

**<sup>68</sup>Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for  
prostate cancer imaging: version 1.0**

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## **ABSTRACT**

The aim of this guideline is to provide standards for the recommendation, performance, interpretation and report of <sup>68</sup>Ga-PSMA PET/CT for prostate cancer imaging. These recommendations will help to improve accuracy, precision and repeatability of <sup>68</sup>Ga-PSMA PET/CT for prostate cancer essentially needed for implementation of this modality in science and routine clinical practice.

**Preamble**

The Society of Nuclear Medicine (SNM) 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 nonprofit medical association that facilitates communication worldwide between individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985. SNM and EANM members are physicians, technologists, and scientists specializing in the research and practice of nuclear medicine.

The SNM 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 SNM/EANM, has undergone a thorough consensus process in which it has been subjected to extensive review. The SNM 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 SNM 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**

<sup>68</sup>Ga-PSMA positron emission tomography/computed tomography (PET/CT) is a non-invasive diagnostic technique to image prostate cancer with increased prostate-specific membrane antigen (PSMA, glutamate carboxypeptidase II, EC 3.4.17.21) expression. PSMA is a membrane protein primarily present in all prostatic tissues. Increased PSMA expression is seen in a variety of malignancies, however most notably in prostate cancer [1]. Nearly all adenocarcinomas of the prostate demonstrate PSMA expression in the majority of primary and metastatic lesions [2-3]. Immunohistochemical studies have shown that PSMA

expression increases in case of de-differentiated, metastatic or hormone-refractory disease [4] and its expression level is a significant prognosticator for disease outcome [5].

<sup>68</sup>Ga is most often obtained from a <sup>68</sup>Ge/<sup>68</sup>Ga generator system. <sup>68</sup>Ga decays with 89% yield by positron emission and has a half-life of 67.63 min. Several low-molecular-weight ligands for human PSMA, linked with a chelator for <sup>68</sup>Ga complexation, are clinically available for PET/CT imaging. <sup>68</sup>Ga-labeled PSMA ligands were first radiosynthesized and validated in preclinical models at Johns Hopkins University [6]. Later, <sup>68</sup>Ga-PSMA-11 was developed by the Heidelberg group [7]: Eder et al demonstrated high affinity to human PSMA and specific internalization into prostate cancer cells. <sup>68</sup>Ga-PSMA-11 biodistribution was shown to correspond well to known cellular expression of PSMA across organs [8]. Other ligands (<sup>68</sup>Ga-PSMA-617, <sup>68</sup>Ga-PSMA-I&T) demonstrated similar distribution and imaging properties [9-10]. Due to their similarity <sup>68</sup>Ga-PSMA-11, <sup>68</sup>Ga-PSMA-617, and <sup>68</sup>Ga-PSMA-I&T will henceforth be abbreviated <sup>68</sup>Ga-PSMA. PET surrounds the patient with a ring of detectors capable of detecting the photons produced by the positron/electron annihilation that follows positron emission. PET measures the three-dimensional distribution of <sup>68</sup>Ga-PSMA, producing quantitative images that allow for non-invasive assessment of PSMA expression.

## Goals

This guideline intends to assist physicians in recommending, performing, interpreting and reporting the results of <sup>68</sup>Ga-PSMA PET/CT for initial diagnosis, staging and restaging of prostate cancer. It covers patient selection, image acquisition, interpretation and reporting. This document aims to provide clinicians with the best available evidence, to inform where robust evidence is lacking, and to help them to deliver the best possible diagnostic quality study for their patients.

This guideline also presents standardized quality control (QC)/quality assurance (QA) procedures and imaging procedures for static <sup>68</sup>Ga-PSMA PET/CT [11]. Adequate precision,

accuracy, repeatability, and reproducibility are essential for the clinical management of patients and the use of <sup>68</sup>Ga-PSMA PET/CT within multicenter trials. A standardized imaging procedure will help to promote the appropriate use of <sup>68</sup>Ga-PSMA PET/CT and enhance subsequent research. Quantification of <sup>68</sup>Ga-PSMA PET/CT is defined here as measuring relative PSMA concentrations using standardized uptake value (SUV) [12] because the SUV represents the most commonly used semi-quantitative parameter for analysis of tracer uptake. It has to be highlighted that for Ga-labeled PSMA-ligands the amount of data dealing with quantification is sparse.

