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SYSTEMATIC REVIEW

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Investigating the significance of SPECT/CT-SUV for monitoring ^{177}Lu-PSMA-targeted radionuclide therapy: a systematic review

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Abstract

Background Quantitative molecular imaging via single-photon emission computed tomography-derived standardised uptake value (SPECT/CT-SUV) is used to assess the response of metastatic castration-resistant prostate cancer (mCRPC) patients to targeted radionuclide therapy (TRT) with [^{177}Lu]Lu-PSMA. This imaging technique determines the radiopharmaceutical distribution and internal dosimetry in patients who receive TRT. However, there is limited evidence regarding the role of image quantification in monitoring changes induced by [^{177}Lu]Lu-PSMA. This systematic examines the role of quantitative SPECT/CT-SUV during [^{177}Lu]Lu-PSMA TRT and assesses whether SUV changes correlate with quantitative imaging and biomarkers.

Methods A systematic review was conducted in accordance with the PRISMA guidelines. The MEDLINE/PubMed databases were searched from January 2016 to July 2024 to identify relevant articles. The inclusion criterion was the use of quantitative SPECT/CT-SUV during [^{177}Lu]Lu-PSMA TRT for patients with mCRPC. The records were screened to determine their eligibility. The abstracts of 62 records were screened, and 28 were excluded because they were not relevant; the full texts of 34 original papers were retrieved and assessed for eligibility.

Results A total of five studies were included in this systematic review (two prospective studies and three retrospective studies). The sample sizes of the studies ranged from 6 to 73 patients. The highest number of lesions analysed was 144. Three studies reported the SPECT/CT-SUV following cycle 1, and only one study reported the correlation with pretherapy PET/CT ($r=0.9$, $p=0.005$). SPECT/CT-SUV changes between the first two to three cycles were reported in one study. None of the studies reported the SPECT/CT-SUV for normal organs. One study reported correlations between SPECT/CT-derived SUV and PET/CT-derived SUV in target and nontarget tissues.

Conclusion Quantitative SPECT/CT-SUV can be used to predict responses to subsequent PSMA-TRT cycles. Disease burden and tumour heterogeneity are the leading causes of TRT individualisation.

Keywords ^{177}Lu-PSMA, ^{68} Ga-PSMA, Quantitative SPECT/CT, Standardised uptake value, Prostate cancer, Targeted radionuclide therapy

Introduction

Prostate cancer (PCa) is the second leading cause of cancer-related death among males worldwide [1]. Androgen deprivation therapy is used for primary prostate cancer and is a critical element of systemic treatment for recurrent or metastatic prostate cancer. However, in some cases, primary prostate cancers exhibit androgen resistance and develop into metastatic castration-resistant

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prostate cancer (mCRPC). mCRPC patients cannot be cured because they are refractory to chemotherapy. As a result, new prostate-specific membrane antigen (PSMA) targeting probes/ligands/molecules have been developed for mCRPC patients [2–7]. Due to its expression in prostate cancer cells, PSMA enables the use of positron emission tomography (PET) imaging via PSMA-targeting probes labelled with ^{68}Ga and ^{18}F [8, 9]. Consequently, it enables treatment through PSMA-targeting probes labelled with betta and alpha emitters such as ^{177}Lu ^{225}Ac [10, 11]. A new emerging [^{161}Tb]Tb-PSMA targeted therapy probe showed similar properties to ^{177}Lu but emitted a high proportion of conversion and low-energy Auger electrons [11, 12]. Furthermore, the PSMA receptor enables endocytosis of bound proteins on the cell surface into an endosomal compartment, which permits PSMA-labelled radioisotopes to enter the cell. The PSMA expression density increases depending on the Gleason score of castration-resistant prostate cancers, thus making PSMA an ideal target for radionuclide therapy [2–7, 13].

