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Patient outcomes following a response biomarker-guided approach to treatment using 177Lu-PSMA-I&T in men with metastatic castrate-resistant prostate cancer (Re-SPECT)

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Abstract

Background: ^{177}LuPSMA is an effective treatment in metastatic castrate-resistant prostate cancer with trials adopting a standardised dose interval. Adjusting treatment intervals utilising early response biomarkers may improve patient outcomes.

Objective: This study evaluated progression-free survival (PFS) and overall survival (OS) based on treatment interval adjustment utilising ^{177}LuPSMA 24-h SPECT/CT (^{177}Lu-SPECT) and early prostate-specific antigen (PSA) response.

Design: Retrospective analysis of a clinical ^{177}Lu-PSMA-I&T treatment programme.

Methods: In all, 125 men were treated with 6-weekly ^{177}LuPSMA-I&T [median 3 cycles, interquartile range (IQR): 2–4], median dose 8.0 GBq [95% confidence interval (CI): 7.5–8.0]. Imaging screening involved ^{68}GaPSMA-11 PET/diagnostic CT. ^{177}Lu-SPECT/diagnostic CT was acquired following each therapy, and clinical assessments 3-weekly. Following dose 2 (week 6), a composite PSA and ^{177}Lu-SPECT/CT imaging response [partial response (PR), stable disease (SD), and progressive disease (PD)] determined ongoing management. Response group (RG) 1 (marked reduction in PSA/imaging PR) break in treatment until subsequent PSA rise, then re-treatment. RG 2 (stable or reduced PSA and/or imaging SD) 6-weekly treatments until six doses, or no longer clinically benefitting. RG 3 (rise in PSA and/or imaging PD) recommended for an alternative treatment.

Results: Overall PSA50% response rate (PSARR) was 60% (75/125), median PSA-PFS 6.1 months (95%CI: 5.5–6.7), and median OS 16.8 months (95%CI: 13.5–20.1). 35% (41/116) were classified as RG 1, 34% (39/116) RG 2, and 31% (36/116) RG 3. PSARRs by RG were 95% (38/41), 74% (29/39), and 8% (3/36); median PSA-PFS rates were 12.1 months (95%CI: 9.3–17.4), 6.1 months (95%CI: 5.8–9.0), and 2.6 months (95%CI: 1.6–3.1); and OS rates were 19.2 months (95%CI: 16.8–20.7), 13.2 months (95%CI: 12.0–18.8), and 11.2 months (95%CI: 8.7–15.6) for RG 1, 2, and 3, respectively. The median months of 'treatment holiday' for RG 1 was 6.1 months (IQR: 3.4–8.7). Nine men had received prior ^{177}LuPSMA-617 and were retreated with ^{177}LuPSMA-I&T, with a PSARR of 56% on re-treatment.

Conclusion: Personalising dosing regimens using early response biomarkers with ^{177}LuPSMA has the potential to achieve similar treatment responses to continuous dosing while allowing treatment breaks or intensification. Further evaluation of early response biomarker-guided treatment regimens in prospective trials is warranted.

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Plain Language Summary

Lutetium-PSMA therapy is a new therapy for metastatic prostate cancer that is well tolerated and effective. However, not all men respond equally, with some responding very well and others progressing early. Personalising treatments require tools that can accurately measure treatment responses, preferably early in the treatment course, so adjustments to treatment can be made. Lutetium-PSMA can measure tumour sites after each therapy by taking whole body 3D images at 24 h using a small radiation wave from the treatment itself. This is called a SPECT scan. Previous work has shown that both prostate-specific antigen (PSA) response and changes in tumour volume on a SPECT scan can predict how patients will respond to treatment as early as dose 2. This study demonstrates that stratifying how men are treated based on the results of the 6-week SPECT scan and PSA response potentially allows a third of men to have break in treatment and that these men have both longer time to disease progression and OS. Men with an increase in tumour volume and increase in PSA early in treatment (6 weeks) had shorter time to disease progression and OS. Men with early biomarker disease progression were offered alternative treatments early in an attempt to allow the opportunity to allow a more effective potential therapy, if one was available. The study is an analysis of a clinical programme, and was not a prospective trial. As such, there are potential biases that could influence results. Hence, while the study is encouraging for the use of early response biomarkers to guide better treatment decisions, this must be validated in a well-designed clinical trial.

