**PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 2.0**

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**ABSTRACT**

The aim of this updated guideline is to provide standards for the recommendation, performance, interpretation and reporting of PSMA PET/CT for prostate cancer imaging. Procedures and characteristics are reported for a variety of available PSMA small radioligands. Clinical scenarios for the use of PSMA-ligand PET/CT are discussed. This document aims to provide clinicians and technicians with the best available evidence, to support the implementation of PSMA PET/CT imaging in research and routine practice.

**Preamble**

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international scientific and professional organization founded in 1954 to promote the science, technology, and practical application of nuclear medicine. The European Association of Nuclear Medicine (EANM) is a professional non-profit medical association founded in 1985 that facilitates communication worldwide between individuals pursuing clinical and research excellence in nuclear medicine. SNMMI and EANM members are physicians, technologists, and scientists specializing in the research and practice of nuclear medicine.

The SNMMI and EANM will periodically define new guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service to patients throughout the world. Existing practice guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.

Each practice guideline, representing a policy statement by the SNMMI/EANM, has undergone a thorough consensus process in which it has been subjected to extensive review. The SNMMI and EANM recognize that the safe and effective use of diagnostic nuclear medicine imaging requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published practice guideline by those entities not providing these services is not authorized.

These guidelines are an educational tool designed to assist practitioners in providing appropriate 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. For these reasons and those set forth below, both the SNMMI and the EANM caution against the use of these guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by the physician or medical physicist in light of all the circumstances presented. 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 forth 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 includes both the art and the science of 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 recognized that adherence to these 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.

**Introduction**

Prostate-specific membrane antigen (PSMA)-directed positron emission tomography/computed tomography (PET/CT) is a non-invasive diagnostic technique to image PSMA positive lesions in individuals with prostate cancer. PSMA is a transmembrane protein with extracellular binding site. PSMA tissue expression is high on the cell surface of prostatic tissues including prostate cancer and low inmany organs. PSMA is also termed glutamate carboxy-peptidase II, referring to its role in neuronal glutamate synthesis in the neurochemistry context, or folate hydrolase 1 (FOLH1), referring to the encoding gene.

Increased PSMA expression is seen most notably in prostate cancer, but has also been found in the neovasculature of a variety of other malignancies [1]. Most adenocarcinomas of the prostate express high levels of PSMA in primary and metastatic lesions [2, 3]. Elevated PSMA expression in conjunction with its role in glutamate and folate metabolism may be associated with a survival advantage for tumour cells in conditions of cellular stress [4, 5]. The regulation of PSMA is complex, with the involvement of androgen receptor (AR), PI3K/Akt, and DNA damage response pathways [6]. Elevanted PSMA expression level has been associated with advanced metastatic or hormone-refractory disease [7], poor disease outcome [8], and the presence of deficient DNA damage repair pathways [9].

**Definitions**

The following definitions are made in accordance with Boellaard et al [10]:

PSMA-ligand: Refers to a group of ligands ([68Ga]Ga-PSMA-11, [68Ga]Ga-PSMA-I&T, [18F]F-DCFPyL, [18F]F-PSMA-1007, and [18F]F-rhPSMA-7.3) that targets the prostate-specific membrane antigen.

PET/CT: An integrated or multimodality PET/CT system is a physical combination of PET and CT, which allows sequential acquisition of the PET and CT portions. The patient remains in the same position for both examinations.

PET/MRI: An integrated or multimodality PET/MRI system is a physical combination of PET and MRI, which allows sequential or simultaneous acquisition of the PET and MRI portions. The patient remains in the same position for both examinations. PSMA-ligand PET/MRI has been reported for several applications, including staging at initial diagnosis or biochemical recurrence (BCR). However, PET/MRI protocols are outside the scope of this guideline.

PSMA-ligand PET: A detector system that measures the three-dimensional (3D) distribution of PSMA-ligands, producing semi-quantitative images that allow non-invasive assessment of PSMA expression.

A PSMA-ligand PET/CT examination may cover various coaxial imaging ranges. These are described as follows (defined in Current Procedural Terminology 2016):

Whole-body PET: From the top of the head through the feet.

Skull base to mid-thigh PET: From the base of the skull to mid-thigh. This range covers most of the relevant portions of the body in many oncological diseases (standard for both Europe and the USA). If indicated, cranially extended imaging may also cover the brain in the same scan (vertex to mid-thigh).

Standardized uptake value (SUV): Quantification of PSMA-ligand PET/CT is defined here as measuring relative PSMA-ligand concentrations using standardized uptake value (SUV) [11] because SUV represents the most commonly used semi-quantitative parameter for analysis of tracer uptake.

Maximum standardized uptake value (SUVmax): SUVmax is defined as the SUV of the single voxel in a particular lesion with highest uptake on the attenuation corrected PET image.

CT applies a combined X-ray source and detector rotating around the patient to acquire tomographic data. CT generates 3D images of tissue density, which allows for attenuation correction of PET and anatomical/tumour visualisation with a high spatial resolution. A PET/CT examination can include different types of CT scans depending on the CT characteristics, the dose and the use (or not) of oral and/or intravenous contrast agents:

Low-dose CT scan: A CT scan performed only for attenuation correction (CT-AC) and anatomical correlation of PET findings (with reduced voltage and/or current of the X-ray tube settings), i.e. a low-dose CT is not intended for a dedicated radiological interpretation. This scan delivers less radiation to the patient.

Diagnostic CT scan: A CT scan with or without intravenous and/or oral contrast agents, commonly using higher X-ray doses than low-dose scans for higher resolution imaging. A diagnostic CT scan should be performed according to applicable local or national protocols and guidelines.

Biochemical recurrence (BCR): Recurrence of prostate cancer due to rising PSA after definitive surgical or radiation therapy.

Biochemical persistence (BCP): Persistence of prostate cancer due to continuously elevated PSA despite surgical treatment.

Radioligand therapy (RLT): Internal radiation of prostate cancer lesions by the application of PSMA-directed therapeutic radioligands.

Non-metastatic castration-resistant prostate cancer (nmCRPC): Castration-resistant prostate cancer with no detected metastases on whole-body cross-sectional imaging (CT/MRI) and bone scan.