### **Definitions**

**PET/CT:** An integrated or multimodality PET/CT system is a physical combination of PET and CT which allows sequential acquisition of PET and CT portions. The patient remains in the same position within both examinations. A <sup>68</sup>Ga-PSMA 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:** Base of the skull to mid-thigh. Covers most of the relevant portions of the body in many oncological diseases (standard for both Europe and the US). If indicated, cranially extended imaging may also cover the brain in the same scan (vertex to mid-thigh). In PET/CT studies, attenuation correction and scatter correction are performed using the CT data.

**Computed tomography (CT)** applies a combined X-ray source and detector rotating around the patient to acquire tomographic data. CT generates three-dimensional images of tissue density, which allows for attenuation correction of PET and tumor 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: CT scan that is 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 a priori for a dedicated radiological interpretation.

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

### **Appropriateness of Use Criteria**

It should be highlighted that data from prospective multicenter trials are not yet available. For interested readers, Perera et al provided a meta-analysis of the literature available to date on <sup>68</sup>Ga-PSMA PET/CT for recurrent and primary prostate cancer [13]. The criteria outlined in this article are based on the currently available evidence, the current use and experience of <sup>68</sup>Ga-PSMA PET/CT shared by the authors. Currently, the specific use varies between institutions, mainly based on experience and availability of the <sup>68</sup>Ga-PSMA ligand.

#### 1. Localization of tumor tissue in recurrent prostate cancer

Most studies, mainly retrospective data, are available on the use of <sup>68</sup>Ga-PSMA PET/CT for localization of prostate cancer in the setting of biochemical recurrence [8-9, 14-20]. Here, the use is especially recommended in patients with low PSA-values between 0.2 and 10 ng/ml to identify the site of recurrence and to potentially guide salvage therapy. Higher sensitivities are noted in patients with shorter PSA doubling times and those with higher initial Gleason scores [20].

#### 2. Primary staging in high-risk disease before surgical procedures or planning external beam radiation

In patients with high-risk disease (Gleason score >7, PSA >20 ng/ml, clinical stage of T2c – 3a) the likelihood of lymph node and bone metastases is increased. Several studies demonstrate the superiority of <sup>68</sup>Ga-PSMA PET/CT as compared to CT, MRI or bone scan for

detection of metastases for initial staging at primary diagnosis [21-24]. The detection of radiologically occult lymph node metastases can significantly influence patient management, although the impact on overall survival of improved sensitivity by <sup>68</sup>Ga-PSMA PET/CT remains unanswered. A contrast enhanced <sup>68</sup>Ga-PSMA PET/CT can replace abdominopelvic CT for the detection of lymph node metastases. In addition, preliminary data show that <sup>68</sup>Ga-PSMA PET/CT is also more accurate for detection of bone metastases [24]. Nevertheless, for local tumor delineation (if requested by the urological surgeon) pelvic MRI cannot be replaced. It is still under investigation and discussion whether additional functional imaging by bone seeking agents (e.g. bone scintigraphy, <sup>18</sup>F-NaF PET/CT) has relevant additional value after performance of <sup>68</sup>Ga-PSMA PET/CT, e.g. in patients with PSMA-negative tumors or densely sclerotic bone lesions.

### **Emerging Clinical Applications**

#### 1. Staging before and during PSMA-directed radiotherapy (mainly in metastatic castration-resistant prostate cancer)

Imaging before PSMA-directed therapy (e.g. radioligand therapy) is crucial to determine the presence and intensity of target-expression [25-28]. Low PSMA-expression in target lesions poses a contraindication for radioligand therapy. Of note, <sup>68</sup>Ga-PSMA PET can be false negative in up to 5% of patients with prostate cancer. In addition, it has been reported that in advanced metastatic castration-resistant prostate cancer, metastases (mainly in the liver) can lose PSMA-expression [29-31].

