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GUIDELINES

EANM procedure guidelines for radionuclide therapy with ^{177}Lu-labelled PSMA-ligands (^{177}Lu-PSMA-RLT)

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Abstract
Prostate-specific membrane antigen (PSMA) is expressed in most prostate cancers and can be identified by PSMA-ligand imaging, which has already become clinically accepted in several countries in- and outside Europe. PSMA-directed radioligand therapy (PSMA-RLT) with Lutetium-177 (^{177}Lu-PSMA) is currently undergoing clinical validation. Retrospective observational data have documented favourable safety and striking clinical responses. Recent results from a prospective clinical trial (phase II) have been published confirming high response rates, low toxicity and reduction of pain in metastatic castration-resistant prostate cancer (mCRPC) patients who had progressed after conventional treatments. Such patients typically survive for periods less than 1.5 years. This has led some facilities to adopt compassionate or unproven use of this therapy, even in the absence of validation within a randomised-controlled trial. As a result, a consistent body of evidence exists to support efficacy and safety data of this treatment. The purpose of this guideline is to assist nuclear medicine specialists to deliver PSMA-RLT as an "unproven intervention in clinical practice", in accordance with the best currently available knowledge.

Keywords Radionuclide therapy · Prostate cancer · Lutetium · PSMA · Nuclear medicine · Theranostics

Preamble

The European Association of Nuclear Medicine (EANM) is a professional non-profit medical association that facilitates communication worldwide among individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985.

These guidelines are intended to assist practitioners in providing appropriate nuclear medicine care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by medical professionals taking into account the unique circumstances of each case. Thus, there is no implication that an approach differing from the guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set out in the guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources or advances in knowledge or technology subsequent to publication of the guidelines. The practice of medicine involves not only the science but also the art of dealing with the prevention, diagnosis, alleviation and treatment of disease.

The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognised that adherence to these

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guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

Purpose

The purpose of this guideline is to assist nuclear medicine practitioners in:

1. Identifying patient candidates for PSMA-RLT, when performed as an "unproven intervention in clinical practice" in accordance with the Helsinki declaration (Art. 37), recognising that, currently, no therapeutic PSMA-targeting radiopharmaceutical with regulatory approval is available worldwide. An ongoing prospective randomised phase III trial is expected to define PSMA-RLT efficacy in the future.
2. Providing an expert consensus in favour of performing these treatments by reasonably balancing risks versus benefits.
3. Summarising potential toxicity from therapy, defining used amounts of radiotracer and providing information about the uncertainties that come with applying a treatment in such an early state of clinical development.
4. Describing the value of dosimetry in guidance to select a safe and efficacious treatment with ^{177}Lu-PSMA.
5. Providing a base for the harmonisation of PSMA-RLT protocols.

Ethics

Usually, EANM guidelines only reference radiopharmaceutical therapies that have been approved for routine use in at least one European country. However, PSMA-targeting radioligand therapy (PSMA-RLT) has been invented in the academic, non-commercial research setting in the USA and Europe and has recently been translated into clinical practice through the courage and efforts of treating physicians and their patients suffering from incurable and lethal disease. The situation is similar to peptide receptor radionuclide therapy (PRRT) of neuroendocrine tumours, which was introduced in the mid-1990s in several European countries. Acquiring phase III data supporting radioactive drugs took more than 15 years to achieve EMA/FDA approval [1]. Dosimetry and initial results are similarly promising for PSMA-RLT. In line with the declaration of Helsinki, it is considered ethically justified (and a legally recognised necessity of excuse) to apply a well-reasoned but unapproved intervention compared with withholding such a promising treatment from patients due to formal regulatory or administrative issues. EANM strongly advocates the development of PSMA-RLT within the context of adequately powered, multicentre clinical trials with appropriate endpoints, but also acknowledges that unproven interventions with PSMA-RLT may be offered individually on the basis of compassionate use and in accordance with the best actual knowledge. This is the motivation for this EANM guideline. Please note that this guideline does not seek to pre-empt authorization of PSMA-RLT, and the EANM stresses that national rules regulating the use of unproven interventions have to be respected.

