Dosimetry in Lu-177-PSMA-617 prostate-specific membrane antigen targeted radioligand therapy

Review article

Nuclear Medicine Communications

Dosimetry in Lu-177-PSMA-617 prostate-specific membrane antigen targeted radioligand therapy: a systematic review

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Background **^{177}Lu-prostate-specific membrane antigen (PSMA) gained popularity as a choice of agent in the treatment of patients with advanced prostate cancer or metastatic castration-resistant stage of prostate carcinoma (mCRPC) diseases. However, this treatment may cause fatal effects, probably due to unintended irradiation of normal organs. We performed an extensive systematic review to assess the organs at risk and the absorbed dose received by tumor lesions in ^{177}Lu-PSMA therapy.**

Design **In this review, published peer-reviewed articles that cover clinical dosimetry in patients following peptide radionuclide ligand therapy using ^{177}Lu-PSMA have been included. Two senior researchers independently checked the articles for inclusion. A systematic search in the database was made using *PubMed*, *Publons* and *DOAJ*. All selected articles were categorized into three groups: (1) clinical studies with the technical description of dosimetry in ^{177}Lu-PSMA therapy (2) organ dosimetry in ^{177}Lu-PSMA therapy or (3) tumor dosimetry in ^{177}Lu-PSMA therapy.**

Result **In total, 182 citations were identified on PSMA therapy and 17 original articles on ^{177}Lu-PSMA dosimetry were recognized as eligible for review. The median absorbed dose per unit of administered activity for kidneys, salivary, liver, spleen, lacrimal and bone marrow was 0.55, 0.81, 0.1, 0.1, 2.26 and 0.03 Gy/GBq, respectively. The median absorbed dose per unit of activity for tumor lesions was found in a range of 2.71–10.94 Gy/GBq.**

Conclusion **^{177}Lu-PSMA systemic radiation therapy (SRT) is a well-tolerated and reliable treatment option against the management of the mCRPC stage of prostate carcinoma. Lacrimal glands and salivary glands are the major critical organs in ^{177}Lu-PSMA SRT. Besides, tumors receive 3–6 times higher absorbed doses compared to organs at risk. *Nucl Med Commun* 43: 369–377**

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Keywords: **^{177}Lu-PSMA, critical organs, organ dosimetry, tumor dosimetry**

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Introduction

Over the past decade's different sources of ionizing radiation are effectively used in the treatment of various cancers [1]. External beam radiation therapy (EBRT) and brachytherapy are an integral part of cancer treatment for several years [2,3]. This article mainly focuses on evolving systemic radiation therapy (SRT). Unlike EBRT and brachytherapy, SRT uses systemic administration of radiopharmaceutical comprising α or β^-emitting radionuclides for treatment [4]. The SRT has evolved and become popular again by the introduction of various targeted radiolabelled molecules and antibodies, which are associated with the delivery of radioactive atoms to the tumor lesions [5,6]. Some examples are, ligands directed towards the prostate-specific membrane antigen (PSMA) and somatostatin analogs to target the somatostatin receptor to treat prostate cancer and neuroendocrine tumors, respectively. This type of SRT is referred to as peptide radionuclide ligand therapy (PRLT) for prostate cancer, which is 7.1% of all newly diagnosed cancers worldwide [7,8].

The number of prostate cancer cases has been rapidly increasing over the past decades in worldwide populations [9]. One of the advanced and progressive stages of prostate cancer is a metastatic castration-resistant stage of prostate carcinoma (mCRPC) [10]. PSMA is an excellent target for radionuclide therapy. PSMA is overexpressed in all kinds of prostate cancers and radiolabelled PSMA targeting ligands binds to the extracellular space of PSMA receptors, resulting in irradiation of cells, DNA damage and eventually leading to cellular apoptosis [11]. Several clinical trials have also demonstrated a successful reduction in serum prostate-specific antigen (PSA) levels, tumor size and improvement in patients' overall survival following administration of radiolabelled PSMA [12–15]. Among all other radionuclides, Lutetium-177(^{177}Lu) gained popularity as a choice of radionuclide in SRT mainly due to its ideal emission characteristics and physical properties, which allow maximum delivery of ^{177}Lu-PSMA activity to the targeted prostate cancer cells [16]. In previous studies, It has been demonstrated that the expression of ^{177}Lu-PSMA increases further in

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patients with advanced prostate cancer or mCRPC diseases [17,18]. Besides, the utility of this treatment has been explored in patients who are ineligible to receive other therapies [17]. Several retrospective studies showed the efficacy of treatment with ^{177}Lu-PSMA [19–22].