#### 2. Targeted biopsy after previous negative biopsy in patients with high suspicion of prostate cancer

Initial data indicate <sup>68</sup>Ga-PSMA 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 add in localization of primary prostate cancer [32-33], and may add value for directed biopsies in the prostate cancer surveillance population who undergo repeated



biopsies. Preferably <sup>68</sup>Ga-PSMA PET should be combined with multiparametric MRI for this application to allow for a) potential image-guided fusion biopsy using the MRI for anatomical correlation and b) adding information from multiparametric MRI to potentially increase the diagnostic confidence [32].

### 3. Monitoring of systemic treatment in metastatic prostate cancer

RECIST 1.1 is limited by the high prevalence of non-measurable lymph node and bone metastases. Bone scan is limited by a potential flare phenomenon. Monitoring of systemic disease might become a potential application for <sup>68</sup>Ga-PSMA PET/CT. However, whether <sup>68</sup>Ga-PSMA PET/CT overcomes limitations of other modalities and proves superior has not been demonstrated yet [34].

#### **Regulatory issues**

As of December 2016, no <sup>68</sup>Ga-PSMA tracer has been approved by the European Medicines Agency or the United States Food and Drug Administration. <sup>68</sup>Ga-PSMA imaging is usually performed within the confines of a research study or on basis of regulations for non-approved radiopharmaceuticals.

#### **Qualifications and responsibilities of personnel**

See European Association of Nuclear Medicine procedure guidelines for tumor PET imaging or the Society of Nuclear Medicine and Molecular Imaging Procedure Standard for General Imaging [35-36].

#### **Procedure/specification of the examination**

##### **Necessary data for requesting <sup>68</sup>Ga-PSMA PET/CT**

Request for <sup>68</sup>Ga-PSMA PET/CT should be accompanied by a concise summary of the patient's history with focus on diagnosis, risk group, 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:
  - a. Primary prostate cancer
    - i. PSA and Gleason score
  - b. Biochemical recurrence:
    - i. PSA and PSA kinetics
    - ii. Prior treatment (e.g. prostatectomy, external beam radiation therapy)
  - c. Current prostate cancer medications: Androgen Deprivation Therapy (ADT) or other AR targeted treatments.
  - d. Relevant symptoms (bone pain, frequent urination, nocturia, hematuria, dysuria, impotence, erectile dysfunction or painful ejaculation)
  - e. Previous imaging findings
3. Relevant co-morbidities:
  - a. Non-prostate malignancies
  - b. Allergies
  - c. Renal failure

### **Patient preparation**

Patients do not need to fast and are allowed to take all their medications. Preclinical data indicate that PSMA-expression is increased in castration-resistant prostate cancer and under ADT [37-39]. However, the clinical impact of ADT on <sup>68</sup>Ga-PSMA PET/CT performance requires further study.

Patients should be well hydrated before the study and during the uptake time (e.g. oral intake of 500 mL of water during a 2 h period prior to acquisition). Voiding immediately before imaging acquisition is recommended. Despite this, in some circumstances, high residual activity in the urinary system might lead to so called “halo-artefacts” in PET (Figure 1). Activity in ureters might lead to false positive findings. Furosemide administration (20 mg

i.v, shortly before or after administration of <sup>68</sup>Ga-PSMA) may be especially useful in these situations. Furosemide should not be administered in patients with medical contraindications to furosemide administration including allergies (e.g. sulfa allergies).

### **Hyperthyroidism and kidney failure**

<sup>68</sup>Ga-PSMA 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 taken into account. For details we refer to the European Society of Urogenital Radiology Contrast Media Guidelines [40].

### **Radiopharmaceuticals**

Products: <sup>68</sup>Ga-PSMA-11 [7], <sup>68</sup>Ga-PSMA-617 [41], <sup>68</sup>Ga-PSMA-I&T [42]; in this manuscript all referred to as <sup>68</sup>Ga-PSMA

Nuclide: [<sup>68</sup>Ga], Gallium-68

Dosage/activity: 1.8-2.2 MBq (0.049-0.060 mCi) per kilogram bodyweight

Administration: Intravenous

<sup>68</sup>Ga-PSMA should be manufactured under Good Manufacturing Practice (GMP) conditions and quality control should follow the governing pharmacopoeia monograph or national regulations; whichever is applicable. The committee further notes that tracer development is ongoing and <sup>18</sup>F-labeled probes are currently under evaluation.