**PSMA-ligand PET – a novel class for prostate cancer imaging**

PSMA-ligands for PET/CT imaging were first radiosynthesized and validated in preclinical models at Johns Hopkins University [12, 13]. Later, [68Ga]Ga-PSMA-11, developed by the Heidelberg group [14], demonstrated high affinity to human PSMA and specific internalization into prostate cancer cells. [68Ga]Ga-PSMA-11biodistribution was shown to correspond to known cellular expression of PSMA across organs [15]. Other 68Ga-PSMA-ligands ([68Ga]Ga-PSMA-617, [68Ga]Ga-PSMA-I&T) demonstrated similar biodistribution and imaging properties [16, 17]. During this time, several 18F-labelled ligands have also been developed and assessed in clinical trials [18-21].

The radiopharmaceuticals [68Ga]Ga-PSMA-11, [68Ga]Ga-PSMA-I&T, [18F]F-DCFPyL, [18F]F-PSMA-1007, and [18F]F-rhPSMA-7.3 are most advanced in the process of clinical implementation, and/or regulatory approval. Most clinical evidence is based on [68Ga]Ga-PSMA-11 since it has been in use the longest. A small comparative prospective study demonstrated similar uptake in tumour lesions of [18F]F-DCFPyL and [18F]F-PSMA-1007 [22]. However, there is no head-to-head prospective study with lesion validation to directly compare the diagnostic accuracy of different PSMA-ligands. Radioligands differ in terms of radionuclide label, underlying radiochemistry and associated organ biodistribution. Different physiologic distribution and image interpretation pitfalls were noted [23]. However, there is no evidence to date that one specific PSMA radioligand has superior diagnostic accuracy with improved clinical outcome compared to another. Due to their similarity [68Ga]Ga-PSMA-11, [68Ga]Ga-PSMA-I&T, [18F]F-DCFPyL, [18F]F-PSMA-1007, and [18F]F-rhPSMA-7.3 are considered a common class of PSMA-directed small-ligand radiotracers for PET/CT and will henceforth be collectively referred to as PSMA-ligands.

**Goals**

This guideline intends to assist physicians in recommending, performing, interpreting and reporting the results of PSMA-ligand PET/CT for initial diagnosis, staging, and restaging of prostate cancer. In this intent this document covers patient selection, image acquisition, interpretation and reporting. Specific advice is given for the most common PSMA small radioligands available and for clinical scenarios with frequent use of PET/CT, including staging, restaging and assessment of suitability of PSMA radioligand therapy (RLT). This document aims to provide clinicians and technicians with the best available evidence, to inform them where robust evidence is lacking, and to help them to deliver the best possible diagnostic efficacy and study quality for their patients.

Adequate precision, accuracy, repeatability, and intra- and inter-center reproducibility are essential for the clinical management of patients. A standardized imaging procedure will help to promote the appropriate use of PSMA-ligand PET/CT and enhance subsequent research.

**Appropriateness of Use Criteria**

Since the introduction of PSMA-ligand PET/CT, several prospective multicenter trials have reported on the diagnostic and clinical value of PSMA-ligand PET/CT. The criteria outlined in this guideline are based on the currently available evidence. The specific use varies between institutions based on experience and availability. An overview focusing on appropriate use criteria has been recently published [24]. The most important indications are summarized in **Table 1**. Current evidence for these indications is reported in the following sections.

|  |  |
| --- | --- |
| **Routine clinical use** | |
|  | Initial staging of high-risk prostate cancer |
|  | Localization of recurrent (BCR) or persistent (BCP) prostate cancer following curative intent therapy |
|  | Localization of prostate cancer which is non-metastatic by conventional imaging (nmCRPC) |
|  | Staging before PSMA-directed radioligand therapy for metastatic prostate cancer |
| **Potential clinical applications** | |
|  | Guidance of prostate biopsy |
|  | Imaging metastatic prostate cancer |
|  | Monitoring of systemic treatment in metastatic prostate cancer |

**Table 1: Indications for PSMA-ligand PET/CT.**

Initial staging of high-risk prostate cancer

In patients with high-risk features (Gleason score >7, PSA >20 ng/mL, clinical stage T2c – 3a), the likelihood of distant metastases is increased. PSMA-ligand PET imaging demonstrated higher accuracy for disease localization in individuals with newly diagnosed prostate cancer compared with conventional imaging. In the Phase III multicenter randomized ProPSMA trial, [68Ga]Ga-PSMA-11 PET/CT resulted in 27% greater accuracy when compared with CT and bone scan for staging of individuals with initial high-risk prostate cancer [25]. Findings were validated by histopathology, imaging, or biochemistry at 6-month follow-up.

In two Phase II/III multicenter studies, [18F]F-DCFPyL and [68Ga]Ga-PSMA-11 PET/CT demonstrated high specificity (≥95%) for detection of pelvic lymph node metastases in individuals with intermediate or high-risk prostate cancer undergoing radical prostatectomy [26, 27]. However, due to low sensitivity in the 40% range, a negative PSMA PET scan cannot exclude the presence of pelvic lymph node micrometastases due to the intrinsic limitations of current PET technology. Other trials are underway to assess the impact of the inclusion of PSMA-ligand PET in clinical management pathways on patient survival [28].

Such Phase III prospective level evidence underlines the value of PSMA-ligand PET for accurate disease localization and risk stratification in individuals with newly diagnosed prostate cancer and high-risk features.

Localization of recurrent (BCR) or persistent (BCP) prostate cancer following curative intent therapy

BCR is defined as an increase in PSA to ≥0.2 ng/mL, measured at 6 to 13 weeks following prostatectomy and confirmed by a second PSA level >0.2 ng/mL [29]. BCP is defined as persistently elevated PSA ≥0.1 ng/mL more than 6 weeks after prostatectomy [30].

In patients who have undergone curative-intent radiation therapy, BCR is defined as a rise in PSA of ≥2 ng/mL above the nadir achieved after radiotherapy with or without androgen deprivation therapy (ADT) [31]. In patients with BCR or BCP, precise tumour localization with stratification of local, locoregional, or distant disease is critical for subsequent management.

Several prospective multicenter studies reported on the accuracy of PSMA-ligand PET in these settings. [68Ga]Ga-PSMA-11 and [18F]F-DCFPyL PET/CT demonstrated high patient- and region-level detection rate and positive predictive value for the localization of prostate cancer in the setting of BCR or BCP [32-34]. Accuracy was superior to conventional imaging [35], [18F]F-choline PET/CT [36] and [18F]F-fluciclovine PET/CT [37] in head-to-head assessments. Interobserver agreement of [68Ga]Ga-PSMA-11 is high [38]. The PSMA-ligand PET detection rate was associated with PSA level and doubling time [32, 39], Gleason score [35] and PSMA expression of the primary [40, 41]. The accuracy of PSMA-ligand PET translated into a significant impact on management in several prospective studies [42, 43]. Trials are underway to assess the impact on patient survival [44].