In the previous literature, it has been shown that normal physiological expression of PSMA takes place in healthy organs such as the salivary glands, the lacrimal glands, the liver, the kidneys and the bone marrow also known as target organs [23–25]. This normal physiological expression of PSMA results in unintended irradiation of healthy organs and tissues. This may cause fatal effects in salivary glands, lacrimal glands and kidneys, probably leading to xerostomia, lacrimal gland toxicity and renal toxicity, respectively and thus limiting the total therapeutic dose delivery and the number of treatments cycles [26,27]. All these organs are therefore referred to as organs at risk or critical organs for PSMA-SRT. To avoid toxicity, personalized dosimetry could play an important role by adjustment of treatment cycles and assessment of radiation dose received by target organs in each cycle.

For an effective SRT treatment with ^{177}Lu-PSMA, it is necessary to ensure maximum dose delivery into the tumor, while minimizing radiation burden to the organs at risk. In EBRT, it is an established practice to use standard software for the verification and planning of treatment doses [28]. Whereas, SRT uses two approaches for personalized dosimetry; the planning approach, also known as pre-therapeutic dosimetry or verification approach also called post-therapeutic dosimetry. The first approach estimates the maximum administered therapeutic activity to attain a desired absorbed dose and the second approach calculates the absorbed dose after administration of a therapeutic dose of the radiopharmaceutical [29]. In both approaches, raw data of imaging time points are processed and analyzed, activities of different organs and tumor tissues should be converted into time-activity curves and in the end, absorbed dose estimates must be calculated for each organ and tissue. The first report related to ^{177}Lu-PSMA-617 absorbed dose estimates for different organs and tumor sites was published in 2015 [30]. Thereafter multiple studies have been performed for the estimation of absorbed doses in different organs and tumor sites using multi-time-point imaging, single-time-point imaging, multiple blood and urine samples post administration of ^{177}Lu-PSMA [31–37]. Cumulative activity in target organs and tumor lesions can be determined using least square fitting, mathematical integrations, scaling factors or by using numeric models in an integrated software [30,35–39]. Besides various software programs comprising different kinetic models and human phantoms of different sex, age and sizes have been used for absorbed dose calculations [31–35]. The absorbed dose estimates for body organs and tumor lesions in ^{177}Lu-PSMA-617 SRT are generally performed using the medical internal radiation dose schema [40]. However, the accuracy of dose estimation can be improved by the use of more sophisticated voxel-based dosimetry methods which include inhomogeneous activity distribution in the area of interest, the actual size of an organ, multi-single photon emission computed tomography/computed tomography (SPECT/CT) images and simulation codes [36,41].

Several articles have assessed the therapeutic efficacy, toxicities and quality of life associated with ^{177}Lu-PSMA-SRT treatment [42–45]. To achieve therapeutic success in SRT, it is important to escalate the gap between tumor-absorbed dose and organs at risk. However, to our knowledge, no systemic review has assessed the effectiveness of novel ^{177}Lu-PSMA treatment based on the kinetics and dosimetry results, which could guide nuclear medicine physicians to manage the administered activity and treatment cycles for patients with mCRPC. Therefore, we performed an extensive systematic review of the past 6 years of scientific literature covering dosimetry in ^{177}Lu-PSMA therapy. Specific aims were to: (1) assess the organs at risk and maximum tolerance limit in ^{177}Lu-PSMA therapy and (2) assess the dose received by tumor lesions.

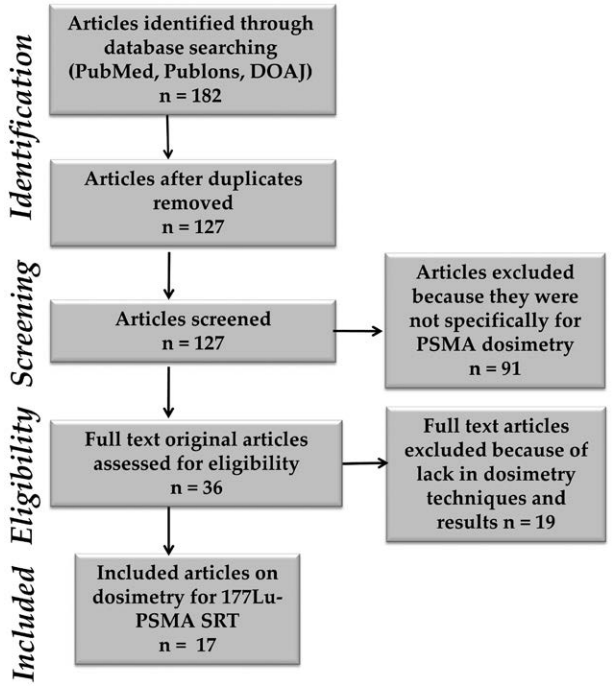
Materials and methods

In the present study, we referred to the guidelines mentioned in the Cochrane handbook [46]. The strategy for searching articles was designed to find out published peer-reviewed articles that cover clinical dosimetry in patients following PRLT for mCRPC using ^{177}Lu-PSMA. Two researchers with more than 10 years of experience independently checked the articles for inclusion based on the study title and abstract. Disagreements between the researchers were resolved by the discussion. A systematic search in the database was made using *PubMed*, *Publons* and *DOAJ*. The terms used for the article searching were PRLT, ^{177}Lu-PSMA and ^{177}Lu-PSMA dosimetry with 'AND' and 'OR' logical operator. Inclusion criteria were: original articles published in the English language; articles published between January 2014 and July 2021; patients with mCRPC of any age; pretherapeutic or post-therapeutic dosimetry; prospective or retrospective studies with any number of patients and patients received ^{177}Lu-PSMA therapy in a single cycle or multiple cycles. The case reports, editorials, dose estimates generated from phantoms and preclinical studies were excluded. A detailed flowchart is provided in Fig. 1 which demonstrates how we reached at final 17 articles eligible for review.

