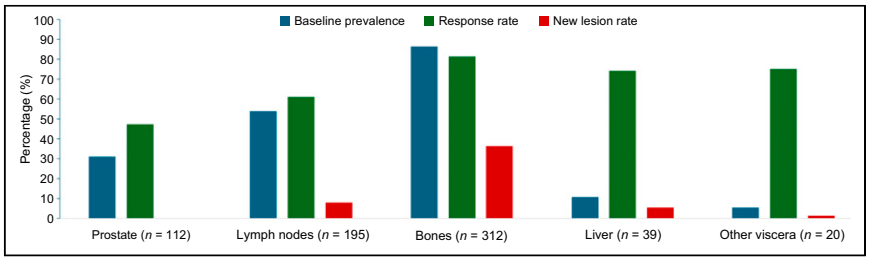


FIGURE 3. [^{177}Lu]Lu-PSMA RPT outcomes by anatomic site across entire treatment course (cycles 2–6). Baseline prevalence represents proportion of total cohort (n = 361) with disease involvement at each site at treatment initiation. Response rate indicates percentage of patients with site-specific involvement who achieved response in that site. Denominators for these percentages are number of patients with involvement at that specific site at baseline, as indicated on x-axis. New lesion rate reflects cumulative new lesion development in that site at any point during treatment.

Bone was the primary site of treatment failure despite being the most common site of early response. Although 81% of baseline bone lesions responded, 64% of new lesions were osseous at cycle 2, increasing to at least 90% by cycles 4–6. This bone-predominant pattern persisted after treatment pause, with 93% demonstrating osseous progression at recurrence. In contrast, lymph nodes demonstrated favorable outcomes both during and after treatment, with 61% response rates and only 8% new lesions during RPT, followed by 16% new lesions after treatment pause.

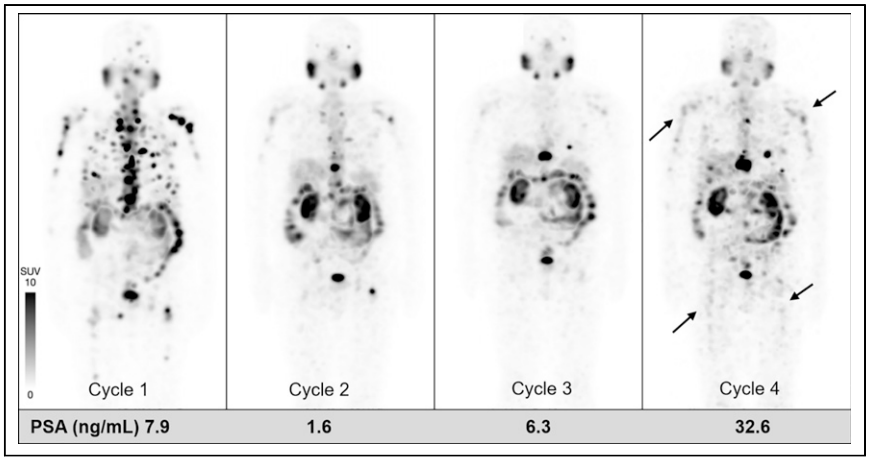


FIGURE 4. Serial SPECT/CT maximum-intensity projections showing initial biochemical and imaging response followed by progression with emergence of PSMA low-avidity osseous metastases (arrows, cycle 4).

Of the 132 patients with new osseous lesions, 67% developed PSMA low-avidity osseous disease components amid heterogeneous PSMA expression. PSMA low-avidity osseous progression either represents low–tumor-cell-density marrow-infiltrative disease or decreased expression of PSMA over time under therapeutic pressure. It is not feasible to distinguish between these two without tissue correlation. A PSMA low-avidity infiltrative growth pattern has been previously described in primary infiltrative lesions (*17*). Low-level osseous disease may develop because of a geometric challenge, with diffusely distributed cells limiting the effect of β-particle crossfire. Notably, PFS and OS did not differ significantly between patients with and without PSMA low-avidity osseous disease, suggesting that PSMA low-avidity bone lesions carry equivalent prognostic weight to overtly PSMA-avid osseous disease.

Qualitative imaging revealed substantial heterogeneity; 28% of patients showed mixed response patterns, with some patients demonstrating response in certain sites whereas progressing in others. This nonuniform response across different organs during therapy has been well documented (*3*,*18*,*19*) and is undetectable by PSA alone. In clinics, tailored approaches such as continuing RPT while treating oligoprogressive sites with stereotactic radiotherapy or liver-directed therapies have been proposed (*3*,*18*). Combination approaches targeting bone, such as combining RPT with ^{223}Ra, have shown early feasibility but require further investigation to demonstrate survival benefit. The occurrence of new PSMA-positive lesions in the context of an overall decrease in whole-body tumor burden may signify treatment failure. In our cohort, patients with a mixed disease pattern had an intermediate prognosis, with a median PFS of 4.3 mo and a median OS of 12.6 mo, falling between those with an imaging-defined response and progression, confirming that even partial imaging progression carries meaningful survival consequences.