### **Recommendations for <sup>68</sup>Ga-PSMA application and administered activity**

<sup>68</sup>Ga-PSMA is injected as intravenous bolus. Currently optimal injected activity is still under debate. Majority of published data is based on an injected activity of approximately 1.8-2.2 MBq per kilogram body weight. Variation of injected activity may be caused by the short half-life of <sup>68</sup>Ga and variable elution efficiencies obtained during the lifetime of the <sup>68</sup>Ge/<sup>68</sup>Ga radionuclide generator. Low output of the <sup>68</sup>Ge/<sup>68</sup>Ga radionuclide generator could pose a major limitation in institutions with high demand as it decreases the number of patients that

can be examined per <sup>68</sup>Ga-elution and subsequent <sup>68</sup>Ga-PSMA production. Flushing of the administration syringe should be done with at least the same volume of saline (NaCl 0.9 %) and subsequent emptying into the i.v. access is recommended to maximize use of dispensed activity.

### **Uptake time**

A 60 min interval is recommended for uptake time with an acceptable range of 50 to 100 minutes [8]. Increased lesion detection has been reported with delayed imaging up to 3-4 hours after injection [8]. However uptake times of greater than 100 min raise concerns with regard to practicality and necessary patient activity in view of the radiotracer half-life. The interval between <sup>68</sup>Ga-PSMA injection and imaging should be recorded. If the 1 hour scan leads to indeterminate findings, a late scan at 3 hours p.i. may help to identify lesions in close proximity to the ureter or the bladder [8], or lesions with a low PSMA expression and slower accumulation of the tracer.

### **PET/CT acquisition protocol**

The patient should be positioned 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 (FOV). 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 in the radiotherapy department (e.g. the same radiotherapy table top, laser alignment, immobilization devices and measures).

CT scan should be performed from the skull-base to mid-thigh followed by the PET acquisition. CT acquisition parameters (such as 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, if there are focal symptoms or

disseminated disease, coverage may be extended to include the entire lower extremity and/or the skull. Additional acquisitions (such as deep inspiration chest CT) may be performed. If intravenous CT contrast is used, contrast-enhanced CT in the portal venous phase 80 s after intravenous injection of contrast agent (1.5 ml per kilogram bodyweight, maximum 120 ml) and during shallow breathing is recommended in case of no contraindication for contrast media.

PET-acquisition should start from the mid-thigh to the base of the skull-base to exploit the reduced <sup>68</sup>Ga-PSMA ligand uptake in the urinary system after pre-scan voiding. Acquisition should proceed from the lower end of the axial field of view cranially in order to minimize misalignment for the urinary bladder which tends to fill up during the time of the examination. PET scans are acquired in 3D-mode with an acquisition time of usually 3-4 min per bed position. Overall, PET coverage should be identical to the anatomical CT scan range.

### **PET/CT image reconstruction**

Image acquisition should be performed in 3D acquisition mode with appropriate data corrections (attenuation correction, scatter correction, correction for random coincidences). The diagnostic CT scan may be used for attenuation correction. The presence of a positive contrast agent minimally impacts visual PET image quality and interpretation [35]. PET reconstruction should be performed with and without attenuation correction to identify potential reconstruction artefacts caused by the correction algorithm. 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 for a <sup>68</sup>Ga-PSMA PET/CT protocol is given in Table 1.

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Patient preparation:	Hydration with e.g. oral intake of 500 mL of water 2 h prior to acquisition
Activity:	1.8-2.2 MBq <sup>68</sup> Ga-PSMA per kilogram

	bodyweight
Administration:	i.v., flushing with at least the same volume of saline
Concomitant medication:	Furosemide (20 mg i.v.)
Uptake time:	60 min (acceptable range: 50 to 100 min)
Patient position:	Arms elevated above the head
CT protocol:	FOV: base of the skull-base to mid-thigh; Phase: portal venous (80 s after contrast agent, 1.5 ml per kilogram bodyweight)
PET protocol:	FOV and acquisition: from mid-thigh to base of the skull-base; 3-4 min per bed position
PET reconstruction:	ordered-subsets expectation maximization; attenuation correction from CT data

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**Table 1: Protocol example for <sup>68</sup>Ga-PSMA PET/CT image acquisition and reconstruction.**

## **Documentation and reporting**

### Contents of the report

#### 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 relevant diagnostic tests, especially PSA level and prior imaging findings should be summarized. 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

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 furosemide injection. The time interval between administration of <sup>68</sup>Ga-PSMA 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. Dosimetric parameters should be included as required by regulations. The report should state whether CT with or without CT contrast agent was used for CT attenuation correction.