Articles selected using the above-mentioned search strategy were categorized into three groups:(1) clinical studies with the technical description of dosimetry in ^{177}Lu-PSMA therapy (2) organ dosimetry in ^{177}Lu-PSMA therapy or (3) tumor dosimetry in ^{177}Lu-PSMA therapy. Clinical studies should at least describe the patient population, the administered activity of ^{177}Lu-PSMA,

imaging and dosimetry methodology. Dosimetry articles should focus on absorbed dose estimates ^{177}Lu-PSMA in organ, tissues and tumor lesions. All data were replicated into a Microsoft Excel sheet. Two reviewers took out the following information from finalized articles: first author, number of patients, age, dosimetry data used for study, cumulative activity estimation, dosimetry method used, dosimetry software used, absorbed dose estimates per unit administered activity for kidneys, salivary, liver, spleen, lacrimal, bone marrow and different tumor sites.

Fig. 1



Flowchart represents selection of dosimetry article in ^{177}Lu-prostate-specific membrane antigen (PSMA) therapy.

Statistical analysis

Box and whisker plot was used to demonstrate the distribution of organ dosimetry data compiled from different pieces of literature. The top and bottom of boxes represent the upper and lower quartile whereas the upper and lower end of whiskers represent the upper and lower extremes of data and a line in the box is used to represent the median value. A bar graph was used to represent and compare individual tumor dosimetry data extracted from different studies. All statistical analyses were performed using MATLAB R2020a.

Results

Results of the systematic search are indicated in Fig. 1. In total, 182 citations were identified from database searches on PSMA therapy and prostate cancer treatment. A total of 55 duplicates were removed, and 127 citations were considered further for the screening. The remaining 91 articles were excluded after screening because they were not specifically for PSMA dosimetry. Finally, 36 articles on PSMA therapy were identified. Of these, 19 original articles were excluded and 17 original articles on ^{177}Lu-PSMA dosimetry were recognized as eligible for systematic review.

All studies selected in this review were prospective. Table 1 demonstrates each of the selected articles in terms of sample size, age, number of treatment cycles received by patient population and administered activity. The sample size in those articles ranged from 4 patients to 30 patients. Among the 17 selected studies, 3 studies have not stated the mean age of patients included for the dosimetry analysis. The median of the mean age group of patients selected from the article was 69 years (IQR, 67–71 years). The median treatment cycle among

Table 1 Characteristics of different ^{177}Lu-prostate-specific membrane antigen (PSMA) dosimetry studies

Study	Number of patients	Age (years)	Average number of treatment cycles received by each patient	Mean injected activity (GBq)
Delker *et al.*, [30]	5	68 (range: 54–81)	2	3.6 (range: 3.4–3.9)
Kabasakal *et al.*, [38]	7	63.9±3.9[a]	1	0.19±0.011[a]
Okamoto *et al.*, [31]	18	NS	4	7.4
Scarpa *et al.*, [39]	10	68 (range: 56–82)	3	6.1±0.3[a]
Hohberg *et al.*, [47]	9	69	1	5.52±0.15[a]
Kratochwil *et al.*, [22]	4	71.9±5.59[a]	2	6
Fendler *et al.*, [32]	15	73 (range: 54–81)	2	4.85
Yadav *et al.*, [48]	26	66.30±9.95[a]	1	2.52±1.3[a]
Kabasakal *et al.*, [49]	7	71±5.2[a] (range: 66–82)	1	5.2±1.8[a]
Violet *et al.*, [33]	30	70.03±7.36[a] (range: 67–75)	4	7.8 (range: 5.7–8.7)
Jackson *et al.*, [37]	30	71 (range: 67–75)	1	7.5
Ozkan *et al.*, [50]	10	NS	4	6.48± 0.55[a]
Kamaldeep *et al.*, [51]	30	63.67±8.08[a] (range: 49–79)	5	4.94±0.45[a]
Paganelli *et al.*, [52]	13	NS	4	5.5
Brosch-Lenz *et al.*, [36]	15	69.26±8.84[a]	1	7.99±0.79[a]
Rosar *et al.*, [35]	24	71 (range: 61–88)	3	6.4 (range: 3–10.9)
Prive *et al.*, [26]	10	67.2±4.77[a]	2	4.47±0.16[a]