Diverse PSMA peptides and antibodies labelled with ^{68}Ga and ^{177}Lu are used as diagnostic and therapeutic agents in mCRPC. In 2020, the United States Food and Drug Administration (FDA) approved using PSMA-11 for targeted PET imaging [4]. However, PSMA-617, derived from modified PSMA-11, showed increased binding affinity to PSMA in PCa cells [14]. PSMA expression in PCa is associated with androgen independence and metastasis [15]. Quantitative positron emission tomography/computed tomography (PET/CT) [^{68}Ga]Ga-PSMA imaging showed a highly significant association with changes in serum Prostate-specific antigen (PSA) levels during targeted radionuclide therapy (TRT) [16, 17]. Moreover, quantitative biomarkers derived from imaging and blood tests, such as PSMA-PET and FDG-PET, can assess patients' responses to PSMA-targeted therapy with [^{177}Lu]Lu-PSMA-617 [16, 18–21]. In quantitative PET/CT studies, SUV is used as a surrogate measure of tissue function within an ROI and is defined mathematically as the ratio between the radionuclide concentration in the ROI (kBq/ml) and the total injected activity (kBq) normalised to the patient's body weight (in g, either the total body weight or lean body mass) [22]. Thus, quantitative PSMA PET using the standardised uptake value (SUV) provides evidence of the heterogeneity of PSMA expression among metastases and is a biomarker for PSA response following [^{177}Lu]Lu-PSMA therapy [16, 18–21].

Patients with mCRPC and positive pretherapy [^{68}Ga]Ga-PSMA avidity can be treated with the [^{177}Lu]Lu-PSMA ligand. [^{177}Lu]Lu-PSMA-617 (Novartis-Pluvicto™, Basel, Switzerland) was approved by the FDA in March 2022 [23].

PSMA-PET/CT-derived SUV metrics have been extensively investigated before, and after [^{177}Lu]Lu-PSMA targeted therapy and are correlated with clinical outcomes [18, 20, 24, 25]. Therefore, single-photon emission computed tomography-derived standardised uptake value (SPECT/CT-SUV) has the potential to be an early indicator of treatment response during subsequent therapy cycles. This systematic review highlights the importance of using quantitative SPECT/CT-SUV following the [^{177}Lu]Lu-PSMA therapy cycle and examines its correlation with PSMA PET/CT imaging and PSA changes.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26]. This review includes original and systematic review papers published in English between January 2016 and July 15th, 2024.

Eligibility criteria

The inclusion criteria were as follows: 1) patients 18 years or older with mCRPC; 2) patients who received [^{177}Lu]Lu-PSMA targeted radionuclide therapy (TRT), and 3) patients who underwent quantitative SUV analysis via SPECT/CT. Records were identified from MEDLINE/PubMed (Accessed 15/07/2024, https://pubmed.ncbi.nlm.nih.gov/advanced/).

Search strategy

The search strategy was as follows: (((177Lu) AND (PSMA)) AND (prostate cancer)) AND (SUV)) (Fig. 1).

Data extraction and analysis

The records were screened for eligibility, and the relevant data were extracted and analysed. The abstracts of 62 records were screened, and 28 studies were excluded because of non-relevance to the review's main topic, such as a lack of quantitative SPECT/CT data. Thus, 34 full-text original papers were assessed for eligibility; one could not be retrieved. No systematic reviews were found. Most papers evaluated the PET/CT-SUV value ($n=27$) [17, 18, 20, 24, 25, 27–49]); one was an internal dosimetry assessment on mice with no human data [50]. Five original papers were included in this systematic review (three retrospective studies and two prospective studies) [51–55].

Risk of bias assessment

The risk of bias in the studies included was assessed. The Risk of Bias in Non-randomised Studies of