Keywords: lutetium-PSMA, metastatic prostate cancer, SPECT, response biomarker

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Introduction

^{177}LuPSMA is an effective treatment in metastatic castrate-resistant prostate cancer (mCRPC) with trials predominantly adopting a standardised dose interval and course of treatment. The randomised TheraP trial allowed 'treatment holidays' in (7%) men with an exceptional response to ^{177}LuPSMA-617 based on ^{177}LuPSMA 24-h SPECT (^{177}Lu-SPECT) and prostate-specific antigen (PSA) response, while the VISION trial utilised continuous fixed-interval dosing until treatment was no longer clinically benefitting.[1,2] Adjusting treatment intervals utilising early response biomarkers may lead to improved patient outcomes. This study evaluates patient outcomes [progression-free survival (PFS) and overall survival (OS)] based on a response-guided treatment interval adjustment utilising both ^{177}Lu-SPECT/CT and PSA response biomarkers.

Materials and methods

Screening

Men with mCRPC, who had progressed on at least one line of androgen receptor signalling inhibition and either failed or were ineligible for prior taxane chemotherapy, were considered for treatment on a clinical treatment programme. All men underwent screening with ^{68}Ga-PSMA-11(PSMA) PET CT and diagnostic CT of the chest, abdomen, and pelvis. Men were eligible if they had a standardised uptake value (SUV) maximum >15 on PSMA PET at $\geqslant 1$ site, and SUVmax >10 at all measurable sites not impacted by partial voluming with no sites of soft tissue metastatic disease on diagnostic CT not meeting PSMA PET criteria. All patients required an eGFR >30 mL/min, Hb >70 g/L, platelets $>70\times10^9$/L.

Production

PSMA-I&T precursor (ABX, Germany) in sodium acetate buffer was added to non-carrier added [^{177}Lu] $LuCl_3$ according to institutional production protocol. Radiochemical purity was determined using high-pressure liquid chromatography and thin-layer chromatography.

Imaging procedures and analysis

Screening ^{68}GaPSMA PET/CT and diagnostic CT were performed in all patients prior to consideration for treatment. All patients treated had ^{177}Lu-SPECT/CT (vertex to mid-thighs) acquired 24 h after each ^{177}LuPSMA-I&T injection using a Discovery 670 system and a Tandem NM/CT 870 DR (GE Healthcare, Milwaukee, WI, USA) with the following parameters: medium energy collimators, 3 bed positions, 60 projections over 360° with an acquisition time of 10 s per frame, 128×128 matrix and $4.42 \times 4.42\,mm^2$ pixel size. An energy window centred on 208 keV ± 10% with a 165 keV ± 6.5% scatter window was used. A non-contrast low-dose CT scan was performed immediately after. In those studies that had all data available for quantitation, the SPECT projection images were reconstructed with an iterative Ordered Subset Estimation Maximum algorithm that used 4 iterations and 10 subsets using SPECTRA Quant™ (MIM Software, Inc, Cleveland, OH, USA). No pre- or post-reconstruction filters were applied. CT-based Attenuation Correction, Dual Energy Window Scatter Correction, collimator-based Resolution Recovery, and quantitative conversion to SUV were performed during the reconstruction. The conversion from counts to units of activity was calculated based on a cylinder phantom with known activity.[3] SPECT quantification was undertaken in 77% (96/125), with the remainder missing key data require for reconstruction of analysable quantitative data (scatter windows).

Visual imaging analysis

All ^{177}Lu-SPECT/CT (vertex to mid-thigh) images were evaluated visually by an experienced nuclear medicine physician to assess for treatment response, as per clinical protocol. A significant response on imaging (between baseline and week-6 Lu-SPECT/CT) was defined as a marked reduction (>30%) in visual tumour volume at all sites of involved disease, no new sites of PSMA avid tumour deposits and no new sites of PSMA negative tumour deposits on diagnostic CT [imaging partial response (PR)]. Stable disease (SD) was classified as no visible marked change in tumour volume (>30%), no new sites of PSMA avid disease and no new sites of PSMA negative disease on diagnostic CT (imaging SD). Progressive disease (PD) was defined as visual increase in tumour volume (>30%) ± new sites of disease and/or the presence of new sites of PSMA-negative disease progression on diagnostic CT (imaging PD).