Indications

Patients with metastatic, castration-resistant prostate cancers (mCRPC) who have exhausted or are ineligible for approved alternative options and with adequate uptake of PSMA-ligands on the basis of a pre-therapy imaging study can be considered for treatment. PSMA-ligand PET demonstrates high disease detection rates and superior reproducibility when compared with recently approved ^{18}F-fluciclovine PET [2, 3]. Thus far, there is no agreement on what should be considered an "adequate" uptake at one of the PSMA-ligand PET agents. Following the example of other theranostic agents, e.g. DOTA-TOC and DOTA-TATE, adequate uptake is generally one with at least higher uptake than that of normal organs, such as the liver. The reported outrider phase II trial on ^{177}Lu-PSMA617 required a baseline ^{68}Ga-PSMA11 PET SUV_{max} at dominant sites of tumour involvement to be at least 1.5 times the SUV_{mean} of liver, but it also included FDG PET/CT to exclude patients with active disease sites lacking PSMA expression [4]. Patients with liver metastases negative on PSMA-ligand PET should be ruled out, even if the remainder of the disease demonstrates intense PSMA expression. The final decision must be based on clinical assessment and careful evaluation of imaging findings.

The decision whether a patient is ineligible for a particular alternative treatment is commonly beyond the expertise of a nuclear medicine physician. With regard to androgen deprivation therapy (LHRH-analogues/-antagonists and first-generation antiandrogens), secondary hormone manipulations (abiraterone, enzalutamide), chemotherapy or the radionuclide therapy with ^{223}Radium-dichloride, the advice of a board-certified uro-/oncologist is necessary. Review at a multidisciplinary tumour board involving uro-/oncology, nuclear medicine and radiation oncology should be the standard procedure. The individual indication of PSMA-RLT should be a decision of the multidisciplinary tumour board. Whenever possible,

PSMA-RLT should be performed in a trial setting to allow for prospective data acquisition.

The right to self-determination is accorded a high value in EANM member states, and patients cannot be forced to accept priority recommendations. In any case, it should be documented that the patient has been informed about potential risks and benefits of these options by an expert in the respective field (e.g. a board-certified uro-/oncologist).

Contraindications

1. Life expectancy is less than 6 months (ECOG performance status > 2); unless the main objective is alleviating suffering from disease-related symptoms.
2. Unacceptable medical or radiation safety risk for isolation on a nuclear medicine therapy unit (if required by national regulations).
3. Unmanageable urinary tract obstruction or hydronephrosis; in patients with diagnosed or who are at high risk of urinary retention, ^{99m}Tc-MAG3 or ^{99m}Tc-DTPA renal scintigraphy should be considered as a baseline exam.
4. Progressive deterioration of organ function (GFR < 30 mL/min or creatinine > 2-fold upper limit of normal (ULN); liver enzymes > 5-fold ULN).
5. Myelosuppression:
   a. Total white cell count less than 2.5×10^9/L
   b. Platelet count less than 75×10^9/L
6. Conditions which require timely interventions (radiation therapy, surgery), e.g. spinal cord compression and unstable fractures, PSMA-RLT might be performed afterwards upon patient's condition. Borderline cases should be evaluated within the multidisciplinary tumour board for the individual benefit-to-risk ratio.

Radiopharmaceutical

According to the definitions of article 1 nos. 6–9 of the European directive 2001/83/EG, the here described ^{177}Lu-PSMA-ligands represent medicinal products. According to article 32001/83/EG in particular situations, drugs can be used without formal approval, but national regulations must be considered. With regard to the aspects of production and quality control (QC), the recommendations of the joint IAEA, EANM, and SNMMI practical guidance on PRRT in neuroendocrine tumours should be considered [5]. In line with this guidance, < 2% radiochemical impurities due to free ^{177}Lu should be found, and quality control should include both high-performance liquid chromatography and instant thin layer chromatography methods.

Current clinical knowledge is predominantly based on two low molecular weight PSMA-ligands termed PSMA-617 and PSMA-I&T. Radiolabelled with the beta minus particle emitter ^{177}Lu, these two radioligands share comparable biodistribution and hence dosimetric features; thus, we provide recommendations for the exchangeable application for both ligands.

Dosimetry

Development of second-generation ligands is still work in progress; new ligands or other radionuclides can be assessed, once sufficient dosimetry data become available, to adjust the treatment regimen without introducing unforeseeable risks. An overview of the current knowledge about specific absorbed doses for kidneys and salivary glands of ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA-I&T is provided in Table 1. Table 1 shows only results of publications which corrected for the individual patients' organ masses. Established tolerance limits for red marrow are 2 Gy (single exposure) [12], kidneys are 28–40 Gy (depending on risk factors; data for ^{177}Lu-PRRT considered more appropriate than literature data for external beam radiotherapy) [13, 14], and salivary glands are 35 Gy [15, 16].