### Description of the findings

Quality issues of the <sup>68</sup>Ga-PSMA PET/CT study, e.g. 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 such as metals) should be mentioned.

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

In the general review, attention should be paid to prostate gland/bed, seminal vesicles, regional and distant lymph nodes, bones, lungs and liver. Regions that may relate to any symptoms given on referral forms should also be given specific attention. In addition to semi-quantitative values <sup>68</sup>Ga-PSMA ligand accumulation should be reported as low, moderate or intense by comparison to the background uptake [16]. Tumor lesions usually appear as focal

tracer uptake higher than adjacent background. However, strict criteria for visual interpretation have not been established and are currently being explored within an EANM initiated study. The presence of a corresponding lesion on CT for each region of tracer accumulation should be reported.

#### Normal uptake and important pitfalls

Normal and variable PSMA-ligand uptake can be found in the following tissues: lacrimal gland, salivary glands, liver, spleen, small intestine, colon and kidney (Figure 2). Usually tumor lesions inside and outside the prostate gland show a strong tumor-background-ratio compared to the surrounding tissue [8, 32]. <sup>68</sup>Ga-PSMA ligands are excreted foremost 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. Further imaging after infusion of normal saline and/or application of furosemide may be useful in such cases. Of note, approximately 5% of all prostate cancers do not exhibit significant PSMA overexpression [21, 43]. Due to high background activity in the liver potential liver metastases can be obscured. This is compounded by the observation that liver metastases tend to lose PSMA-expression in advanced metastatic disease. Therefore, in advanced disease, the accompanying CT scan should be optimized to enhance detection of liver metastases.

Immunohistochemical and <sup>68</sup>Ga-PSMA PET data have shown that increased PSMA-expression can also be found in the neovasculature of non-prostate cancers such as colon cancer, esophageal cancer, thyroid cancer, lung cancer, renal cell carcinoma and brain tumors as well as in benign tissue [1, 44-48]. So far, a variety of mainly case reports exist showing increased PSMA uptake in non-prostate cancer related lesions. An important pitfall is relevant PSMA-ligand uptake in coeliac ganglia of the autonomic nervous system which are prone to be misinterpreted as retroperitoneal lymph node metastases [49]. Moreover,



uptake in Paget's bone disease, in stellate and other ganglia as well as in ribs (without morphologic correlation on CT) may cause mis-interpretation of findings [50].

Complementary information: Comparison with previous examinations should be part of the <sup>68</sup>Ga-PSMA PET/CT report. <sup>68</sup>Ga-PSMA PET/CT studies are more valuable if they are interpreted in the context of other imaging examinations (CT, PET/CT, MRI etc.) and clinical data.

Assessment of response to therapy: <sup>68</sup>Ga-PSMA PET/CT has not yet been validated for response monitoring in prostate cancer patients. In principle, for assessment of response to therapy, the extent and the intensity of the PSMA-ligand uptake should be documented and compared to prior measurements. The reliability of the results reported will depend on having comparable patient preparation, injection and scanning protocols, as well as comparable data analysis.