Quantitative imaging analysis

^{177}Lu-SPECT/CT was analysed semi-quantitatively by a nuclear medicine physician utilising MIM (LesionID™), MIM Software (Inc., Cleveland, OH, USA) software and a standardised semi-automated workflow to delineate regions of interest with a minimum SUV cut-off of 3 and lesion size ⩾ 0.2 mm.[4] All lesions identified quantitatively were manually reviewed and physiologic activity was removed. Whole body quantitation derived total tumour volume (TTV), SUVmax, and SUVmean for PSMA-SPECT at baseline and week 6.[5] 77% (96/125) men had analysable baseline and week-6 ^{177}Lu-SPECT/CT data. Quantitative analysis was derived retrospectively in patients with full analysable datasets, with the quantitative findings not included in clinical decisions. Clinical decisions regarding patient treatments were undertaken using visual assessment of the baseline and week-6 ^{177}Lu-SPECT/CT.

Study treatment

All men received a minimum two doses of ^{177}LuPSMA-I&T at 6-weekly intervals. A median 8 GBq [interquartile range (IQR): 8–8.5] was administered at each dose *via* slow intravenous injection. Blood was prospectively collected prior to each cycle and at 3-weekly intervals for biomarkers including haemoglobin, platelets, lactate dehydrogenase, alkaline phosphatase, albumin, and PSA. Following dose 2 of ^{177}LuPSMA (week 6), a composite of PSA response and imaging findings (imaging PR, SD, PD) were utilised to determine ongoing management. Response group (RG) 1: [marked reduction (50%) in PSA and imaging PR] break in treatment until subsequent PSA rise, then consider re-treatment. RG 2: [stable or reduced PSA (<50%) and/or imaging SD] ongoing 6-weekly treatments until six doses, or no longer clinically benefitting. RG 3: (rise in PSA and/or imaging PD) consider referral to an alternative treatment. All patients were followed for subsequent PSA progression and OS.

Statistical analyses

We measured PSA decline from baseline ⩾50% (PSA50) at any timepoint, PSA-PFS, and OS.[6,7] In patients with a treatment break PSA-PFS was defined from the date at which PSA rose, without PSA response to subsequent treatment. The Kaplan–Meier method was used to characterise time-to-event endpoints and estimate medians (presented with 95%CIs). Differences in TTV, SUVmax, SUVmean between the RGs were assessed using one-way analysis of variance. We correlated RG with time-to-event outcomes, using univariable Cox proportional hazards regression. p Values below 5% were considered significant but interpreted conservatively in view of the multiple tests.

Results

Patient characteristics

In all, 125 men underwent ^{177}LuPSMA-I&T therapy between May 2019 and April 2022. All men had mCRPC, 99% (124/125) had prior androgen receptor signalling inhibitors, and 70% (88/125) prior docetaxel. Mean age was 75 years (70–80) (Table 1). Patients received a median of three doses up to a maximum of 10 (IQR 2-4). 6% (9/125) had been previously treated on a clinical trial with ^{177}LuPSMA-617. Overall, 60% (75/125) had a PSA reduction >50% (PSARR). At the time of analysis, 42% (52/125) were deceased. In those assigned to an RG, 35% of men (41/116) were classified as RG 1, 34% (39/116) RG 2, and 31% (36/116) RG 3. Patients who had previously treated with ^{177}LuPSMA-617 on trial (9/125) were not assigned to a RG, with results reported separately.

Patient outcomes

In the overall study population, the median PSA-PFS was 6.1 months (95%CI: 5.4–6.7) and OS was 16.8 months (95%CI: 13.5–20.1). There was a significant difference in PSA-PFS between RGs, with RG 1 PSA-PFS [12.1 (9.3–17.4) months], RG 2 PSA-PFS [6.1 (5.8–9.0) months], and RG 3 PSA-PFS [2.6 (1.6–3.1) months; $p < 0.0001$). A significant difference was also noted in OS between RG 1 [19.2 (16.8–20.7) months], RG 2 [13.2 (12.0–18.8) months], and RG 3 [11.2 (8.7–15.6) months; $p < 0.0005$) (Figure 1). Similarly, PSA50%RR was also significantly different between RGs ($p < 0.0001$) (Table 2).