According to the European directive 2013/59/Euratom (translated into national regulations since 6th Feb. 2018), exposures of target volumes are to be individually planned and verified, taking into account that doses to non-target volumes should be as low as reasonably achievable. The directive also indicates that in radiotherapeutic practices other than standardised therapeutic nuclear medicine practices, a medical physics expert shall be closely involved. Therapy with ^{177}Lu-PSMA falls within the non-standardised category, especially when individualised dosimetry is performed, and most national regulations now demand involvement of a medical physics expert with specialised training in this process. To meet regulatory requirements in situations where patients are unable to tolerate multiple serial imaging required for dosimetry, simplified methodologies would be favoured. However, the validity of such methods has yet to be extensively investigated. Dosimetry assessments can also be performed after a treatment cycle to validate the efficacy of future administrations. However, the tumour-absorbed doses from subsequent cycles may be lower due to the therapy effect from the initial cycle(s). Physiological uptakes in normal organs do not seem to be influenced by previous therapy cycles [10].

- For performing optimal dosimetry, sequential imaging over several time points, preferably using quantitative 3D techniques such as SPECT/CT, should be performed. As the late time point determines the absorbed doses to organs or tumours to a large extent, scans should be

Table 1 Absorbed dose estimates for critical organs under ^{177}Lu-PSMA-617 or ^{177}Lu-PSMA-I&T therapy. Only studies with mass correction for kidneys were included

No.	Ligand	No. of patients	Methods	Kidney (Gy/GBq ± SD)	Salivary Gl. (Gy/GBq ± SD)	Reference
1	^{177}Lu-PSMA-617	15	qSPECT at 1, 24, 48 and 72 h	0.6 ± 0.2	1.0 ± 0.6	Fendler et al. [6] and Delker et al. [7]
2	^{177}Lu-PSMA-617	6	Planar+SPECT/CT at 4, 24, 48 and 120 h	0.8 ± 0.3	1.9 ± 1.2	Kabasakal et al. [8]
3	^{177}Lu-PSMA-617	10	Planar at 0.5, 4, 24, 72 and 96 h	0.6 ± 0.4	0.56 ± 0.25	Scarpa et al. [9]
4	^{177}Lu-PSMA I&T	18	Planar at 0.5, 2, 24, 144 h	0.7 ± 0.2	0.6 ± 0.4	Okamoto et al. [10]
5	^{177}Lu-PSMA-617	30	SPECT at 4, 24 and 96 h	0.4 ± 0.2	0.6 ± 0.4	Violet et al. [11]
Mean				0.5 ± 0.2	0.8 ± 0.5	

performed after at least 4–7 days post-application. For organ-based dosimetry, the individual patients' organ masses should be determined for dose-limiting organs.

- The minimal standard would be dosimetry based on a single imaging time point, preferably quantitative with 3D techniques at least three or more days post-application [17–19]. For organ-based dosimetry, the individual patients' organ masses should be determined and the range of population effective half-lives quoted to describe the uncertainty in the dose measurement.
- In cases where no dosimetry is performed, the mean values given in Table 1 provide a rough estimate of the absorbed dose coefficient to kidneys and salivary glands. However, these values are only valid in normal pharmacokinetic behaviour; when renal function is impaired, the absorbed dose delivered to organs (notably red marrow by bone lesions expressing PSMA) might be elevated considerably. The small number of patients used to estimate these absorbed dose coefficients should be noted and a continued effort made to further document and enhance similar dosimetry findings. Thus, this approach is not adequate to predict treatment-related toxicity in an individual patient, and close follow-up is recommended to assess toxicity.
- Whenever possible, individual tumour/normal-organ dosimetry should be reported, preferably according to the EANM guidance document on good dosimetry reporting [20]. Possible dosimetry protocols have been proposed previously, and EANM dosimetry guidelines are in preparation.
- PSMA-RLT is not considered a risk for external radiotherapy adverse outcome. In case of emergencies like pain exacerbation, imminent spinal cord compression or fracture risk, external radiotherapy should be considered with close communication between radiation oncology and nuclear medicine. An individual report of the personalised dosimetry by ^{177}Lu-PSMA therapy will help in determining the right additional treatment option.

Radiation protection

Several publications provide data on external radiation exposure, excretion and effective half-life from ^{177}Lu-PSMA patients. Exposure rates from patients are indicated in Table 2. Kurth et al. [21] assessed the maximum effective dose to individual members of the public per treatment cycle to ~ 139 ± 53 μSv when the patient was discharged from the clinic after 48 h. As the data were obtained in Germany with a minimum hospitalisation of 48 h post-application, the data cannot be easily translated into out-patient treatment. Demir et al. [22] describe a setting in which patients were discharged 6 h post-application. The effective dose to caregivers the authors report, measured with TLD, was 202 ± 43 μSv (N = 23) in 5 days. Values for measured dose rates and the terminal half-life of the whole-body excretion are given in Table 2. Depending on local legal requirements, more data and dose assessments are needed for the exposure scenarios anticipated.