NS, not stated; PSMA, prostate-specific membrane antigen.
[a]Results displayed are mean±SD

Table 2 Overview of data and dosimetry technique used by different authors for absorbed dose estimation in ^{177}Lu-prostate-specific membrane antigen (PSMA) therapy

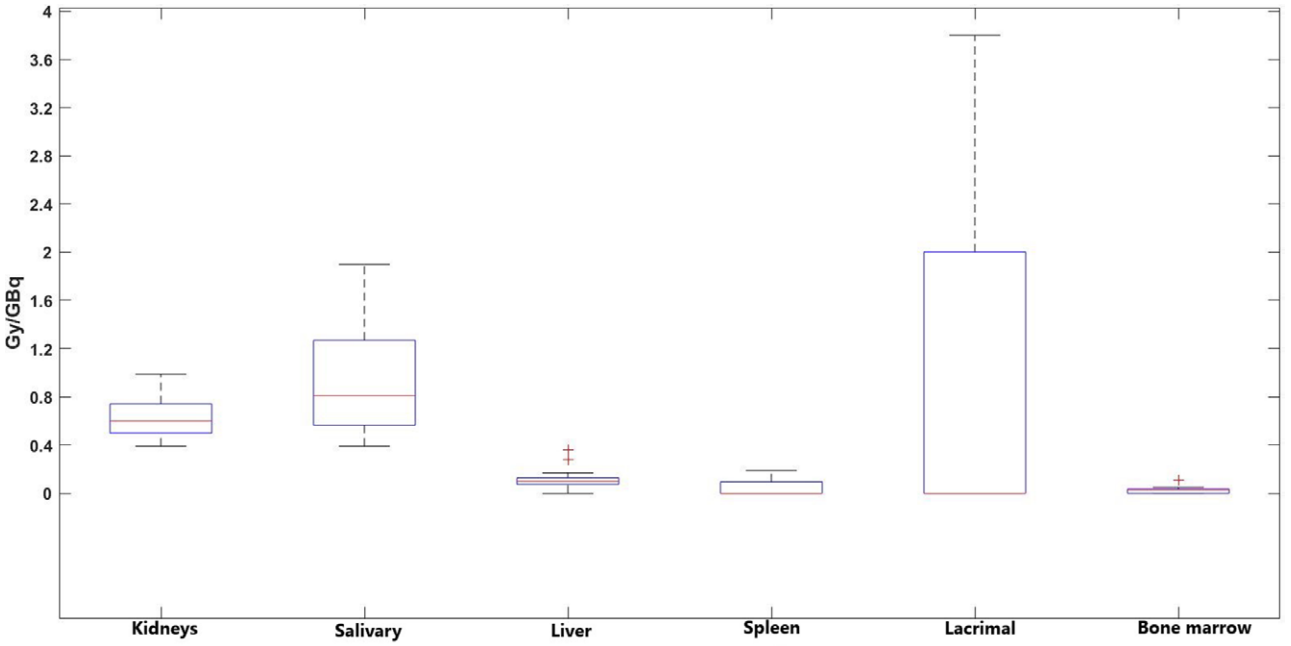
Study	Dosimetry data	Calculation of number of disintegrations	Dosimetry method/software
Delker *et al*., [30]	Sequential planar WB images, sequential 3D SPECT/CT images and multi blood samples	Monoexponential nonlinear least squares fit using MATLAB	Organ specific S values (RADAR) & linear mass scaling for cross irradiation
Kabasakal *et al*., [38]	Sequential planar WB images, sequential 3D SPECT/CT images and multi blood samples	Fitting model of OLINDA EXM program & MATLAB biexponential fitting program	OLINDA EXM 1.1 & blood-based model published by Wessels *et al*., [53]
Okamoto *et al*., [31]	Sequential planar WB images	Manual ROI based analysis	OLINDA/EXM
Scarpa *et al*., [39]	Multi planar WB images with single SPECT/CT	Excel script and Hermes software	OLINDA/EXM 1.1
Hohberg *et al*., [47]	Multi planar WB images	Biexponential fit using the nonlinear least squares method	OLINDA/EXM1.1
Kratochwil *et al*., [22]	Multi blood samples, urine samples and WB planar scans	ROI technic in PMOD, curve fitting toolbox MATLAB and trapezoidal approximation	OLINDA/EXM
Fendler *et al*., [32]	Sequential 3D SPECT/CT	Monoexponential nonlinear least squares fit using MATLAB	Organ specific S values (RADAR) & linear mass scaling for cross irradiation
Yadav *et al*., [48]	Sequential planar WB images, multi blood and urine samples	OLINDA/EXM kinetic input model; monoexponential; biexponential. Equation derived by Sgouros for BM dosimetry [54]	OLINDA/EXM 1.0 and Equations derived by Sgouros for BM dosimetry [54]
Kabasakal *et al*., [49]	Multi planar WB, SPECT images and multi point blood samples	Conjugate view method with Geometric background subtraction, VOI with 40 % threshold and OLINDA/EXM 1.1 fitting model	OLINDA/EXM 1.1
Violet *et al*., [33]	Sequential 3D SPECT/CT	Voxel dose maps, 3-phase exponential clearance model	GATE-derived voxel dose kernel & OLINDA sphere model
Jackson *et al*., [37]	Sequential 3D SPECT/CT	Tri exponential model and scaling factor	Radiation transport S-factor for a tissue medium and OLINDA sphere model
Ozkan *et al*., [50]	Multi planar WB scans	Xeleris Functional Imaging Workstation (manual ROI) & MIRD scheme	MIRD scheme pamphlet no. 16 & OLINDA/EXM 1.1
Kamaldeep *et al*., [51]	Multi planar WB scans, urine samples & exponential modeling (EXM) module of OLINDA/EXM 1.0	Bioexponential model with Origin (R) software	OLINDA 2.0 software
Paganelli *et al*., [52]	Multi planar WB scans, single SPECT/CT and multi blood samples	Xeleris 3.0 workstation, MimVista software and exponential modeling of OLINDA	OLINDA/EXM
Brosch-Lenz *et al*., [36]	Multi-SPECT/CT	Hybrid VOI/voxel-wise approach and MATLAB	Monte carlo simulation, OLINDA/EXM 2.0,Voxel S value, GATE
Rosar *et al*., [35]	WB multi planar and SPECT/CT images	Trapezoidal method, trapezoidal integration and monoexponential integration	QDOSE, IDAC-Dose 2.1
Prive *et al*., [26]	Multi-SPECT/CT and blood samples	MIRD Pamphlet No.26 & EANM dosimetry committee guidelines [55,56]	MIRD Pamphlet No.26 & EANM dosimetry committee guidelines [55,56]