Table 1. Patient characteristics.

Characteristic	*N* = 125
Age (years)	75 (70–80)
Years since diagnosis	6 (3–9)
Prior systemic treatments	
LHRH agonist/antagonist	100% (125/125)
Chemotherapy	70% (88/125)
Docetaxel	70% (88/125)
Cabazitaxel	35% (44/125)
Androgen receptor signalling inhibitor	99% (124/125)
PSA	76 (26.7–258.5)
LDH	242 (211–301)
Platelets	220 (177–271)
Haemoglobin	116 (103–127)
Sites of disease	
Bone	97% (93/96)
Lymph nodes	47% (45/96)
Visceral	20% (19/96)

Numbers are presented as absolute counts (percentage) or median (interquartile range).
LDH, lactate dehydrogenase; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen.

Response group 1. Men in RG 1 received a median 3 (IQR: 2–4) doses of ^{177}LuPSMA-I&T. They had a 95% (38/41) PSA50%RR, and median reduction in PSA of 83% (IQR: −97 to −70). Median PSA50%RR at dose 2 was 49% (IQR: 69.1–23.3). In this RG, PSA-PFS was 12.1 months (95%CI: 9.3–17.4) and OS 19.2 months (95%CI: 16.8–20.7). All men in RG 1 had a treatment break due to significant treatment response, with a median 6.1 months (IQR: 3.4–8.7) of treatment 'holiday' prior to a subsequent rise in PSA and consideration for re-treatment. 51% (21/41) of these men had received prior chemotherapy. Median age of those not receiving chemotherapy in RG 1 was 82.5 years.

Response group 2. Men in RG 2 received a median 4 doses (IQR: 3–5) ^{177}LuPSMA-I&T. No