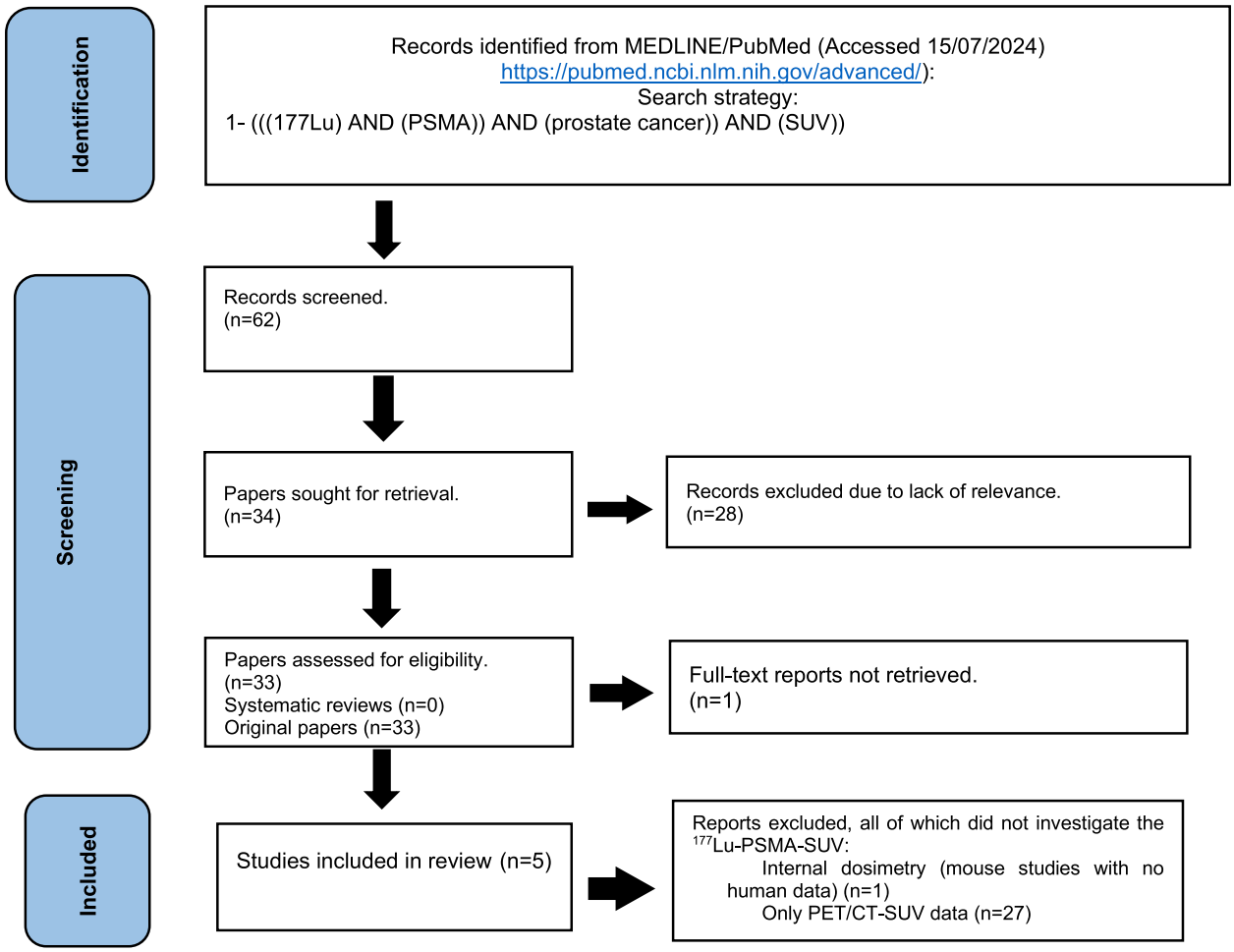

Fig. 1 PRISMA flow diagram for the study selection process

Interventions (ROBINS-I) tool was used to address the following risk of bias domains: (1) bias arising from the SPECT/CT-SUV reconstruction process; (2) bias due to selection; (3) missing outcome data; (4) measurement of the outcome; and (5) selection of the reported results. The overall risk of biased judgement (low = 1, intermediate = 2 and high = 3) was summarised for each specific outcome (Table 1). The highest ROBINS-I level determined the overall ROBINS-I for each study in any assessed domain [56].

