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GUIDELINES

^{68}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 reporting of ^{68}Ga-PSMA PET/CT for prostate cancer imaging. These recommendations will help to improve accuracy, precision, and repeatability of ^{68}Ga-PSMA PET/CT for prostate cancer essentially needed for implementation of this modality in science and routine clinical practice.

Keywords PSMA · PET · Prostate cancer · Staging · Restaging · Guideline

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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 nonprofit medical association that facilitates communication worldwide between individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985. 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

^{68}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 transmembrane 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].

^{68}Ga is most often obtained from a ^{68}Ge/^{68}Ga generator system. ^{68}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 ^{68}Ga complexation, are clinically available for PET/CT imaging. ^{68}Ga-labeled PSMA ligands were first radiosynthesized and validated in preclinical models at Johns Hopkins University [6]. Later, ^{68}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. ^{68}Ga-PSMA-11 biodistribution was shown to correspond well to known cellular expression of PSMA across organs [8]. Other ligands (^{68}Ga-PSMA-617, ^{68}Ga-PSMA-I&T) demonstrated similar biodistribution and imaging properties [9, 10]. Notably, still there are no data directly comparing the different ligands and most of the published clinical work is based on ^{68}Ga-PSMA-11. Due to their similarity, ^{68}Ga-PSMA-11, ^{68}Ga-PSMA-617, and ^{68}Ga-PSMA-I&T will henceforth be abbreviated ^{68}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 ^{68}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 ^{68}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 efficacy and study quality for their patients.

This guideline also presents standardized quality control/quality assurance (QC/QA) procedures and imaging procedures for static ^{68}Ga-PSMA PET/CT [11]. Adequate precision, accuracy, repeatability, and reproducibility are essential for the clinical management of patients and the use of ^{68}Ga-PSMA PET/CT within multicenter trials. A standardized imaging procedure will help to promote the appropriate use of ^{68}Ga-PSMA PET/CT and enhance subsequent research. Quantification of ^{68}Ga-PSMA PET/CT is defined here as measuring relative PSMA concentrations using standardized uptake value (SUV) [12] because 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

Definitions are based on the European Association of Nuclear Medicine procedure guidelines for tumour PET imaging, version 2.0 [13]:

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 ^{68}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 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: 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 ^{68}Ga-PSMA PET/CT for recurrent and primary prostate cancer [14]. The criteria outlined in this article are based on the currently available evidence, the current use and experience of ^{68}Ga-PSMA PET/CT shared by the authors. Currently, the specific use varies between institutions, mainly based on experience and availability of the ^{68}Ga-PSMA ligand.

Localization of tumour tissue in recurrent prostate cancer

Most studies, mainly retrospective data, are available on the use of ^{68}Ga-PSMA PET/CT for localization of prostate cancer in the setting of biochemical recurrence [8, 9, 15–21]. 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 [21].

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 T2c – 3a) the likelihood of lymph node and bone metastases is increased. Several studies demonstrate the superiority of ^{68}Ga-PSMA PET/CT as compared to CT, magnetic resonance imaging (MRI) or bone scan for detection of metastases for initial staging at primary diagnosis [22–25]. The detection of radiologically occult lymph node metastases can significantly influence patient management, although the impact on overall survival of improved sensitivity by ^{68}Ga-PSMA PET/CT remains unanswered. A contrast-enhanced ^{68}Ga-PSMA PET/CT can replace abdomino-pelvic

CT for the detection of lymph node metastases. In addition, preliminary data show that ^{68}Ga-PSMA PET/CT is also more accurate for detection of bone metastases [25]. Nevertheless, for local tumour delineation (if requested by the urological surgeon), pelvic MRI cannot be replaced. It is still under investigation and discussion whether additional functional imaging with bone0seeking agents (e.g. bone scintigraphy, ^{18}F-NaF PET/CT) has relevant additional value after performance of ^{68}Ga-PSMA PET/CT, e.g. in patients with PSMA-negative tumours or densely sclerotic bone lesions.

Emerging clinical applications

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 [26–29]. Low PSMA expression in target lesions poses a contraindication for radioligand therapy. Of note, ^{68}Ga-PSMA PET can produce false negatives 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 [30–32].

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

Initial data indicate ^{68}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 [33, 34], and may add value for directed biopsies in the prostate cancer surveillance population who undergo repeated biopsies. Preferably, ^{68}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 [33].

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 ^{68}Ga-PSMA PET/CT. However, whether ^{68}Ga-PSMA PET/CT overcomes limitations of other modalities and proves superior has not been demonstrated yet [35].

Regulatory issues

As of December 2016, no ^{68}Ga-PSMA tracer has been approved by the European Medicines Agency or the United States Food and Drug Administration. ^{68}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 tumour PET imaging, version 2.0 or the Society of Nuclear Medicine and Molecular Imaging Procedure Standard for General Imaging [13, 36].

Procedure/specification of the examination

Necessary data for requesting ^{68}Ga-PSMA PET/CT

Requests for ^{68}Ga-PSMA 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:
    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 androgen receptor (AR)-targeted treatments. Recent history of chemotherapy, radium-223 or PSMA-targeted radioligand therapy.
    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 ^{68}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 (Fig. 1). Activity in ureters might lead to false positive findings. Furosemide administration (20 mg i.v, shortly before or after administration of ^{68}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

^{68}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 in Europe [40] and to the American College of Radiology Manual on Contrast Media in the USA [41].