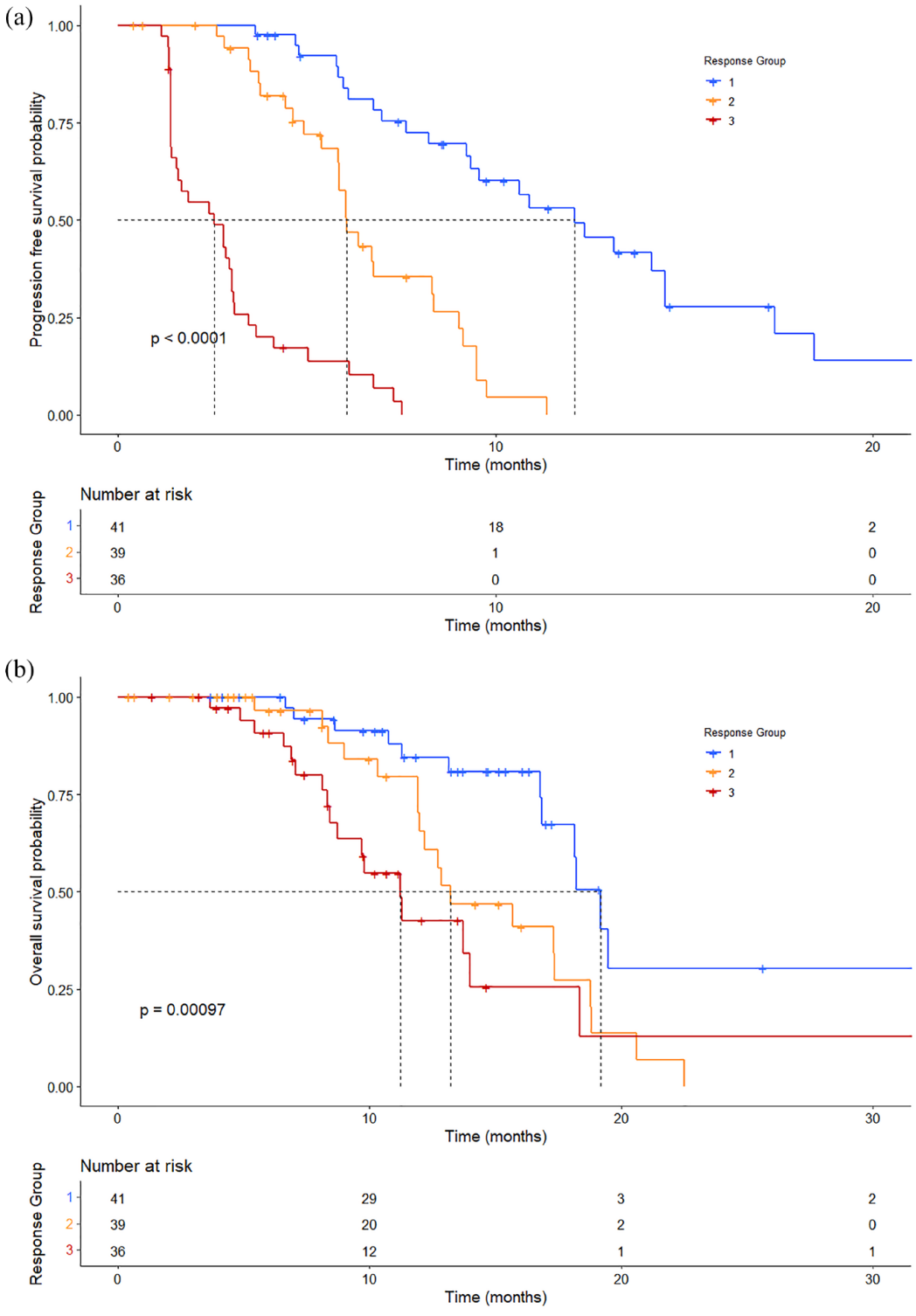

Figure 1. Kaplan–Meier curve for (a) PSA-PFS in patients with marked reduction in PSA and imaging PR (blue) *versus* stable or reduced PSA and/or imaging SD (yellow) and rise in PSA and/or imaging PD (red) and (b) demonstrating OS in the same cohorts.
OS, overall survival; PD, progressive disease; PFS, progression-free survival; PSA, prostate-specific antigen; SD, stable disease.

Table 2. Patient outcomes.

	PSA 50% RR	Median PSA response	OS	PSA-PFS
Overall	60% (75/125)	51.8% (86.2 to −1.6)	16.8 (13.5–20.1)	6.1 (5.4–6.7)
RG 1	93% (38/41)	83% (−97 to −70)	19.2 (16.8–20.7)	12.1 (9.3–17.4)
RG 2	74% (29/39)	61% (89 to −35)	13.2 (12.0–18.8)	6.1 (5.8–9.0)
RG 3	8% (3/36)	−25% (−55 to −1)	11.2 (8.7–15.6)	2.6 (1.6–3.1)

Results presented as median (IQR).
IQR, interquartile range; PFS, progression-free survival; PSA, prostate-specific antigen; OS, overall survival; RS, response group.

patients had a treatment break. This RG had a PSA 50%RR of 74% (29/39), and a median reduction in PSA of 61% (IQR: 89–35). Median PSA 50%RR at dose 2 was 24% (IQR: 38 to −9). Median PSA-PFS 6.1 months (95%CI: 5.8–9.0) and OS 13.2 months (95%CI: 12.0–18.8). It was noted 82% (32/39) of these men had received prior chemotherapy.

Response group 3. Men in RG 3 received a median 3 (IQR: 2–3) doses ^{177}LuPSMA-I&T. The PSA50%RR was 8% (3/36). The three men with a PSA50%RR had new hepatic lesions (2/3) and perinephric soft tissue progression (1/3) on imaging. A PSA rise occurred in 92% (33/36) prior to C3. Median PSA-PFS was 2.6 months (95%CI: 1.6–3.1) and OS was 11.2 months (95%CI: 8.7–15.6). 78% (28/36) of these men had received prior chemotherapy.

Treatment following prior ^{177}LuPSMA-617. 9/125 men had ^{177}LuPSMA-I-&T re-treatment after being treated in a clinical trial of ^{177}LuPSMA-617. All patients had six doses of ^{177}LuPSMA-617. These patients received a median of 2 (IQR: 2–3) additional doses of ^{177}LuPSMA-I&T. PSA50%RR following retreatment was 56% (5/9), with a median PSA-PFS of 4.9 months (95%CI: 1.5–8.3) and OS of 18.4 months (95%CI: 6.4–30).