With respect to staff and precautions after discharge, the same precaution measures should be applied as for those with PRRT with Lu-177 in neuroendocrine tumours [23].

Treatment regimens for the non-compromised patient

^{177}Lu-PSMA-617/^{177}Lu-PSMA-I&T

- Administered activity per treatment: Based on observational data range from 3.7–9.3 GBq (100–250 mCi) [24–27]. A recent phase II study [4] (ACTRN12615000912583, UTN: U1111-1172-4095) and other current phase II studies (NCT03392428, NCT03042312) support *standard activities of 6–8.5 GBq* (160–230 mCi) in most instances. An ongoing phase III study (NCT03511664) implemented a standard activity of 7.4 GBq at 6-week intervals for a total of four to six cycles.

Table 2 Measured dose rates and terminal half-lives of the whole-body excretion. Data were extracted from Kurth et al. [21] and Demir et al. [22]

	Demir et al. (7.4 GBq)	Kurth et al. (6.1–6.6 GBq)
Effective dose rate @ 1 h	38 ± 7 μSv/h @ 1m	
Effective dose rate @ 4 h	23 ± 6 μSv/h @ 1m	2.8 ± 0.6 μSv/h @ 2m
Effective dose rate @ 24 h	7 ± 2 μSv/h @ 1m	1.6 ± 0.6 μSv/h @ 2m
Effective dose rate @ 48 h	5 ± 1 μSv/h @ 1m	1.1 ± 0.5 μSv/h @ 2m
Terminal clearance $T_{1/2,eff}$ (h)	30 ± 10 h	40 ± 16 h

- Time interval between cycles: 6–8 weeks
- Number of cycles: two to six (depending on response, prognosis and renal risk factors)
- A cumulative kidney absorbed dose of 40 Gy per patient should not be exceeded in patients with a life expectancy > 1 year. However, for activities resulting in kidney absorbed dose close to or higher than this limit, the benefit-to-risk ratio should be evaluated for the individual patient. The maximum cumulative absorbed dose should be distributed over the longest clinically reasonable period. This may justify individual de-escalation regimens or discontinuing treatment (once initial remission is achieved) until progressive disease warrants its re-initiation.
- Response assessment: PSA and post-therapeutic emission scans should be evaluated at every cycle, and additional staging exams using cross-sectional imaging, preferably PSMA-ligand PET, should be considered every 2 cycles.

Interaction with other medicinal products

No clinical interaction studies have been performed. Due to their well-known additive effects on bone marrow suppression, hemi body external irradiation or equivalent, chemotherapy or treatment with radioactive bone seekers should be discontinued for at least 4 weeks.

^{177}Lu-PSMA administration

I.V. or oral hydration as per individual cardiovascular and voiding conditions should be initiated before start of therapy. In patients with low cardiovascular risk, 1–2 L normal saline may be given I.V. at 20 cc/min flow rate. RLT is administered by slow I.V. injection of ^{177}Lu-PSMA.

Some general recommendations for RLT can be considered respecting the patients' individual condition(s):

- Diuretics and moderate laxatives can be given after RLT to support clearance of unbound ^{177}Lu-PSMA.
- Cold packs applied to salivary glands could eventually reduce ^{177}Lu-PSMA uptake during the blood pool phase. The value of cold packs is still controversial.
- Prophylactic antiemetic therapy, e.g. ondansetron.
- Corticosteroids one day before and up to several days after RLT are mandatory in case of cerebral, spinal or other metastases with risk of painful or obstructive swelling; otherwise, they are optional and case dependent.

Follow-up

Follow-up examinations following initiation of ^{177}Lu-PSMA RLT:

- Every 2–3 weeks (depending on baseline conditions), blood cell count should be checked for up to 12 weeks after each cycle.
- PSA follow-up should be performed and interpreted in accordance with the PCWG3 criteria [28].
- Every 6–8 weeks, basic liver and kidney profile should be assessed.
- Physical exam should be performed before each treatment.
- Intra-therapeutic scintigraphy (0–3 days after application) confirms tracer uptake and—when performed at later time points—can serve as imaging to follow-up response of PSMA-positive lesions.