Current prospective evidence underlines the role of PSMA-ligand PET for prostate cancer localization at BCR or BCP and demonstrates superiority over conventional or other forms of molecular imaging.

Localization of prostate cancer which is non-metastatic by conventional imaging (nmCRPC)

nmCRPC is characterized by biochemical disease progression despite sufficient ADT. This is defined by the combined occurrence of several conditions: (a) castrate serum testosterone <50 ng/dL, (b) three consecutive rises in PSA resulting in two 50% increases above the nadir, (c) a PSA >2 ng/mL (EAU, European Association of Urology) or a PSA > 1 ng/mL (PCWG3, The Prostate Cancer Working Group 3), and (d) lack of metastatic spread on conventional imaging [45-48].

PSMA-ligand PET/CT has been studied in the nmCRPC population [49-52]. PSMA-ligand PET/CT detects local or distant lesions in nearly all nmCRPC patients. Distant metastatic disease was noted in more than half of patients [49]. Thus PSMA-ligand PET/CT detects disease extent in patients with nmCRPC patients (defined by conventional imaging) with high accuracy and leads to considerable stage migration [53]. Accurate localization of disease extent by PSMA-ligand PET/CT may aid patient stratification in clinical trials and adds information for therapy guidance. However, the impact on clinical outcome has yet to be determined prospectively.

Staging before PSMA-directed RLT for metastatic prostate cancer

PSMA-ligand PET/CT can be performed in patients with advanced prostate cancer to confirm eligibility for RLT and to assess the likelihood of response to RLT.

Documentation of PSMA expression in metastatic sites is required prior to initiation of RLT. 177Lu-PSMA-617 RLT was approved by the FDA for the treatment of eligible patients with metastatic castration-resistant prostate cancer in March of 2022. The Phase III VISION trial demonstrated improved radiographic progression-free survival (8.7 vs. 3.4 months, hazard ratio 0.40) and overall survival (15.3 vs 11.3 months, hazard ratio 0.62) for PSMA RLT in addition to best standard of care versus best standard of care alone [54]. In the Phase II TheraP trial PSMA RLT was associated with higher PSA response rate, longer progression-free survival, and fewer grade 3 or 4 adverse events when compared with cabazitaxel [55]. Both studies selected patients based on sufficient PSMA expression by PSMA-ligand PET/CT at baseline. Patients who do not meet the VISION PET inclusion criteria, specified in the section on assessment of PSMA expression prior to PSMA-directed RLT, have a poor outcome after PSMA RLT [56]. [68Ga]Ga-PSMA-11 PET was offered for baseline assessment in the VISION study.

The predictive value of PSMA-ligand PET/CT for survival following the initiation of PSMA RLT was demonstrated in a multicenter study. Among 18 pretherapeutic clinicopathologic and PSMA-ligand PET/CT variables, six were independently associated with overall survival [57]. Among these SUVmean of whole-body tumour burden, number of lesions, and the presence of bone or liver metastases were significant survival predictors derived from PET/CT [57]. Association of low PSMA expression or the presence of liver metastases on PSMA-ligand PET/CT with short survival has been confirmed by several studies on PSMA RLT, including trials with additional [18F]F-FDG PET for disease localization [58-61].

**Potential Clinical Applications**

Guidance of prostate biopsy

PSMA-directed prostate biopsy after previous negative MRI-guided or standard transrectal ultrasonography prostate biopsy in patients with high suspicion of prostate cancer.

Initial data indicate that PSMA-ligand PET may be valuable for guidance of repeated biopsy in patients with high suspicion of prostate cancer and prior negative biopsies as it has been shown to improve the localization of primary prostate cancer [62-64], and may add value for directed biopsies in the prostate cancer surveillance population who undergo repeated biopsies. In the prospective PRIMARY study, the addition of [68Ga]Ga-PSMA-11 PET to multiparametric MRI significantly improved the negative predictive value (91% vs. 72%, p<0.001) and the sensitivity (97% vs. 83%, p<0.001) for clinically significant prostate cancer [65]. Preferably PSMA-ligand PET should be combined with multiparametric MRI for this application to allow: (a) potential image-guided fusion biopsy using the MRI for anatomical correlation, and (b) the addition of information from multiparametric MRI to potentially increase the diagnostic confidence [62].

Imaging metastatic prostate cancer

Imaging assessment of metastatic prostate cancer typically includes bone scan for osseous metastases and CT or MRI for nodal, soft tissue, and visceral metastases. Several studies have demonstrated high diagnostic performance of PSMA-ligand PET/CT for staging of advanced prostate cancer [66, 67]. The diagnostic accuracy of PSMA-ligand PET/CT for bone assessment was superior to that of bone scan [68, 69]. When compared with conventional imaging, the superior accuracy of PSMA-ligand PET/CT allows for accurate identification of PCWG3 clinical trial target populations, especially in patient subgroups with nmCRPC or visceral metastatic disease [53]. In patients with oligometastatic disease, PSMA-PET-guided metastasis-directed treatment was associated with high rates of treatment response [70-72].

While PSMA-ligand PET/CT may be an emerging staging tool for metastatic prostate cancer, its impact on management and patient outcome has not yet been sufficiently assessed.

Monitoring of systemic treatment in metastatic prostate cancer

Despite the proven superiority of PSMA-ligand PET for prostate cancer staging, its role in monitoring treatment response remains less clear. Achieving an objective response to cancer treatment is a key endpoint of clinical research and practice. In metastatic prostate cancer, treatment response is currently evaluated using conventional imaging (CT and bone scan) according to the Prostate Cancer Working Group Criteria 3 (PCWG3) guidelines [46]. Several studies assessing different imaging readouts demonstrate the value of PSMA-ligand PET for assessment of prostate cancer response [73-79]. Recently, the PSMA PET Progression (PPP) criteria [80] and the Response Evaluation Criteria In PSMA-imaging (RECIP) 1.0 [79] were proposed for standardized response assessment. PPP criteria were formed by expert recommendation, whereas RECIP were additionally validated by overall survival in a multicenter cohort of patients undergoing 177Lu-PSMA RLT [79].