Table 1 Risk of bias assessment using the ROBINS-I tool

Bias	Wang et al. (2019) [52]	Pathmanandavel et al. (2023) [54]	Grkovski et al. (2023) [55]	Song et al. (2024) [51]	Neubauer et al. (2024) [53]
SPECT/CT reconstruction process (SUV phantom validation)	Intermediate	Intermediate	Low	High	High
Selection (study type and sample size)	High	Low	Intermediate	Intermediate	Intermediate
Missing outcome data (SUV metrics)	Low	Low	Low	Low	Low
Measurement of the outcome	Low	Low	Low	Low	Low
Selection of the reported result	Low	Low	Low	Low	Low
Overall ROBINS-I (low = 1, intermediate = 2, high = 3)	1.6	1.2	1.2	1.6	1.6

Effect measures

The effect measure was evidence supporting the use of quantitative SPECT/CT-SUV as a validated tool for [^{177}Lu]Lu-PSMA targeted therapy response assessment in prostate cancer patients.

Synthesis methods

Studies presenting quantitative SUV data were analysed. Due to the lack of standardised reporting of SUV-derived SPECT/CT evidence for comparison studies, a meta-analysis was not performed. Instead, a qualitative assessment of the included papers was conducted.

Results

This systematic review included five papers (two prospective studies [54, 55] and three retrospectives [51–53] that investigated quantitative [^{177}Lu]Lu-PSMA targeted therapy SPECT/CT-SUV in response to therapy assessment. Neubauer et al. (2024) [53] analysed the most extensive patient sample group ($n=73$) with 144 lesions. The studies by Song et al. (2024) [51] and Pathmanandavel et al. (2023) [54] reported sample sizes of 56 and 32 patients, respectively; however, the number of analysed lesions was not specified. The small sample size was reported by Grkovski et al. (2023) [55] and Wang et al. (2019) [52] ($n=6$ and $n=9$, respectively). The attached supplementary file details each study's treatment data and imaging quantitative reporting criteria.

Only one study reported SUV changes on sequential [^{177}Lu]Lu-PSMA post-therapy SPECT/CT cycles [54]. Pathmanandavel et al. (2023) reported a decrease in total lesions averaged SPECT/CT-SUV_{max} by −49% and SUV_{mean} by −20% between cycles 1 and 3 [54]. Moreover, Pathmanandavel et al. (2023) reported a strong positive correlation ($r=0.87$, $p<0.001$) between total tumour volume (TTV) from PSMA-PET and TTV from SPECT [54].

However, studies examining the correlation between SUV [^{177}Lu]Lu-PSMA post-treatment SPECT and SUV changes on PET-PSMA reported comparable findings. Grkovski et al. (2023) reported a strong positive correlation between SPECT/CT and PET/CT SUV_{max} ($r=0.9$, $p=0.005$), with a decrease in PET SUV_{max} lesions by −65% (range: −82% to 44%; $p<0.05$) between baseline and post-therapy assessments. Wang et al. (2019) similarly reported strong correlations between baseline PET/CT and SPECT/CT lesions SUV_{mean} following the first therapy cycle for the recruited nine patients who divided into two groups of five patients received [^{177}Lu]Lu-PSMA-617 ($r=0.837$ at 2 h) and four patients received [^{177}Lu]Lu-EB-PSMA-617 ($r=0.683$ at 72 h) [52]. Additionally, there was a strong correlation between physiological uptake SUV_{max} values in normal organs between baseline PET and first cycle SPECT using [^{177}Lu]Lu-PSMA-617 ($r=0.827$ at 0.5 h) and [^{177}Lu]Lu-EB-PSMA-617 ($r=0.868$ at 24 h) [52].

Regarding patient sample sizes, Neubauer et al. (2024) analysed the largest group of patients ($n=73$), including 144 lesions. [53]. The studies by Song et al. (2024) and Pathmanandavel et al. (2023) reported sample sizes of 56 and 32 patients, respectively [51, 54]; however, the number of analysed lesions was not specified.