EANM, European Association of Nuclear Medicine; MIRD, medical internal radiation dose; ROI, region of interest; SPECT/CT, single photon emission computed tomography/computed tomography; VOI, volume of interest; WB, whole body.

the publications was 2 (IQR,1–4). All studies except for that by Kabasakal *et al*. [38] performed post-therapeutic dosimetry for normal organs and tissues. The median administered activity among post-therapeutic activity was 5.76 GBq (IQR, 4.91–6.71 GBq). Table 2 describes data used for the dosimetry assessment, method for the estimation of the number of disintegrations, dosimetry method or software used by authors in their respective studies. Out of 17 dosimetry studies, six studies adopted planar imaging approach, five studies adopted multi-SPECT/CT imaging approach and the rest six adopted both planar and SPECT/CT approach for absorbed dose calculation. For the estimation of absorbed dose estimates, two studies used RADAR software, 11 studies used OLINDA software and four studies employed a voxel-based approach.

Out of 17 dosimetry studies, 15 studies reported absorbed dose estimates for kidneys and salivary, whereas 12 studies reported dose estimates for the liver, five studies for the spleen; seven studies for the lacrimal glands and 12 studies for the bone marrow. The median absorbed dose per unit of GBq activity for kidneys, salivary, liver, spleen, lacrimal and bone marrow was 0.55 Gy/GBq (IQR, 0.49–0.72 Gy/GBq), 0.81 Gy/GBq (IQR, 0.58–1.24 Gy/GBq), 0.1 Gy/GBq (IQR, 0.1–0.12 Gy/GBq), 0.1 Gy/GBq (IQR, 0.1–0.16 Gy/ GBq), 2.26 Gy/GBq (IQR, 1.12–2.55 Gy/GBq) and 0.03 Gy/GBq (IQR, 0.02–0.03 Gy/GBq), respectively (Fig. 2). Table 3 describes the detailed mean absorbed dose estimates for different organs with ^{177}Lu-PSMA in all studies. Among all 17 dosimetry studies, only six articles reported the results of tumor dosimetry for ^{177}Lu-PSMA therapy (22, 30–33, 35, 39, 51–54). A bar chart is used for the comparison of the mean absorbed dose per unit administered activity of bone lesions and lymph nodes in all studies (Fig. 3). The median absorbed dose per unit of GBq activity for bones, lymph nodes, soft tissue deposit, primary tumor site, lung tumor sites, liver tumor sites and other metastatic tumors was 4.95 Gy/GBq (IQR, 3.72–5.27 Gy/GBq), 3.75 Gy/GBq (IQR,

Fig. 2



Box plot showing absorbed dose per unit administered activity (Gy/GBq) for different body organs from ^{177}Lu-prostate-specific membrane antigen (PSMA) therapy.