**Implementation in clinical guidelines**

Recommendations for prostate cancer staging in national and international clinical guidelines are under evaluation. PSMA-ligand PET/CT was included in various urology or oncology guidelines and consensus documents for imaging primary disease, BCR, BCP or metastatic prostate cancer. Recommendations were made following different guideline formats. Therefore, the wording of statements on the role of PSMA-ligand PET/CT are cited directly from the respective document text and summarized in **Table 2**. In the interest of brevity, **Table 2** does not present full statements or complete summaries of all available national and international guidelines. For full statements, background, strength of recommendations, or underlying evidence, we refer to the respective clinical guideline/consensus document.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Document led by** | **Initial staging** | **Localization of BCP** | **Localization of BCR** | **Metastatic\*** | **Reference** |
| EAU | “more accurate” | “offer” | “perform” | N/A | [45, 47, 48] |
| ESMO | “better sensitivity and specificity than CT or bone scan” | N/A | “replacing conventional imaging” | N/A | [81] |
| ASCO | “consider” | “should be offered” | “should be offered” | N/A | [82] |
| NCCN | “equally effective, if not more effective” compared to conventional imaging | “equally effective, if not more effective” compared to conventional imaging | “equally effective, if not more effective” compared to conventional imaging | N/A | [83] |

**Table 2: Wording of clinical guidelines on the value of PSMA-ligand PET/CT for primary, biochemical persistence (BCP), biochemical recurrence (BCR) and metastatic prostate cancer assessments.** N/A, not evaluated. \*PSMA-ligand PET/CT is required before PSMA-directed RLT.

Currently, several guidelines highlight the superior accuracy of PSMA-ligand PET for the staging of primary disease (EAU, ESMO, NCCN) or consider additional value (ASCO) in this setting. PSMA-ligand PET/CT evaluation of BCR/BCP is recommended in documents produced by the EAU, ASCO and NCCN. All documents summarized in **Table 2** recommend PSMA-ligand PET/CT for the localization of BCR or state superiority over conventional imaging in this setting. No recommendations were made for the assessment of advanced or metastatic prostate cancer outside pre-RLT staging.

**Qualifications and responsibilities of personnel**

See the EANM procedure guidelines for tumour PET imaging version 2.0 or the SNMMI Procedure Standard for General Imaging [10, 84].

**Procedure/specification of the examination**

**Necessary data for requesting PSMA-ligand PET/CT**

A request for PSMA-ligand PET/CT should be accompanied by a concise summary of the patient’s history with a focus on diagnosis, risk group, and oncological history. Aspects that should be considered in the review of the patient’s files are given in the following list:

1. Indication for imaging study
2. Prostate-cancer-specific history:
   1. Primary prostate cancer
      1. PSA and Gleason score
      2. Prior local intervention/biopsy
   2. Biochemical recurrence: PSA and PSA kinetics (if available)
   3. Current or prior prostate cancer treatments with dates: ADT or other AR-targeted treatments. Prior history of AR-targeted treatment, chemotherapy, radium-223, PSMA-targeted therapy, prostatectomy/surgery/biopsy, and/or radiation therapy.
   4. Relevant symptoms (e.g., bone pain, frequent urination, nocturia, hematuria, dysuria, impotence, erectile dysfunction or painful ejaculation)
   5. Previous imaging findings including previous PSMA-ligand PET and tracer subtype if known
3. Relevant co-morbidities:
   1. Non-prostate malignancies
   2. Allergies
   3. Renal failure

**Patient preparation**

Patients do not need to fast and may take all their medications. New onset of androgen deprivation therapy (ADT) was associated with decreased PSMA-ligand uptake on PET in patients with hormone-naïve or hormone-sensitive cancer, possibly due to effective tumour reduction [85, 86]. Therefore, PSMA-ligand PET/CT should be performed before the onset of new ADT whenever possible. The influence of second line androgen modulation in patients with castration-resistant disease has not been clearly defined yet. Signaling pathways and the temporal impact of androgen modulation on clinical PSMA-ligand PET/CT performance require further study.

Patients should be encouraged to drink a sufficient amount of water to ensure adequate hydration before the PET study. In some circumstances, high residual activity in the urinary system may lead to so called “halo-artefacts” in PET. For PSMA-ligands with kidney-dominant excretion (**Table 3**), activity in the ureters and bladder might lead to false positive or negative findings. Furosemide administration (20 mg i.v, shortly before or after administration of PSMA-ligands) may be especially useful in these situations. Furosemide should not be administered in patients with medical contraindications including urinary incontinence, urinary obstruction and hypersensitivity to furosemide. Alternatively, oral hyperhydration (1L) during the uptake time followed by bladder voiding immediately before image acquisition can be considered in patients with adequate bladder control.

**Hyperthyroidism and kidney failure**

PSMA-ligand PET/CT can be performed in patients with hyperthyroidism and kidney failure. However, if intravenous iodinated CT contrast is being considered for the CT protocol, thyroid and renal function should be considered. For details we refer to the European Society of Urogenital Radiology Contrast Media Guidelines in Europe [87] and to the American College of Radiology Manual on Contrast Media in the United States [88].

**Radiopharmaceuticals**

Several 68Ga- and/or 18F-labelled ligands have been developed and assessed in clinical trials [18-20, 25, 89-93]. The majority of current ligands in use are based on a urea-like binding motif and were designed for intravenous administration. **Table 3** summarizes PSMA-ligands that have been reported in the literature and are most advanced in the process of clinical implementation, and/or approval.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | **[68Ga]Ga-PSMA-11** | **[68Ga]Ga-PSMA-I&T** | **[18F]F-DCFPyL** | **[18F]F-PSMA-1007** | **[18F]F-rhPSMA-7.3** |
| Binding motif | Urea-based | Urea-based | Urea-based | Urea-based | Urea-based |
| Half-life | 68 min | 68 min | 110 min | 110 min | 110 min |
| Dominant excretion route | Kidney | Kidney | Kidney | Liver | Kidney |
| Published | 2012 [14] | 2015 [17, 94] | 2011 [13], 2015 [18] | 2016 [19] | 2020 [20] |
| Status | Extensive retrospective data; completed phase 2/3; Approved\* | Extensive retrospective data | Extensive retrospective data; completed phase 2/3; Approved\* | Extensive retrospective data; completed phase 2/3; Approved\* | Extensive retrospective data; under Phase 3 (NCT04186819 and NCT04186845) |

**Table 3: PSMA-ligands for PET/CT imaging.** Characteristics and current status. \*Refers to regulatory approval for clinical use and distribution on a national or international level.