Quantitative analysis of Lu-SPECT

Quantitative analysis of the baseline and week-6 ^{177}Lu-SPECT was possible in 77% (96/125) (Figure 2). Quantitative ^{177}Lu-SPECT characteristics of RGs 1–3 are detailed in Table 3. There was a significant difference in baseline ^{177}Lu-SPECT SUVmean between RGs, with the highest SUVmean in RG 1 ($p < 0.01$). The difference in Δ SUVmax between RGs was more significant with a large drop in SUVmax by week 6 in RG 1, and almost no change in Δ SUVmax in RG 3 ($p < 0.01$). A similar result was found with Δ SUVmean (Table 3).

Discussion

This study has found that early response biomarker-guided PSMA-targeted radionuclide therapy utilising a combination of PSA and ^{177}Lu-SPECT/CT response at week 6 may effectively stratify responders and limited/ non-responders. This enabled significant treatment de-intensification with fewer administered doses in responders and early transition to potentially more effective alternative treatments [second-line chemotherapy, poly (ADP-ribose) polymerase (PARP) inhibitors, or targeted alpha therapies] in non-responders, with similar PFS and OS to the published literature.[1,2,8]

The response biomarkers utilised to inform patient care in this clinical programme included the PSA response at the first timepoint following the 6-dose ^{177}LuPSMA and a change in tumour volume or new lesions on the 6-week ^{177}Lu-SPECT/CT. Change in week-6 ^{177}Lu-SPECT tumour volume and rise in PSA at week 6 of ^{177}LuPSMA-I&T therapy have been previously shown to predict early PFS.[4] Utilising these biomarkers allowed 35% of men (in RG 1) to have a significant treatment break, a median 6 months, with retreatment at first subsequent PSA rise. These men had durable PFS and OS outcomes. Such measures as treatment 'holidays' may potentially improve quality of life in men who often have treatment fatigue and side effects. Conversely, there is an opportunity cost in continuing an expensive treatment that is not controlling disease burden. Identifying patients with early disease progression