Regarding SPECT/CT-SUV validation, only Grkovski et al. (2023) used cylindrical and six-spherical National Electrical Manufacturers Association (NEMA), International Electro-technical Commission (IEC), and Body Phantom inserts [55]. Cylindrical homogenous phantoms were implemented for SUV validation in the studies by Wang et al. (2019) [52] and Pathmanandavel et al. (2023) [54]. The most recent studies by Neubauer et al. (2024) and Song et al. (2024) did not report phantom validation methods. [51, 53]. The SPECT/CT imaging time points varied: two studies (Wang et al. (2019) and Grkovski et al. (2023)) used 3–5 time points [52, 55], while the other studies (Pathmanandavel et al. (2023), Song et al. (2024), and Neubauer et al. (2024)) used a single time point [51, 53, 54].

The SPECT/CT-SUV thresholds also differed among studies. Pathmanandavel et al. (2023) and Neubauer et al. (2024) used a threshold of ≥ 3 [53, 54]. In contrast, the liver parenchyma SUVmax was used as a threshold by Song et al. (2024) [51], and a 50% SUVmax threshold from PSMA-PET/CT was applied to SPECT/CT by Grkovski et al. (2023) [55]. Wang et al. (2019) [52] used visual assessment as a threshold to include up to six large lesions with a spherical shape and high uptake.

Additionally, clinical outcome data from PSA progression-free survival (PSA-PFS) was reported by three studies [51, 53, 54]Song et al. (2024) identified a > 30% reduction in early Lu-TTV on SPECT/CT after 2–3 cycles of therapy, correlating with improved overall survival (median OS not reached vs. 6 months, $p=0.008$) and PSA-PFS (median 6 months vs. 1 month, $p<0.001$) [51].

Discussion

This systematic review explored the feasibility of applying quantitative SPECT/CT-SUV to assess the [^{177}Lu]Lu-PSMA therapy response. Our findings suggest that SPECT/CT-SUV holds potential as a quantitative tool for therapy response monitoring, particularly in early TRT cycles, and could complement PET/CT in clinical decision-making. Significant changes were reported in SPECT/CT SUV_{max} and SUV_{mean} derived from [^{177}Lu]Lu-PSMA across multiple TRT cycles, particularly cycles 1 and 3 [54]. However, a robust positive correlation exists

between SUV_{max} on SPECT/CT after the first cycle of [^{177}Lu]Lu-PSMA TRT and baseline PET/CT SUV_{max} [55]. Moreover, a strong correlation ($r=0.83$, $p<0.001$) was reported between the SUVmean of [^{177}Lu]Lu-PSMA and baseline [^{68} Ga]Ga-PSMA, highlighting the potential of sequential quantitative SPECT/CT as reliable predictors of PET-PSMA SUV changes [52]. Furthermore, the SPECT/CT-derived area under the curve (AUC) strongly correlated with [^{68} Ga]Ga-PSMA SUV_{max} and SUV_{mean} values, indicating that SPECT/CT-SUV could be a useful quantitative tool for early monitoring of therapy response between subsequent therapy cycles.

Despite the potential utility of SPECT/CT-SUV metrics, several studies provided limited reporting on SUV-specific metrics, only presenting SUV_{mean} values correlated with PSA progression-free survival (PSA-PFS) and overall survival (OS). The [^{177}Lu]Lu-PSMA-derived SUV_{max} or SUV_{mean} showed no significant correlation with PSA-PFS or OS in these studies [51, 53, 54]. However, PSA changes were significantly correlated with [^{68} Ga]Ga-PSMA-derived SUV and TLR changes before and after two therapy cycles of [^{177}Lu]Lu-PSMA TRT [34].

[^{68}Ga]Ga-PSMA is highly recommended for mCRPC patient selection and for predicting response to [^{177}Lu]Lu-PSMA treatment [38]. Many studies have examined the PET-PSMA-derived SUV to assess patient eligibility for [^{177}Lu]Lu-PSMA therapy and response assessment [3, 6, 24, 25, 29, 34, 57–63]. During [^{177}Lu]Lu-PSMA therapy cycles, the high expression of PSMA by PCa resulted in better uptake [17, 20, 64]. Therefore, [^{177}Lu]Lu-labelling with PSMA ligands led to a significant decline in serum PSA in 80.3% of patients [65]. Accordingly, SPECT/CT-SUV can be used to adjust treatment activity and patient stratification.