PSMA-ligand PET/CT is performed using an approved product, within the confines of a research study, or on the basis of regulations for non-approved radiopharmaceuticals, respectively. Due to ongoing development, a non-complete overview of the current radioligand availability is summarized here:

[68Ga]Ga-PSMA-11, [18F]F-DCFPyL and [18F]F-PSMA-1007 were assessed in Phase II/III prospective clinical trials. Several new drug applications for [68Ga]Ga-PSMA-11 and [18F]F-DCFPyL were approved by the United States Food and Drug Administration in 2020 [95], 2021 [96, 97], and 2022[98]. Since the start of 2021, a [68Ga]Ga-PSMA-11 radiolabelling kit has been approved for clinical use by the Australian Therapeutic Goods Administration (TGA) [99]. [18F]F-PSMA-1007 is available under a type of expanded access in France [100]. Furthermore, multiple European institutions hold local manufacturing licenses for 68Ga- and 18F-based PSMA-ligands and [68Ga]Ga-PSMA-11 radiolabelling kits are available in several European countries. PSMA-ligands should be manufactured under Good Manufacturing Practice (GMP) conditions and quality control should follow the governing pharmacopoeia monograph or national regulations; whichever is applicable.

[68Ga]Ga-PSMA-I&T and [18F]F-rhPSMA-7.3 have been assessed extensively including published data on dosimetry and diagnostic performance. [18F]F-rhPSMA-7.3 is currently under phase III prospective clinical investigation (NCT04186819 and NCT04186845).

The committee further notes that tracer development is ongoing. Several novel low-molecular-weight ligands for human PSMA, including compounds with a different binding motif or radionuclide label, are under development (NCT04868604, NCT04838626 among others). Moreover, albumin binder conjugates are currently under development [101].

**PSMA-ligand application and administered activity**

The administration protocol is summarized in **Table 4**. PSMA-ligands are injected via intravenous bolus. Injected activity and uptake time have been defined in the prescribing information for [68Ga]Ga-PSMA-11, [18F]F-DCFPyL and [18F]F-PSMA-1007, and in clinical trial protocols for [18F]F-rhPSMA-7.3 (NCT04186819 and NCT04186845). For 68Ga-labelled ligands, variation in injected activity may be caused by the short half-life of 68Ga and variable elution efficiencies obtained during the lifetime of the 68Ge/68Ga radionuclide generator. Cyclotron produced gallium may help alleviate the issues related to low output of the 68Ge/68Ga radionuclide generator [102]. Flushing of the administration syringe should be done with at least the same volume of saline (NaCl 0.9 %) and subsequent emptying into the intravenous access is recommended to maximize use of the dispensed activity.

**Uptake time**

Recommended uptake time is around 60 min for most radioligands (**Table 4**). The interval between PSMA-ligand injection and imaging should be recorded. If the acquisition leads to indeterminate findings, a late scan, beyond 120 min, may be considered. Late scans may aid in the identification of lesions located near the ureter or the bladder [15].

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Item** | **[68Ga]Ga-PSMA-11** | **[68Ga]Ga-PSMA-I&T** | **[18F]F-DCFPyL** | **[18F]F-PSMA-1007** | **[18F]F-rhPSMA-7.3** |
| Activity | 111-259 MBq (3–7 mCi) | 111-259 MBq (3–7 mCi) | 296-370 MBq (8-10 mCi) | 210-280 MBq (3-4 MBq/kg body mass) | 296 MBq (8 mCi) |
| Uptake time | 60 min (acceptable range: 50 to 100 min) | 60 min (acceptable range: 50 to 100 min) | 60 min | 90-120 min | 60 min |
| Consider hydration\* and/or furosemide (20 mg intravenous) | yes | yes | yes | no | no |

**Table 4: Patient preparation and PSMA-ligand administration. \***e.g. oral intake of 1 L of water 1 h prior to acquisition.

**PET/CT acquisition protocol**

In accordance with [10], the patient should be positioned supine with both arms elevated above the head, as tolerated by the patient, to avoid beam-hardening artefacts in the abdominal and pelvic regions as well as artefacts caused by truncation of the measured field of view. If PET/CT data are used for radiation therapy planning, the examination should be performed in the exact position used for radiotherapy, employing the same positioning devices as are used by the radiotherapy department whenever feasible (e.g. the same radiotherapy table top, laser alignment, immobilization procedures).

The CT scan should be performed from the vertex to mid-thigh, followed by the PET acquisition (described below). CT acquisition parameters (e.g. kV, mAs, pitch in helical CT, dose modulation etc.) should be in accordance with institutional protocols. The CT protocol may be modified according to clinical requirements. For instance, the skull should be included in patients with known metastatic disease. In the case of focal symptoms or disseminated disease, coverage may be extended to include the respective body part. Additional acquisitions (e.g. deep inspiration chest CT) may be performed. If intravenous CT contrast is used, contrast-enhanced CT in the portal venous phase after intravenous injection of contrast agent in cases where there is no contraindication for contrast media.

PET-acquisition should start from the mid-thigh and extend to the vertex to exploit reduced PSMA-liganduptake in the urinary system after pre-scan voiding.Acquisition should proceed from the lower end of the axial field of view cranially to minimize misalignment of the urinary bladder, which tends to fill up during the time of the examination in patients with hydration procedures. PET scans are acquired in 3D-mode with an acquisition time of usually 1-4 min per bed position (or equivalent speed using continuous table movement) adjusted to the injected activity [103]. Overall, PET coverage should be identical to the anatomical CT scan range.

**PET/CT image reconstruction**

Image acquisition should be performed in 3D mode with appropriate data corrections (attenuation correction, scatter correction, correction for random coincidences). The diagnostic CT scan may be used for attenuation correction. PET reconstruction should be performed with and without attenuation correction to identify potential reconstruction artefacts caused by the correction algorithm [10]. Reconstructed images should be labelled accordingly (e.g., PET AC, PET NAC, CT CE) and stored in the local picture archiving and communication system. An example of a PSMA-ligand PET/CT protocol is given in **Table 5.**

|  |  |
| --- | --- |
| Patient position | Arms elevated above the head, supine |
| CT protocol | FOV: vertex to mid-thigh; Optional contrast phase: portal venous |
| PET protocol | FOV and acquisition: start from mid-thigh to vertex |
| PET reconstruction | ordered-subsets expectation maximization; attenuation correction from CT data |

**Table 5: Example protocol for PSMA-ligand PET/CT image acquisition and reconstruction. FOV, field of view.**

**Definitions of volumes of interest**

SUV can be normalized to body mass, lean body mass, or body surface area, and may change significantly between different modes of normalization. Therefore, the same mode should be used for serial examinations. The recommended tumour uptake metric is the maximum SUV (SUVmax), which can be measured and documented for key lesions. Quality control steps should be undertaken on a regular basis to minimize SUV measurement errors and to maintain image quality associated with PET/CT scanner equipment.