Table 3 Summary of absorbed dose per unit administered activity (Gy/GBq) obtained from different studies on organ dosimetry for ^{177}Lu-prostate-specific membrane antigen (PSMA)

Study	Absorbed doses per unit administered activity (Gy/GBq)[a]					
	Kidneys	Parotid	Liver	Spleen	Lacrimal	Bone marrow
Delker *et al.*, [30]	0.6	1.4	0.1	0.1	NS	0.01±0.005
Kabasakal *et al.*, [38]	0.88±0.40	1.17±0.31	0.28±0.09	NS	NS	0.03±0.01
Okamoto *et al.*, [31]	0.72±0.21	0.55±0.14	0.12±0.06	NS	3.8±1.4	NS
Scarpa *et al.*, [39]	0.60±0.36	0.56±0.25	NS	NS	1.01±0.69	0.04±0.03
Hohberg *et al.*, [47]	0.53±0.17	0.72±0.14	NS	NS	2.82±0.76	NS
Kratochwil *et al.*, [22]	0.75±0.19	1.28±0.40	0.1±0.3	0.19± 0.06	NS	0.03±0.01
Fendler *et al.*, [32]	0.55±0.2	1.0±0.6	0.1±0.1	0.1±0.1	NS	0.002±0.005
Yadav *et al.*, [48]	0.99±0.31	1.24±0.26	0.36±0.10	NS	NS	0.048±0.05
Kabasakal *et al.*, [49]	0.82±0.25	1.90±1.19	0.17±0.09	NS	NS	0.030±0.008
Violet *et al.*, [33]	0.39±0.15	0.58±0.43	0.10±0.05	0.08±0.06	0.36±0.18	0.11±0.10
Ozkan *et al.*, [50]	0.70±0.24	1.34±0.78	NS	NS	2.28±1.29	NS
Kamaldeep *et al.*, [51]	0.49±0.17	0.53±0.25	0.07±0.04	0.16±0.08	1.23±0.70	0.03±0.02
Paganelli *et al.*, [52]	0.42(median)	0.65 (median)	0.13 (median)	NS	2.26 (median)	0.036 (median)
Rosar *et al.*, [35]	0.54±0.28 (3D), 0.52±0.27 (Hybrid), 0.49±0.31 (2D)	0.81±0.34 (3D), 0.81±0.34 (HYBRID), 0.75±0.34(2D)	0.10±0.05 (3D), 0.10±0.05 (Hybrid), 0.09±0.04 (2D)	NS	NS	NS
Prive *et al.*, [26]	0.49±0.11	0.39±0.17	0.09±0.01	NS	NS	0.02±0.00

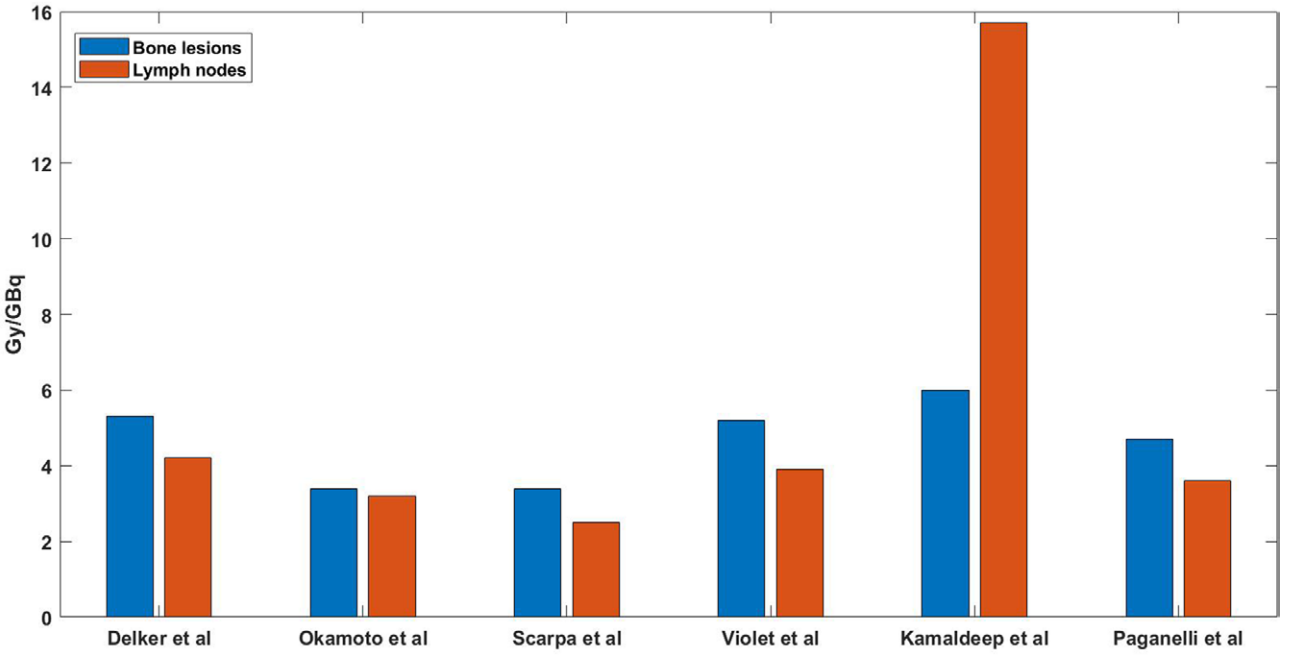
NS, not stated; PSMA, prostate-specific membrane antigen.
[a]Results displayed are mean±SD