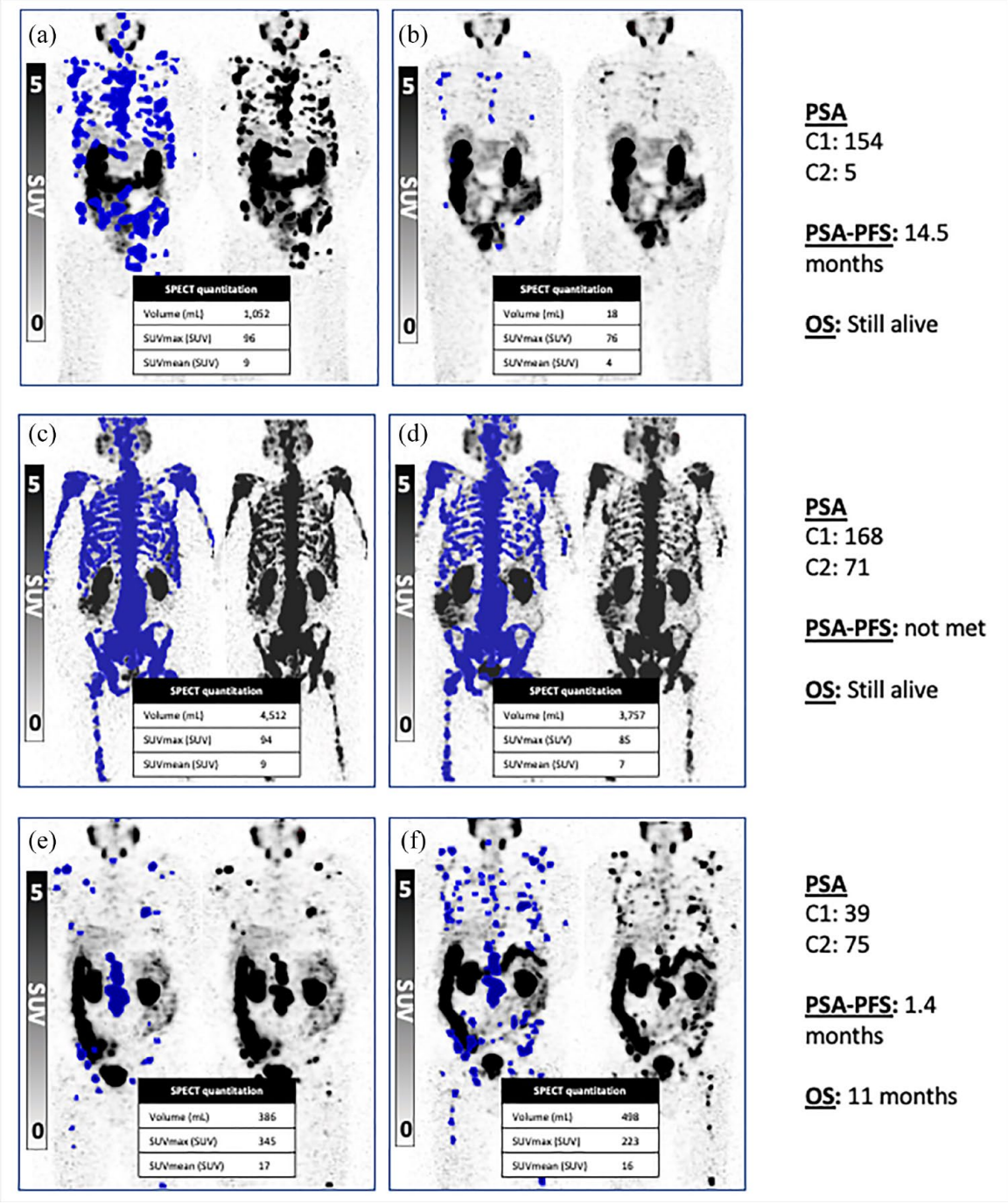

Figure 2. Imaging PR between baseline ^{177}Lu-SPECT (a) and week 6 (b). Imaging SD between baseline ^{177}Lu-SPECT (c) and week 6 (d). Imaging PD between baseline ^{177}Lu-SPECT (e) and week 6 (f).
PR, partial response; SD, stable disease.

using early response biomarkers may allow the opportunity for an alternative potentially effective treatment, such as cabazitaxel chemotherapy, PARP inhibitors, or targeted alpha therapies.[9–11]

RECIP 1.0 is an interim biomarker proposal that utilises a 12-week ^{68}Ga-PSMA PET scan based on its predictive value for disease progression in a multi-centre ^{177}LuPSMA-617 therapy trial.[12]

Table 3. Quantitative imaging subcohort: imaging results by RG.

Lu-SPECT	Overall	RG 1	RG 2	RG 3	Significance
BL TTV (mL)	526 (146–1223)	380 (124–980)	941 (265–1907)	374 (85–873)	<0.01
BL SUVmax	60 (37–88)	69 (47–117)	71 (46–100)	39 (19–67)	NS (0.06)
BL SUVmean	8.7 (7–12)	11 (8–14)	10 (7.8–14)	7 (5.2–8.5)	<0.01
Δ* TTV	−69 (−300 to 5.5)	−107(−260 to −14)	−150 (−574 to −8)	30 (−134 to 116)	NS (0.39)
Δ* SUVmax	−18 (−35 to −1.6)	−32 (−102 to −14)	−19 (−33 to 3)	−5 (−12 to 2)	<0.01
Δ* SUVmean	−1.5 (−3.5 to −0.1)	−3.3 (−6.8 to −1.8)	−1.6 (−2.7 to −0)	−0.5 (−1.4 to +0.2)	<0.01

Results presented as median (IQR).
*Between BL and week-6 Lu-SPECT.
BL, baseline; IQR, interquartile range; RG, response group; SUV, standardised uptake value; TTV, total tumour volume.

RECIP stratifies patients receiving ^{177}Lu PSMA therapy into PR, SD, or PD based on quantitative tumour volume. Similarly, the LUPIN study found that a week-12 quantitative ^{177}Lu-SPECT/CT predicted PSA-PFS in men being treated with ^{177}LuPSMA-617.[3,13] This study demonstrates that moving decision-making earlier to the 6-week timepoint of treatment using^{177}Lu-SPECT/CT + PSA progression is practical and maximises opportunities for personalising treatment response in individual patients. Furthermore, stratification of PR or disease progression on molecular imaging can potentially be made without requiring an additional PSMA-PET/CT procedure. This composite early response biomarker approach warrants further evaluation in prospective trials.