Follow-up examinations after several cycles of ^{177}Lu-PSMA RLT:

- Imaging-based restaging should include a second modality to allow detection of PSMA-negative lesions. This may be a diagnostic CT/MRI as part of an integrated PSMA-ligand PET/CT or PET/MRI exam, a bone scan or a separate FDG PET. Frequency of radiological restaging can be adjusted to the reliability of post-treatment scans and PSA response and would be reasonable every 2–3 cycles in accordance with the PCWG3 criteria [28].

Repeat therapy

Duration of therapy is guided by the individual clinical need by carefully considering cumulative salivary glands' and kidneys' absorbed doses. Blood count, overall medical condition and criteria listed for inclusion and exclusion should be re-evaluated prior to any repeat treatment. Repeat RLT has been applied for a cumulative of up to seven cycles in recent observational studies without excess toxicity [29–31]. Repeat therapy every 6 to 8 weeks allows for recovery of haematotoxicity in most cases and is in line with published protocols for PSMA-RLT and PRRT [1, 26].

Safety

Safety of ^{177}Lu-PSMA RLT was reported as part of several observational trials with overlapping recruitment [6, 24, 26, 27, 32–35]. In these collectives, grades 3–4 haematotoxicity occurred in less than 10% of patients, whilst the first prospective phase II trial published recently reported slightly higher values (see below). Low blood count levels at baseline and diffuse bone marrow involvement were linked to serious haematotoxicity in individual patients [7, 26, 32]. The rate of grades 3–4 events was low for all other categories (less than 5%), including salivary gland function.

A recent phase II trial reported grade 1 dry mouth in 87% patients, grade 1 or 2 transient nausea in 50%, and grade 1 or 2 fatigue in 50% of patients [4]. The most common toxic effects possibly related to ^{177}Lu-PSMA-617 were grade 3 lymphocytopenia in eleven (37%), grade 3 anaemia in four (13%), and grade 3 or 4 thrombocytopenia in four (13%) patients.

In summary, data indicate a favourable safety profile for ^{177}Lu-PSMA RLT.

Efficacy

Efficacy after ^{177}Lu-PSMA RLT was assessed by several meta-analyses and observational trials with overlapping recruitment [6, 24, 26, 27, 32–42]. Largest cohorts were reported by Rahbar et al. and Ahmadzadehfar et al. for ^{177}Lu-PSMA-617 and Heck et al. for ^{177}Lu-PSMA-I&T [26, 36–38].

Biochemical response after repeat RLT, as defined by PSA decline ≥ 50%, is expected in more than half of patients, and partial response by imaging is expected in more than one-third of patients. In a recent phase II trial, 57% achieved a PSA decline of 50% or more [4]. Objective response by imaging in nodal or visceral disease was reported in 82% of patients with measurable disease.

Available data do not indicate differences in efficacy between ^{177}Lu-PSMA-617 and ^{177}Lu-PSMA I&T. Presence of visceral metastases and serum alkaline phosphatase ≥ 220 U/L was associated with poor outcome [26]. Pain and quality of life improved significantly in more than one half of patients within smaller observational trials [6, 24, 27, 34].

Additional considerations and future directions

- Protection for kidneys/salivary glands: Botulinum toxin was suggested to reduce salivary gland activity [43]. 2-PMPA and mannitol have been suggested to reduce kidney absorbed dose [44]. Cooling with icepacks can help lower the uptake of PSMA in the parotid glands [7, 45]. However, none of these concepts has been applied to a larger series of patients. As each additional intervention increases the risks for complications or could introduce its own side effects, none of these experimental approaches can be recommended for routine application today.
- ^{225}Ac-PSMA-targeted alpha therapy (PSMA-TAT) has been applied in patients presenting with a "superscan" pattern, because the shorter tissue penetration range of an alpha particle might translate into a more favourable microdosimetry in case of red marrow infiltration. It has also been applied as an additional escalation step in case of resistance to ^{177}Lu-PSMA-RLT [46]. However, due to the limited knowledge to date, PSMA-TAT is beyond the scope of the present guideline and will be addressed in future updates.

Liability statement

This guideline summarises the views of the EANM Oncology & Theranostics Committee. It reflects recommendations for which the EANM cannot be held responsible. The recommendations should be taken into context of good practice of nuclear medicine and do not substitute for national and international legal or regulatory provisions.

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Compliance with ethical standards

Conflict of interest Author C.K. declares that he has no conflict of interest. Author W.P.F. is a consultant for Endocyte and Ipsen and has received personal fees from Radiomedix. Author M.E. reports personal fees from ABX, Blue Earth Diagnostics and Progenics, outside the submitted work, patent application for rhPSMA and is a member of EANM

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