3.3–4.12 Gy/GBq), 3.39 Gy/GBq (IQR, 2.74–4.03 Gy/GBq), 2.71 Gy/GBq (IQR, 2.42–3 Gy/GBq), 3.52 Gy/GBq (IQR, 2.63–4.41 Gy/GBq), 5.56 Gy/GBq (IQR, 3.38–7.74 Gy/ GBq) and 10.94 Gy/GBq (IQR, 8.52–11.49 Gy/GBq), respectively. The details of mean absorbed dose estimates for tumor lesions are mentioned in Table 4.

Discussion

We have systematically reviewed the published original literature on absorbed dose estimates for ^{177}Lu-PSMA-SRT. The abstracts published in the conferences were not included to prevent overlapping of patient data. In this systematic review, all studies published to date were

Fig. 3



Bar chart showing the distribution of absorbed doses (Gy/GBq) received by tumor lesions (bone and lymph nodes) in different ^{177}Lu-prostate-specific membrane antigen (PSMA) dosimetry studies.

Table 4 Summary of absorbed dose per unit administered activity (Gy/GBq) obtained from different studies on tumor dosimetry for ^{177}Lu-prostate-specific membrane antigen (PSMA)

Study	Tumor site	Absorbed doses per unit administered activity (Gy/GBq)[a]
Delker *et al*., [30]	Bone	5.3±3.7
	Lymph nodes	4.2±5.3
	Soft tissue	2.1±0.8
Okamoto *et al*., [31]	Bone	3.4±2.7
	Lymph nodes	3.2±2.2
	Liver sites	1.2±0.67
	Lung	1.75±0.92
Scarpa *et al*., [39]	Bone	3.40±1.94
	Lymph nodes	2.55±0.42
	Visceral lesions	2.43±0.78
Kratochwil *et al*., [22]	Metastases	12.05±7.07
Fendler *et al*., [32]	Tumor	6.1±4.9
Yadav *et al*., [48]	Tumors	10.94±18.01
Violet *et al*., [33]	Bone	5.28±2.46
	Lymph nodes	3.91±3.93
Kamaldeep *et al*., [51]	Bone	6.03±8.34
	Lymph nodes	15.71±14.72
	Primary site	3.29±2.76
	Liver sites	9.92±3.02
	Lung	5.30±8.22
	Soft tissue deposit	4.68±4.81
Paganelli *et al*., [52]	Bone	4.70 (median)
	lymph nodes	3.64 (median)
Rosar *et al*., [35]	Bone	1.68±1.32 (3D), 1.55±1.28 (hybrid), 1.42±0.99 (2D)
Prive *et al*., [26]	Target lesion	2.14±1.83

[a]Results displayed are mean±SD

incorporated. The main strengths of our study are as follows; first, we identified 17 PSMA dosimetry studies including 263 patients and dose estimates were determined for different body organs and tumor lesions; second, we identified organs at risk with max tolerance limit for ^{177}Lu-PSMA therapy.

Because of the large variability of organ and tumor activity between patients, therefore precise and reliable dose estimates are important for each patient in SRT to ensure maximum dose delivery to the tumor while dose delivered to critical organs within acceptable limits. Our results demonstrate that the lacrimal gland, salivary gland and kidneys are the organs that receive a significant amount of dose in ^{177}Lu-PSMA therapy. The lacrimal gland is the organ that receives the highest absorbed dose followed by the salivary glands and kidneys. The median cumulative absorbed dose received by lacrimal, salivary glands and kidneys were found 9.04 Gy (range: 2.8–28.12 Gy), 4.66 Gy (range: 1.74–9.88 Gy) and 3.08 Gy (range: 1.68–5.32 Gy), respectively. We observed a relatively lower absorbed dose to the liver and spleen following ^{177}Lu-PSMA therapy. Among all the studies some variations in absorbed dose estimates for the organs were noted. Also, due to inter-study variation, the highest variation in absorbed dose estimates was noted for lacrimal glands. This is likely due to the smaller size of the lacrimal gland. Previous studies have shown that interpatient

variability, differences in methodologies, models used for dose assessment, imaging system calibration, time-activity curve fitting, variation in organ volumes, intra-individual size variation, 2D/3D dosimetry approach and the number of imaging time points post-therapy, all are known to induce variations in absorbed dose estimates [31,33,36,47,48,57,58]. The use of various dosimetry software and techniques are also leads to variation in absorbed dose estimates for organs and tissues [59,60].