It should be noted that PSMA-expression is physiologically upregulated after the beginning of ADT [39]. A similar reaction is hypothesized for the use of advanced androgen receptor (AR) targeted therapies (e.g. enzalutamide, abiraterone). Caution has to be taken when interpreting an increase (or potentially decrease) in PSMA-expression shortly after start of a new AR-targeted therapy [38]. PSMA-expression and therefore PSMA PET uptake on serial imaging may be affected by sensitivity or resistance of prostate tumor to ADT and needs further validation. Regarding taxane-based chemotherapy, preclinical data indicate that intensity of PSMA-expression can serve as surrogate parameter for therapy response [51]. In judging the effect of PSMA-directed therapy (e.g. radionuclide therapy) the tumor sink effect has to be taken into account. Hereby, in parallel to data from neuroendocrine tumors, apparent newly observed small lesions on post treatment PET studies should be interpreted with caution in the context of decreasing ligand uptake in other dominant avid lesions, as the former may not necessarily be new [52].

If comparison is performed with other imaging studies (e.g. CT, MRI or bone scintigraphy), change in lesion diameter should be reported.

### Summary and diagnosis/impression

The study has to be clearly identified 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. For prostate cancer imaging it is recommended to structure the summary to the main tumor sites (local tumor involvement, lymph node or bone metastases) and potential other lesions. Whenever possible this should provide a staging assessment (TNM or other) stating whether there are categories of uncertainty. For further reading see also the SNMMI's Procedure Standard for General Imaging and the Royal College of Radiologists' recommendations on reporting [53].

### **Definitions of volumes of interest**

SUV can be normalized to body mass, lean body mass, or body surface area. SUV values may change significantly between different modes of normalization. Therefore the same mode should be used for serial examinations. Recommended tumor uptake metrics is the maximum SUV ( $SUV_{max}$ ), which can be measured and documented for key lesions. The  $SUV_{max}$  is defined as the SUV of the single voxel in a particular lesion with highest uptake on the attenuation corrected PET image. Quality control (QC) steps should be undertaken on a regular basis to minimize SUV measurement errors and to maintain image quality associated with PET/CT scanner equipment. QC steps for <sup>68</sup>Ga-ligand PET/CT have not been validated yet, however a current expert recommendation for routine QC and cross-calibration is given in the Supplemental Material.

### **Radiation exposure to the patient**

The radiation dose with <sup>68</sup>Ga-PSMA PET/CT is the combination of the radiation exposure from the radiopharmaceutical (Table 2) and the CT study. Initial studies have described the

radiation exposure using each of the <sup>68</sup>Ga-labeled PSMA-ligands. The mean dose for a CT scan depends on applications, protocols and CT systems. Recent advances in technology have allowed the radiation doses to be significantly reduced relative to a conventional CT or PET examination.

**Table 2. Data available for radiation dosimetry for <sup>68</sup>Ga-PSMA**

		<sup>68</sup> Ga-PSMA HBED-CC	<sup>68</sup> Ga-PSMA HBED-CC	<sup>68</sup> Ga-PSMA 617	<sup>68</sup> Ga-PSMA- I&T
		Pfob C et al. [54]	Afshar- Oromieh et al. [55]	Afshar- Oromieh et al. [9]	Herrmann et al. [10]
Effective dose coefficient	mSv/MBq	1.71E-02	2.3E-02	2.1E-02	1.99E-02
Urinary bladder wall	mSv/MBq	1.73E-01	1.30E-01	9.03E-02	6.74E-02
Kidneys	mSv/MBq	1.22E-01	2.62E-01	2.06E-01	2.20E-01
Standard injected activity	MBq	150	150	150	150

Based on the available studies (Table 2) the coefficient for effective dose from <sup>68</sup>Ga-PSMA averages  $2.0 \times 10^{-2}$  mSv/MBq resulting in an average effective radiation dose of 3 mSv for an administered activity of 150 MBq. The radiation exposure related to a CT scan carried out as part of an <sup>68</sup>Ga-PSMA 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. Given the variety of CT systems and protocols, the radiation exposure for a <sup>68</sup>Ga-PSMA PET/CT study should be estimated specifically for a given imaging system and protocol. Guidelines provided by radiological societies should be consulted regarding effective dose from the CT examination. The choice of imaging protocol depends on the clinical question and must be considered for every single case.

**Toxicity of the precursor**

PSMA-11

86 µg PSMA-11 per kg body weight administered i.v. in one species (female and male rat) in the single dose acute toxicity was below the no-observed-adverse-effect-level (NOAEL). Based on the referenced study, a safety factor of 1000 can be assumed for a maximum human dose of PSMA-11 of 6.3 nmol or 6 µg per injection for a standardized patient of 70 kg body weight at a maximal concentration of 0.6 µg/mL (AURIGON 770.321.4369).