Generally, treatment response to systemic therapy in mCRPC has been monitored with PSA and radiographic PFS utilising diagnostic CT and bone scan.[14] Like PSMA, PSA is a prostate cancer cell surface receptor, although PSA sheds into the bloodstream, allowing it to be measured in serum.[15] Similar to PSMA, there is heterogeneity of PSA expression, meaning PSA may underestimate true disease volume in a proportion of men with mCRPC.[16] RECIST radiographic progression is undertaken serially at a minimum 8-week intervals and is not a feasible early response biomarker tool. Utilising a combination of both early PSA response and early change on Lu-SPECT/CT provides a potentially stronger composite biomarker than either receptor response utilised in isolation.

Quantitative analysis of the ^{177}Lu-SPECT data demonstrated significant differences in Δ SUVmax and Δ SUVmean between RGs 1 and 3. The majority of patients receiving PSMA-targeted peptide receptor radionuclide therapy will get a drop in PSMA intensity, which is not predictive of OS.[12,17] However, these results suggest the depth of the reduction in SUVmax and SUVmean may be a proxy marker of radiation sensitivity and depth of cell death achieved. Currently, while we can measure PSMA characteristics at baseline to predict treatment response, we do not have an easy measure of radiation sensitivity, which is a significant factor in treatment resistance with ^{177}LuPSMA.[17,18] Treatment failure in RG 3 is likely due at least in part to a combination of both baseline PSMA heterogeneity/intensity and low radiation sensitivity. We can measure PSMA heterogeneity and expression at baseline (SUVmean), but the Δ Lu-SPECT parameters at 6 weeks may give some additional indication of radiation sensitivity, and this warrants further evaluation. Measures that address causes of treatment resistance (PARP inhibitors, targeted alpha therapies) may help improve responses in RG 3.[19–21]

A higher proportion of men in RG 1 were chemotherapy naïve, potentially explaining the better treatment response rates in this group. However, these men were older, many considered not suitable for chemotherapy. The median age of men in RG 1 who had not undergone chemotherapy was 82. Older men with co-morbidities may particularly benefit from a 'touch the earth lightly' treatment paradigm with treatment breaks.[22] Based on these results, ^{177}LuPSMA may be a substitute to

chemotherapy in this patient group with many patients only requiring intermittent therapy to achieve disease control.

There are several significant limitations to this study. This is a not a prospective trial, but a retrospective analysis of a clinical programme. Hence, there are inherent biases in the study and the results can only thus be hypothesis generating. Some patients assigned to RG1 that were given a treatment holiday, elected not to have further treatment at PSA rise. This potentially led to a more limited duration of response in RG1 patients than may have been achieved. Furthermore, the definitions of visual disease response on ^{177}Lu-SPECT was not well defined, being classified as visually >30%. Despite this, the study raises important questions regarding the benefits of using composite imaging and biochemical response biomarkers to guide treatment and personalise ^{177}LuPSMA therapy responses. Further work is required in prospective trials to better define and standardise appropriate response thresholds for both ^{177}Lu-SPECT and early PSA in combination, and the role of image quantification. Randomised trials that address the value of early response biomarkers in ^{177}LuPSMA therapy would appear warranted based on preliminary results of this hypothesis generating data.

Conclusion

Personalising dosing regimens using early response biomarkers with ^{177}LuPSMA has the potential to achieve similar treatment responses to continuous dosing while allowing treatment breaks or intensification. Further evaluation of early response biomarker-guided treatment regimens in prospective trials is warranted.

Declarations

Ethics approval and consent to participate

St Vincent's Hospital institutional review board approved this retrospective study (Re-SPECT project) and the requirement to obtain informed consent was waived (HREC) 2022/ETH00924.

Consent for publication

Not applicable.

Author contribution(s)

Louise Emmett: Conceptualisation; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Visualisation; Writing – original draft; Writing – review & editing.

Nikeith John: Data curation; Investigation; Methodology; Project administration; Writing – review & editing.

Sarennya Pathmanandavel: Data curation; Formal analysis; Methodology; Project administration; Writing – review & editing.

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Megan Crumbaker: Methodology; Project administration; Writing – review & editing.

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Competing interests

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EH – Bayer Prostate Cancer Advisory Board (2022); Merck Urothelial Cancer Advisory Board (2021); Janssen Frailty in Oncology Advisory Board (2021); Ipsen Renal Cancer Advisory Board (2020, 2022)

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Availability of data and materials

Not applicable.

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