Ferdinanadus et al. (2017) investigated the baseline [^{68} Ga]Ga-PSMA PET/CT mean SUV metrics of target/nontarget tissue for 40 consecutive patients treated with one cycle of [^{177}Lu]Lu-PSMA [20]. PSMA-PET intensity uptake was correlated with the [^{177}Lu]Lu-PSMA absorbed dose and PSA progression [17]. However, the response rate is not always correlated with SUV uptake; these findings need to be confirmed in a large patient cohort [17, 20, 64].

Further studies have reported that targeted and non-targeted tissue dosimetry has been investigated following [^{177}Lu]Lu-PSMA targeted therapy cycles [17, 66–70]. The mean SUV values of targeted tissue should be compared to those of reference organs, such as the liver [3]. In contrast, the studies included in this review did not report SPECT/CT-[^{177}Lu]Lu-PSMA-derived SUV metrics for normal (nontargeted) organs. Non-targeted organ dosimetry using SUV-derived metrics could enhance treatment planning by providing insights into the impact of therapy on normal organs, which could help optimise dose distribution and reduce adverse effects.

This review had some limitations. The established dominance of PET/CT-SUV quantification, owing to its superior image resolution and longer history of clinical use, may explain the limited exploration of SPECT/CT-SUV metrics in [^{177}Lu]Lu-PSMA studies. The recent FDA approval of [^{177}Lu]Lu-PSMA-617 has opened new avenues for research, underscoring the need for standardisation in SPECT/CT-SUV protocols. Future studies should focus on validating SUV metrics across larger, more diverse patient cohorts, with unified treatment protocols and robust methodologies for dosimetry comparison between targeted and non-targeted tissues.

Future research should prioritise establishing standardised protocols for SPECT/CT-SUV measurement, including criteria for comparing metrics across different TRT cycles and correlating them with PET/CT-SUV and clinical outcomes such as PSA progression and survival.

Conclusion

The quantitative SPECT/CT-SUV shows a positive correlation between SPECT/CT-derived SUV changes and PSMA-PET SUV changes, thus supporting the feasibility of SPECT/CT-SUV as a quantitative imaging biomarker during [^{177}Lu]Lu-PSMA targeted therapy cycles. Despite these promising findings, small sample sizes, retrospective study designs, and inconsistent SUV reporting standards limit the current evidence base. Finally, a standardised imaging acquisition/processing and reporting system needs to be developed and validated for [^{177}Lu]Lu-PSMA-617. Further clinical investigation is required to ensure the SPECT/CT quantification reliability and validity. Addressing these limitations will be crucial to advancing the clinical application of SPECT/CT-SUV in the monitoring and individualising of PSMA-targeted radionuclide therapy.

Abbreviations

FDA	United States Food and Drug Administration
^{18}F-FDG	Fluorine-18-fluorodeoxyglucose
^{68}Ga	Radioisotope of gallium
H	Hour
OS	Overall survival
^{177}Lu	Radioisotope of lutetium
mCRPC	Metastatic castration-resistant prostate cancer
PCa	Prostate cancer
PSMA	Prostate-specific membrane antigen
PSA	Prostate-specific antigen
PFS	Progression-free survival
SPECT	Single-photon emission tomography
SPECT/CT	Single-photon emission tomography with computed tomography
SUV	Standardised uptake value
SUV_{mean}	Mean standardised uptake value
SUV_{max}	Maximum standardised uptake value
SUV_{peak}	Peak standardised uptake value

TLR	Tumour-to-liver ratio
TRT	Targeted radionuclide therapy
TTV	Total tumour volume

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12880-025-01571-x.

Supplementary Material 1.

Author's contributions

Tahani O. Alkahtani screened the records independently for eligibility and extracted and analysed all the data.

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Data availability

This published article includes all the data generated or analysed during this study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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