### PSMA-617

PSMA-617 was tested in a repeated dose toxicology study in male rats for 22 days. The test item was administered once weekly by i.v. bolus injection on days 1, 8, 15 and 22. No signs of local or systemic intolerance reactions were observed. The NOAEL under the test conditions was 400 µg/kg body weight. This was the highest dose tested (Report: Subchronic toxicity study of PSMA-617 by intravenous administration to male CD® rats. Code No 32508. Correspondence with ABX GmbH on 08/25/2016).

### PSMA-I&T

<sup>nat</sup>Ga-PSMA-I&T was tested in a single dose toxicology study in male and female mice for 14 days. <sup>nat</sup>Ga-PSMA-I&T was administered once by i.v. bolus injection on day 0. No animal showed any adverse reactions during the in-life course of the study that could be attributed to administration of the test article. There were no significant changes in body weights, organ weights, clinical pathology, clinical signs, gross- and histopathologic findings between control groups and those receiving the test article. There were no observable toxic effects of <sup>nat</sup>Ga-PSMA-I&T when dosed at 412 µg/kg (Report: Single Dose Toxicity of Ga-PSMA-I&T in ICR Mice, Study No. GLP-15-001-JZR).

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**FIGURES**

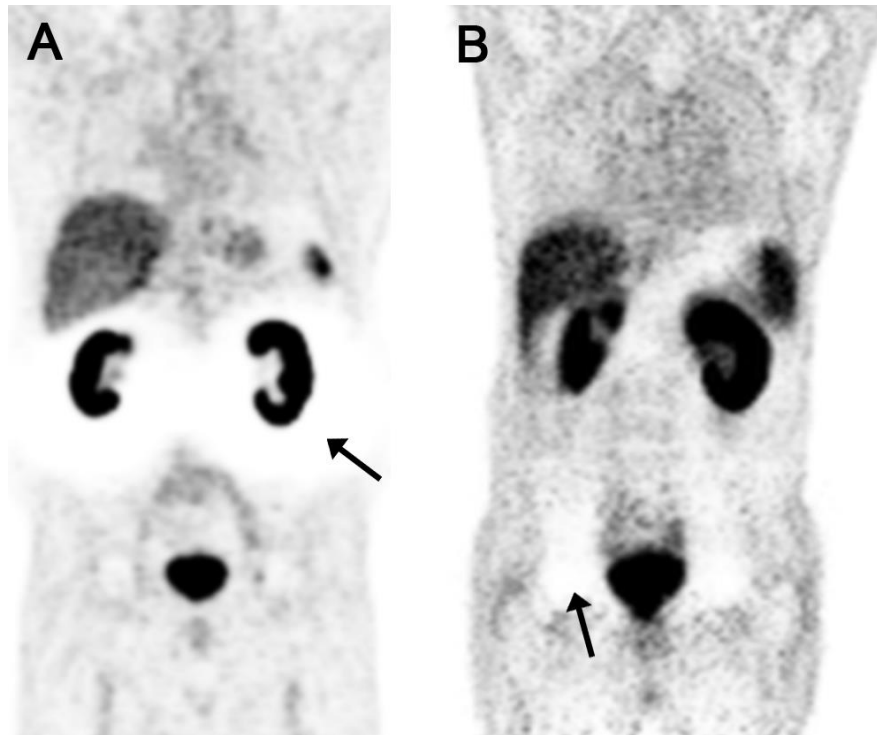


Figure 1. “Halo artifact” in the area surrounding kidneys (A, arrow) and bladder (B, arrow) on CT attenuation corrected coronal PET images acquired after injection of <sup>68</sup>Ga-PSMA-11 without prior Lasix injection (A, 48 min p.i., 149 MBq; B, 68 min p.i., 217 MBq).



Figure 2. Normal body distribution of <sup>68</sup>Ga-PSMA-11. Maximum intensity projection of a 78 year old male patient after injection of 217 MBq <sup>68</sup>Ga-PSMA-11.