Our review study suggests that it is well-tolerated to achieve a number of treatment cycles of ^{177}Lu-PSMA SRT before surpassing the tolerance limit of lacrimal glands, salivary glands and kidneys. The maximum tolerance doses are around 40 Gy for lacrimal, 20 Gy for salivary and 23 Gy for kidneys [61–63]. If we assume that there is no variation in the tracer uptake during three to four treatment cycles with ^{177}Lu-PSMA in normal organs, the estimated absorbed dose would be between 27.12 and 36.16 Gy for the lacrimal glands, 13.98 and 18.64 Gy for the salivary glands and 9.24 and 12.32 Gy for the kidneys. These results indicate that the absorbed doses for the kidneys are far below the above-mentioned dose tolerance limits. No matter what kind of methodology or software is used for dose assessment, lacrimal glands and salivary glands are expected to be critical organs for ^{177}Lu-PSMA SRT since the predicted absorbed dose limit after four treatment cycles are very near to tolerance dose limit and will probably surpass it after five or six therapy cycles. Some studies have suggested lacrimal glands and salivary glands as critical organs [31,32,47]. However, the use of folic acid tablets or external colling using icepacks was found to be an effective strategy to reduce salivary uptake during treatment [7,52]. Assuming maximum tolerable doses for both the lacrimal and salivary glands, based on our dosimetry review with an average dose of 1.96 Gy/GBq for lacrimal and 0.92 Gy/GBq for salivary glands, the maximal administrable activity of ^{177}Lu-PSMA would be between 20 and 21 GBq. High radiation doses to the lens of the eye are also expected due to the high radiation dose to the lacrimal glands. Because of the very low tolerance limit of eye lenses (0.5 Gy/y), they are considered as one of the most sensitive organs of the body [64].

Bone marrow is a tissue that is also known to be at critical risk in SRT [65,66]. In the present review study, the median cumulative bone marrow dose estimated from imaging and blood data was found 0.14 Gy (range: 0.009–0.85 Gy). The absorbed bone marrow doses are substantially below the tolerance limit of 2 Gy [65], even when taking into account an average dose of 0.03 Gy/GBq over five or six therapy cycles. It is expected that therapy-induced myelotoxicity is unlikely to be experienced with ^{177}Lu-PSMA at predicted average activity ranges of six to seven giga becquerels per cycle. Regardless of the lower absorbed dose to bone marrow, there are still high chances of the development of hematotoxicity in patients substantially treated with radiotherapy and chemotherapy. Nevertheless, patients with multiple skeletal metastases from advanced prostate cancer may result in a somewhat higher absorbed dose than estimated in the present review study due to high radioactivity accumulation at metastatic sites. Some studies revealed that such toxicities may occur earlier in patients with a high tumor burden of marrow [67,68]. The common approaches employed for marrow dose estimation are either based on blood samples or imaging [22,30,38,52]. However, in the blood-based dosimetry methods, there are chances of underestimation of bone marrow dose in prostate cancer patients with expensive bone metastasis due to intense uptake in bony lesions which increase the absorbed dose delivered to marrow tissues [69].

For an effective SRT treatment, it is necessary to ensure maximum dose delivery into the tumor, while minimizing radiation burden to the normal organs and tissues. In the present review, we observed that tumor lesions (median 26.74; range 7.56–77.60 Gy) receive a 3–6 times higher radiation dose compared with the lacrimal glands, salivary glands and kidneys. This is due to the high and rapid expression of PSMA on the surface of tumor lesions [70,71].^{177}Lu-PSMA has very fast blood clearance with peaked uptake in the tumor sites at 1 h postinjection and this uptake reduces gradually at 120 h postinjection [72]. Patients with high tumor load demonstrate significantly higher and prolonged retention of activity in tumor lesions, which may reduce the uptake in normal organs and tissues due to lesser availability of radiotracer in extensive tumor load [73]. In the present review study, we observed a larger variation in absorbed dose delivered to different tumor sites, which is possibly due to interpatient variability [74]. Other contributing factors are differences in tumor sites and their radiosensitivity, differences in tumor volume, their function and degree of proliferation [75,76].

Conclusion

Undoubtedly from a dosimetry point of view, ^{177}Lu-PSMA SRT appears to be a well-tolerated and reliable treatment option against the management of metastatic castration-resistant stage of prostate carcinoma. Nevertheless, individualized patient dosimetry is required to determine the maximum administered activity and number of treatment cycles before^{177}Lu-PSMA therapy to prevent organ toxicity. In this review lacrimal glands and salivary glands were found major organs at risk, therefore a cumulative activity of 20–21 GBq of ^{177}Lu-PSMA can be safely administered in 3–4 treatment cycles after considering the tolerance limit of these organs. In this SRT, tumors receive 3–6 times higher absorbed doses compared to organs at risk. However, same time one has to note that the accuracy of dosimetry is limited, therefore the absorbed dose of organs might be underestimated or

overestimated. For more reliable dosimetry estimates, we recommend further studies to use a voxel-based approach with quantitative SPECT/CT.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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