**Quality control and inter-institution performance harmonization**

Clinical interpretation of PSMA-ligand PET/CT is based on visual analysis. Semi-quantitative SUV can be measured and documented for selected lesions. Reproducibility and image quality are of critical importance especially for communication between different centers. A consistent PET/CT scanner quality control program contributes to the minimization of measurement errors and helps maintain high image quality.

Quality assurance should include (a) daily quality control and calibration measurements of both the PET and CT components of the imaging system as previously described in the EANM Procedure guidelines for [18F]F-FDG tumour imaging [10] and (b) cross-calibration of the PET/CT system. Procedures for calibration and cross-calibration have been published for both 18F-based [104, 105] and 68Ga-based [106] PET/CT. Guidance is also provided by the PET/CT manufacturer, UPICT oncology [18F]F-FDG PET/CT protocol [107] and EANM Research Ltd (EARL, Vienna, Austria) accreditation frameworks.

**Normal uptake**

Normal and variable PSMA-ligand uptake can be found in the following tissues: lacrimal gland, salivary glands, liver, gall bladder, spleen, small intestine, colon and kidney (**Figure 1**).

Usually, tumour lesions inside and outside the prostate gland show a high tumour-to-background ratio compared with the surrounding tissue [15, 62]. [68Ga]Ga-PSMA-11, [68Ga]Ga-PSMA-I&T and [18F]F-DCFPyL are excreted primarily via the urinary system and collected in the bladder; a small proportion is cleared through the hepatobiliary system. Thus, small local recurrences might be missed if the SUV-threshold to judge the PSMA-ligand uptake in soft-tissue structures near the urinary bladder is not adjusted properly. Hydration and/or application of furosemide and/or repeat late acquisition may be useful in such cases.

[18F]F-PSMA-1007 shows higher liver and gall bladder accumulation due to hepatobiliary excretion and no or only minimal excretion via the urinary system [108]. Liver uptake is also higher with [18F]F-rhPSMA-7.3 than with 68Ga-PSMA-11 and excretion is mainly via the urinary tract. However, retention in the urinary system is usually low at the time of imaging and can be further lowered by application of furosemide [20, 109].

Approximately 5% of all prostate cancers, especially neuroendocrine types, do not exhibit significant PSMA overexpression [110, 111]. Owing to high background activity in the liver, potential liver metastases can be obscured. As neuroendocrine liver metastases often lose PSMA-expression, cross-sectional imaging is important for liver assessment [112-114].

**Important pitfalls**

A large number of case reports present imaging findings in PSMA-ligand PET not associated with prostate cancer. Different reviews outline the most important pitfalls and try to give evidence on their biological bases [115-117]. Immunohistochemical and PSMA-ligand PET data have shown that increased PSMA-expression can also be found in the neovasculature of non-prostate solid tumours or in benign processes [1, 118-122]. An important pitfall is PSMA-ligand uptake in ganglia of the autonomic nervous system. Pronounced tracer accumulation can be found especially in the celiac ganglia, which are prone to misinterpretation as retroperitoneal lymph node metastases [123]. For 18F-labelled PSMA-ligands, visually recognizable uptake is also reported for other ganglia, especially in the sacral and cervical regions [23, 124, 125]. Ganglia can be differentiated from lymph node metastases by location (adjacent to neuroforamina) or shape (often linear or comma-shaped) [126].

Using the 18F-labelled compounds [18F]F-PSMA-1007 and [18F]F-rhPSMA-7.3, interpretation of bone lesions is more challenging compared to [68Ga]Ga-PSMA-11 [23, 125, 127, 128]. A number of benign bone lesions accumulate PSMA and result in false positives on PSMA-PET/CT, including fractures, osteophytes, benign bone lesions (fibrous dysplasia, hemangioma) or unknown etiology. In the literature, clinically insignificant bone uptake was reported as unspecific bone uptake (UBU, [128]) or non-specific bone lesions (NSBU, [127]), and the nature of these lesions was mainly assessed by clinical follow-up with histological verification performed in few cases. Characteristic CT or MRI findings of benign lesions can help interpretation and comparison to any available previous studies should be performed. In separate matched-pair comparisons with [18F]F-PSMA1007, [18F]F-DCPyL and [68Ga]Ga-PSMA11 demonstrated lower rates of equivocal skeletal findings [23, 129].

Typical locations for PSMA-avid benign bone lesions are the ribs and pelvis and the intensity of tracer uptake is generally lower than for bone metastases. However, definite discrimination by quantitative measurement is not possible. In the case of single lesions (especially in the ribs) and the absence of a definite morphological correlate typical for malignancy, interpretation of a metastasis should be cautious to avoid over-staging. Consequent application of PROMISE criteria for image interpretation can help to avoid false positives [130].

Some studies have shown that AR inhibition can increase PSMA expression in prostate cancer lesions [131, 132]. However, the extent of this upregulation and its exact timing are not completely understood. Time interval to PET/CT must be considered to prevent falsely defining disease progression shortly after initiation of AR-targeted therapies. The increase in PSMA-ligand uptake might be transient, since it is more visible during the first weeks of ADT and has a tendency to decrease over time [85].

**Complementary information**

Comparison with previous examinations should be part of the eachPSMA-targeted PET report. Assessment is more valuable if the examination is interpreted in the context of other imaging examinations (bone scan, CT, PET/CT, MRI, etc.) and clinical data.

**Documentation and reporting**

Study identification

The final report should include the full name of the patient, medical record number, date of birth and date of the examination.

Clinical information

At a minimum, the clinical history should include the diagnosis and a brief treatment history, reason for referral and the specific question to be answered. If relevant, the results of adequate diagnostic tests, especially PSA level and prior imaging findings, should be summarized. If the study is being done to assess treatment response, details of the most recent treatment regime (including start/stop dates and agent) should be provided. The type and date of comparison studies should be stated. If no comparison studies are available, a statement should be made to that effect.