We observed temporal clustering of progression events, with nearly two thirds (62%) occurring at cycle 2. Of the PSMA-negative progression events, 59% were detected at cycle 2. Additionally, 32% of all patients who stopped early because of a marked response discontinued after cycle 2. This early progression/response pattern is consistent with prior studies identifying patients with primary treatment resistance or a response after 2 cycles (*4*,*8*). Recent procedure standards emphasize that SPECT/CT at earlier cycles provides crucial information for detecting new lesions and assessing heterogeneous responses (*20*). Early imaging after 1–2 cycles identifies responders who may benefit from treatment holidays (FLEX-MRT NCT06216249; RECIPROCAL NCT07200830) and patients with progressive disease who may benefit from therapy escalation or alternative therapies.

PSMA-negative progression occurred in 6% of patients, predominantly affecting the liver (50%) and lymph nodes (36%). PSMA-negative progression emerged early, with 59% detected at cycle 2 and 27% at cycle 3, suggesting that PSMA-negative disease preexists rather than emerging as a treatment-induced resistance mechanism. This challenges the hypothesis that RPT selects for PSMA-negative clones. Most PSMA-negative progression (73%) was identified on conventional CT rather than functional imaging. Patients in our cohort were not screened with ^{18}F-FDG PET, and it is possible that baseline ^{18}F-FDG PET may have identified a subset of these patients before treatment initiation.

Concordance between PSA and imaging has been shown to be variable and declining over treatment cycles (*14*,*21*,*22*). Although PSA50 by week 12 is associated with improved OS (*21*), PSA does not capture disease distribution, site-specific response, or residual disease burden. Patients may demonstrate a biochemical response despite development of new lesions on imaging (*7*,*8*), and an early stable or rising PSA level does not preclude a subsequent response (*21*).

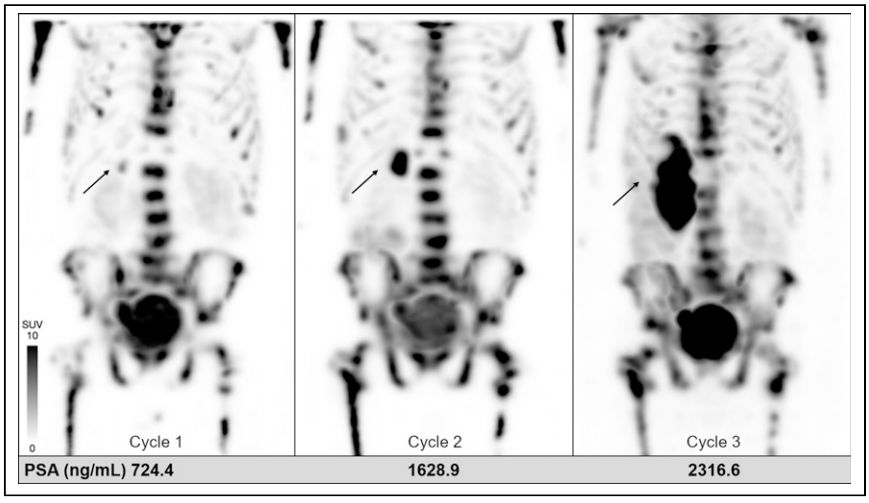


FIGURE 5. Serial SPECT/CT maximum-intensity projections demonstrating disease progression with continuous hepatic lesion growth and increasing PSMA avidity (arrows).