Technical details

As recommended previously [10], study-specific information should include the radiopharmaceutical, the amount of injected activity in megabecquerels (MBq) and/or millicuries (mCi), the route (intravenous) and anatomical site of administration, the date and time of administration and the time of any furosemide injection. The time interval between administration of the PSMA-ligand and the start time of the acquisition should be reported. The part of the body that was covered should be described from the start to the end point. The position of the patient (supine or prone) and the position of the arms (elevated or by the sides) should be stated if non-standard.

Description of the CT part of the examination may be limited to a statement that a low-mAs CT was performed for attenuation correction and anatomical registration of the emission images. If the CT examination was optimized for diagnosis, then a more complete description of the CT protocol and anatomical findings should be provided. Dosimetry parameters should be included as required by local regulations. The report should state whether CT with or without CT contrast agent was used for CT attenuation correction.

Quality issues of the PSMA-ligand PET/CT study, for example, limited due to motion artefacts, potential halo-artefacts due to high activity in the collecting urinary system or the bladder, CT-related artefacts (from radiation attenuating matter/materials e.g. metals, especially hip prostheses which generate beam hardening and affect pelvic visualization) should be mentioned [10].

Description of the location, extent and intensity of PSMA-ligand uptake

In the general review, attention should be paid to the prostate gland/bed, seminal vesicles, vas deferens, regional and distant lymph nodes, bones, lungs and liver. Regions that may relate to any symptoms recorded on referral forms should also be given specific attention. PSMA-ligand accumulation should be reported as low, moderate or intense by comparison to the background uptake [133] and semi-quantitative values may be reported. Deviations from the physiological tracer distribution should be described, particularly in the kidneys, where clinically relevant renal dysfunction/pathology may be unveiled. PSMA-ligand uptake in incidental findings not related to prostate cancer, such as synchronous malignancies, should also be reported. Tumour lesions usually appear as focal tracer uptake higher than the adjacent background. Frameworks for standardized reporting of PSMA-ligand PET/CT have been developed (see below).

Standardized reporting

Standardized reporting is increasingly applied for diagnostic procedures [134]. To date, a number of these systems have been developed to assess lesions in specific organs (e.g. breast, liver, thyroid, prostate). These classifications are usually based on a 5-point (Likert) scale that concords with the probability of a lesion being benign or malignant. In the context of PSMA-ligand PET/CT, a number of frameworks for standardized reporting have been proposed and will undergo modifications over time. Current frameworks are summarized in the following sections.

EANM Delphi Consensus

In 2017, Fanti, et al. [135] published the first effort towards a standardized interpretive approach to PSMA-ligand PET. Seven different readers each provided interpretations of the [68Ga]Ga-PSMA-11 PET/CT scans from 49 patients with BCR. Multiple rounds of Delphi consensus were performed until final agreement was reached. Those final agreements were used as a basis for consensus guidelines on the interpretation of [68Ga]Ga-PSMA-11 PET/CT. The guidelines included (1) that all sites of unexpected increased radiotracer uptake should be reported as “anomalous”, (2) that any anomalous findings should be categorized as “pathologic” if they are suggestive of prostate cancer, and (3) a series of additional and general recommendations for aspects of the final report.

PSMA reporting and data system (PSMA-RADS)

PSMA-RADS proposed in 2018 falls under the umbrella of MI-RADS, a generalizable framework for the interpretation of PET scans utilizing targeted theranostic radiotracers [136]. This reporting system follows the basic structure of other RADS approaches, such as BI-RADS or PI-RADS [136]. Its goal is to convey the imaging specialist’s level of confidence regarding the presence of prostate cancer at both the individual lesion and the scan level, and also to offer recommendations regarding the potential need for any additional work-up. PSMA-RADS includes diagnostic criteria for a series of categories (1, 2, 3, 4 or 5) as well as subcategories (1A, 1B, 3A, 3B, 3C, and 3D). These categories represent increasing likelihood of the presence of prostate cancer, with PSMA-RADS-1 indicating definitively benign findings and PSMA-RADS-5 indicating the definitive presence of prostate cancer. The indeterminate nature of PSMA-RADS-3 lesions has been validated [137] and the system has high inter-reader agreement [138].

Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE)

Also, in 2018, the PROMISE system was proposed as a standardized framework for the evaluation of PSMA-ligand PET [130]. It defines molecular imaging TNM (miTNM) regions and subregions for whole-body staging, similar to the existing pathological/clinical TNM system. PROMISE organizes findings in comprehensible categories to report the location of prostate cancer throughout the body including disease distribution pattern and PSMA expression score. Local tumour is described from miT0 (i.e. absence of local recurrence following local therapy) to miT2 through miT4 for tumoral extent in individuals with intact prostates. Pelvic nodal involvement is categorized as miN1 or miN2 depending on the number of pelvic nodal regions involved. Lastly, extrapelvic metastases are indicated by miM1a, miM1b, or miM1c depending on whether extra-pelvic nodes, bone, or viscera are involved, respectively. miM1b is further divided into unifocal, oligometastatic, disseminated, or bone marrow carcinomatosis.

E-PSMA

Supported by the EANM, an evolution of the earlier Delphi consensus document was developed by a panel of worldwide experts who provided consensus statements for standardized reporting of PSMA-ligand PET [139]. Panelists were selected based on their expertise and publication record in the diagnosis or treatment of prostate cancer, their involvement in clinical guidelines, and according to their expertise in the clinical use of PSMA-ligands. Statements were formed as part of a Delphi consensus process. E-PSMA provides an overview of the experts´ opinion regarding what needs to be included in a report, what different systems for reporting exist, and what is important to report in different clinical settings. Finally, the panelists’ recommendations were summarized in a structured report for PSMA-ligand PET including elements from the PROMISE and RADS systems [130, 136].

The PRIMARY score for prostate cancer diagnosis

Emmett et al assessed patterns of intra-prostatic PSMA and proposed a 5-point PRIMARY score for PSMA-ligand PET/CT detection of prostate cancer. In a prospective multi-center phase II study the PRIMARY score identified clinically significant prostate cancer with high accuracy and inter-reader agreement [140].

Assessment of PSMA expression prior to PSMA-directed RLT

To evaluate eligibility for PSMA-targeted RLT, the following information should be reported: (1) overall visual uptake intensity of prostate cancer lesions in reference to liver ([68Ga]Ga-PSMA-11, [68Ga]Ga-PSMA-I&T, [18F]F-DCFPyL, [18F]F-rhPSMA-7.3) or spleen ([18F]F-PSMA-1007). Uptake greater than that of the reference organ parenchyma will be regarded as positive. Uptake equal to or lower than that of the reference organ in any lymph node with a short axis of at least 2.5 cm or any metastatic soft tissue lesion with a short axis of at least 1.0 cm (for organ and bone with soft-tissue component) will be regarded as negative, in accordance with VISION criteria [141]. Location and extent of PSMA-negative lesions should also be reported. Information on prostate cancer SUV and number of lesions provides additional prognostic information [57].

Assessment of response to therapy

Two proposed frameworks can be used for assessment of response, although there are limitations on the use of these frameworks for hormone-based therapies. PSMA PET Progression (PPP) criteria were proposed based on expert recommendations [80]. PPP criteria include assessment of biochemical or clinical progression along with PSMA-ligand PET lesion count.

The Response Evaluation Criteria In PSMA-imaging (RECIP) were proposed to evaluate drug efficacy using PSMA-ligand PET in metastatic castration-resistant prostate cancer patients [79]. The RECIP design is based on findings from a multicenter analysis of RLT outcomes. Whereas PPP relies on the appearance of new lesions or biochemical or clinical progression, RECIP assesses new lesions along with changes in total PSMA tumour volume. Both frameworks were recently proposed and may need additional validation before widespread implementation. A summary of the PPP and RECIP criteria is presented in **Table 6**.

|  |  |
| --- | --- |
| **Criteria** | **Definition** |
| ***PPP [80]*** |  |
| Progressive Disease | 1. Appearance of ≥2 new PSMA-positive distant lesions   or  **b)** Appearance of 1 new PSMA-positive distant lesion plus consistent clinical and/or laboratory data (including changes in serum PSA, Lactate Dehydrogenase, Alkaline phosphatase levels or ECOG score)  or  **c)** Increase in size or PSMA uptake of ≥1 existing lesions by 30% plus consistent clinical and/or laboratory data |
| ***RECIP 1.0*** [79] |  |
| Complete Response | Absence of any PSMA-uptake on follow-up PET scan |
| Partial Response | ≥30% decrease in PSMA-VOL without appearance of new lesions |
| Progressive disease | ≥20% increase in PSMA-VOL with appearance of new lesions |
| Stable disease | Does not meet the above criteria |

**Table 6. Summary of the PPP and RECIP criteria for PSMA-ligand PET/CT based response assessment.** PSMA-VOL, PSMA-ligand PET derived tumour volume.

It should be noted that assessments of disease progression at early time points following the initiation of androgen-axis-targeted agents can be difficult because the upregulation of PSMA as a result of the interruption of androgen signaling may change the tracer uptake and the apparent extent of disease [142, 143]. As a result, the current proposed response assessment criteria may be of greater value when used at later times of a given systemic therapeutic approach [144].

Summary and diagnosis/impression

Scan interpretation of PSMA-ligand PET studies must be clearly defined as normal or abnormal. Alternatively, a qualitative estimate of the likelihood of a diagnosis and the differential diagnoses should be given. The question asked in the study referral should be directly addressed [10]. For prostate cancer imaging, it is recommended to structure the summary to the main tumour sites (local tumour involvement, lymph node or bone metastases) and potential other lesions. Standardized reporting should be applied for disease location and certainty of diagnosis [130, 135, 136, 139].

**Radiation exposure to the patient**

Radiation exposure from the radiopharmaceutical (**Table 7**) and the CT study contribute to the total radiation dose with PSMA-ligand PET/CT. The mean dose for a CT scan is variable and depends on the protocol and CT hardware. Recent advances in CT technology have allowed for significant radiation dose reduction attributable to that component.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **[68Ga]Ga-PSMA-11** | **[68Ga]Ga-PSMA-I&T** | **[18F]F-DCFPyL** | **[18F]F-PSMA-1007** | **[18F]F-rhPSMA-7.3** |
| Reference |  | [145] | [17] | [146] | [108] | [147] |
| **Effective dose coefficient** | **mSv/MBq** | **0.0169** | **0.0199** | **0.0116** | **0.022** | **0.014** |
| Urinary bladder wall | mGy/MBq | 0.0982 | 0.0674 | 0.0072 | 0.0187 | 0.012 |
| Kidneys | mGy/MBq | 0.3714 | 0.22 | 0.123 | 0.170 | 0.172 |

**Table 7. Radiation dosimetry for PSMA-ligands.**

Based on the available studies (**Table 7**), the coefficient for effective dose from PSMA-ligand application ranges from 0.0116 to 0.022 mSv/MBq resulting in an average effective radiation dose of 3.4 / 4.0 mSv for 200 MBq [68Ga]Ga-PSMA-11 / [68Ga]Ga-PSMA-I&T, or 3.5 / 6.6 / 4.2 mSv for 300 MBq [18F]F-DCFPyL / [18F]F-PSMA-1007 / [18F]F-rhPSMA-7.3. The radiation exposure related to a CT scan carried out as part of a PSMA-ligand PET/CT study depends on the intended use of the CT. Depending on the protocol (low-dose CT and/or diagnostic CT), the effective CT dose ranges from 1 to 20 mSv. Guidelines provided by radiological societies should be consulted regarding effective dose from the CT examination. Given the variety of CT hardware and protocols, the radiation exposure for a PSMA-ligand PET/CT study should be calculated specifically for a given protocol.

**Liability Statement**

This guideline summarizes the views of the EANM Oncology&Theranostics Committee and SNMMI. It reflects recommendations for which the EANM/SNMMI 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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**FIGURES**



**Figure 1. Normal body distribution of PSMA-ligands.** [68Ga]Ga-PSMA-11, [68Ga]Ga-PSMA-I&T, [18F]F-DCFPyL, and [18F]F-rhPSMA-7.3 applications lead to notable kidney uptake. Bladder retention is high for [68Ga]Ga-PSMA-11, [68Ga]Ga-PSMA-I&T and [18F]F-DCFPyL and lower for [18F]F-rhPSMA-7.3. Reference organs for ligands with kidney-dominant excretion are liver and parotid gland. [18F]F-PSMA-1007 leads to high liver uptake due to hepatic excretion. Reference organs for ligands with liver excretion are spleen and parotid gland.

Focal uptake in the pelvic bone is noted on [18F]F-rhPSMA-7.3 PET corresponding to metastatic disease. [68Ga]Ga-PSMA-I&T subpart was modified with permission from [130].