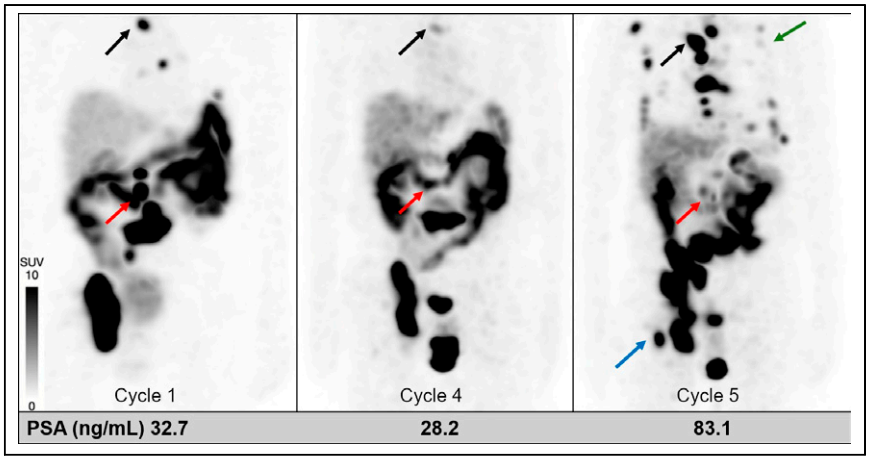


FIGURE 6. Serial SPECT/CT maximum-intensity projections showing mixed response pattern and new osseous lesions with heterogeneous PSMA expression. Black arrows indicate osseous lesions showing initial response followed by progression with high PSMA avidity. Red arrows indicate nodal disease with sustained response across treatment cycles. At progression (cycle 5), new osseous metastases emerged with variable PSMA expression: high avidity (blue arrow) and low avidity (green arrow).

Imaging provides complementary biologic information, identifying a mixed response, oligoprogression, anatomic patterns of failure, PSMA expression heterogeneity, and PSMA-negative progression.

This study had several limitations. We performed a retrospective analysis with variable imaging hardware, acquisition timing, and RPT protocols between centers. We relied on qualitative assessment; partial-volume effects may underestimate uptake in small osseous lesions, and visual size evaluation introduces subjectivity that may affect progression detection. We did not perform interobserver agreement testing. As qualitative assessments and progression rates may be influenced by reader experience and hardware variability, it is unclear whether quantitative analysis would result in the same results as we found with our qualitative approach. An additional limitation is the substantial attrition across treatment cycles. Patients who completed more cycles are likely to represent a selected population with better response and tolerability, introducing survivorship bias.

CONCLUSION

Imaging during [^{177}Lu]Lu-PSMA RPT demonstrates distinct patterns of response and progression. Bone is the primary site of treatment failure, with 64% of new lesions being osseous at cycle 2, increasing to at least 90% by cycles 4–6. Additionally, 67% of patients who developed new osseous lesions demonstrated PSMA low-avidity bone disease components with heterogeneous PSMA expression. PSMA-negative progression was rare, occurred early, and predominantly involved the liver. Mixed response patterns occurred in 28% of patients, a phenomenon undetectable by PSA alone, with PSA and imaging providing complementary information. Posttreatment SPECT/CT, providing critical information on response depth, PSMA expression status, and resistant phenotypes, can guide decisions about treatment.

DISCLOSURE

Thomas Hope has grant funding to the institution from Bayer, GE HealthCare, Lantheus, Janssen, Novartis, and Telix Pharmaceuticals; received personal fees from AstraZeneca, Bayer, Cardinal Health, BlueEarth Diagnostics, Lantheus, Molecular Partners, Novartis, RayzeBio/BMS, and Sanofi; and received fees from and has an equity interest in Curium, AdvanCell, and Utter Therapeutics. Louise Emmett reports being on the scientific advisory board of Clarity Pharmaceuticals and AdvanCell; attending advisory board meetings for Astellas, AstraZeneca, Novartis, and GE; being a speaker for J&J, Astellas, Novartis, and GE; and receiving grant funds from the PCF, Movember, St Vincent's Clinic and Curran Foundations, and ANZUP. Robert Flavell reports receiving grants from NIH/NCI, DOD/CDMRP, the UCSF PICT program, the UCSF Benioff Institute for Prostate Cancer Research, and Shuttle Therapeutics during the conduct of the study; grants and nonfinancial support from Kyntra; grants from Bristol Meyer-Squibb; personal fees from Sabino; equity from Tiller Therapeutics and Seen Therapeutics; and other support and equity from Topaz Therapeutics outside the submitted work. Rahul Aggarwal has received consulting or advisory fees from Alessa Therapeutics, Amgen, AstraZeneca, Bayer, BioXcel Therapeutics, Boxer Capital, Curio Science, EcoR1 Capital, Exelixis, Flare Therapeutics, Guidepoint Inc., Harpoon Therapeutics, Janssen, Merck, MJH Life Sciences, Novartis, PCCTC, Pfizer, Research to Practice, Slingshot Insights, Tersera, and the Washington Research Foundation; research funding to his institution from Amgen, AstraZeneca, Janssen, Merck, Novartis, Xynomic Pharma, and Zenith Epigenetics; and travel expenses from DAVA Oncology. Ivan de Kouchkovsky has received honoraria from Janssen. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What are the patterns of response and progression during [^{177}Lu]Lu-PSMA RPT?

PERTINENT FINDINGS: Bone is both the most common site of early response and also the predominant site of treatment failure, with bone-predominant progression persisting even after treatment pause. PSMA-negative progression was uncommon and tended to present early and involve the liver.

IMPLICATIONS FOR PATIENT CARE: The utilization of post-treatment imaging in addition to PSA is essential to guide management decisions, allowing for the detection of early progression. Future work should focus on controlling osseous disease.

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