Radiopharmaceuticals

Products: ^{68}Ga-PSMA-11 [7], ^{68}Ga-PSMA-617 [42], ^{68}Ga-PSMA-I&T [43]; in this manuscript all referred to as ^{68}Ga-PSMA

Nuclide: [^{68}Ga], gallium-68

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

Administration: intravenous

^{68}Ga-PSMA should be manufactured under good manufacturing practice (GMP) conditions and QC should follow the governing pharmacopoeia monograph or national regulations; whichever is applicable. The committee further notes that tracer development is ongoing and ^{18}F-labeled probes are currently under evaluation.

Recommendations for ^{68}Ga-PSMA application and administered activity

^{68}Ga-PSMA is injected as an intravenous bolus. Currently, the optimal injected activity is still under debate. the majority of published data is based on an injected activity of approximately 1.8–2.2 MBq per kilogram of body weight. Variation of injected activity may be caused by the short half-life of ^{68}Ga and variable elution efficiencies obtained during the lifetime of the ^{68}Ge/^{68}Ga radionuclide

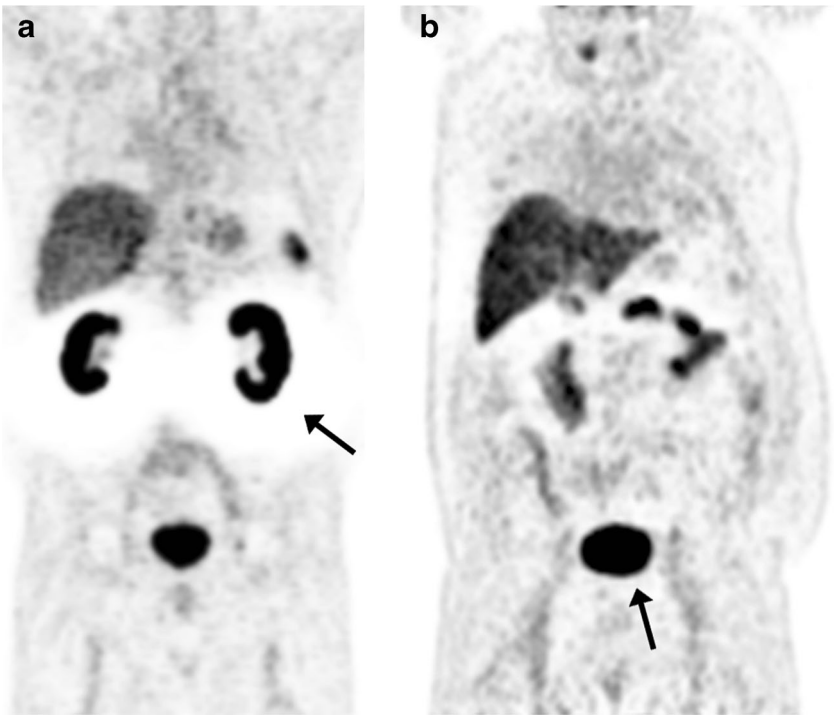

Fig. 1 "Halo artefact" in the area surrounding kidneys (**a**, *arrow*) and bladder (**b**, *arrow*) on CT attenuation-corrected coronal PET images acquired after injection of ^{68}Ga-PSMA-11 without prior Lasix injection (A, 48 min p.i., 149 MBq; B, 68 min p.i., 217 MBq)

generator. Low output of the ^{68}Ge/^{68}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 ^{68}Ga elution and subsequent ^{68}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 min [8]. Increased lesion detection has been reported with delayed imaging up to 3–4 h 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 ^{68}Ga-PSMA injection and imaging should be recorded. If the 1-h scan leads to indeterminate findings, a late scan at 3 h 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. If PET/CT data are used for radiation therapy planning, the examination should be performed in the exact position, employing the same positioning devices as in the radiation therapy department.

CT scans 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 ^{68}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 three-dimensional (3D) mode with an acquisition time of usually 2–4 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 [13]. PET reconstruction should be performed with and without attenuation correction to identify potential 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 ^{68}Ga-PSMA PET/CT protocol is given in Table 1.

Table 1 Protocol example for ^{68}Ga-PSMA PET/CT image acquisition and reconstruction

Patient preparation	Hydration with e.g. oral intake of 500 mL of water 2 h prior to acquisition
Activity	1.8–2.2 MBq ^{68}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

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

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 ^{68}Ga-PSMA and the start time of the acquisition should be reported. The body parts that were covered should be described. Any non-standard position of the patient should be stated.

In case a low-mAs CT was performed for attenuation correction and anatomical registration of the emission images only, description may be limited to a short statement. If a diagnostic CT was performed, then a more detailed 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 contrast-enhanced or non-enhanced CT was used for attenuation correction.

Description of the findings

Quality issues of the ^{68}Ga-PSMA PET/CT study, e.g. motion artefacts, halo artefacts due to high activity in the collecting urinary system, or CT attenuation artefacts (from attenuating materials), should be reported.

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, ^{68}Ga-PSMA ligand accumulation should be reported as low, moderate, or intense by comparison to the background uptake [17]. Tumour 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 (Fig. 2). Usually, tumour lesions inside and outside the prostate gland show a strong tumour–background ratio compared to the surrounding tissue [8, 33]. ^{68}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,

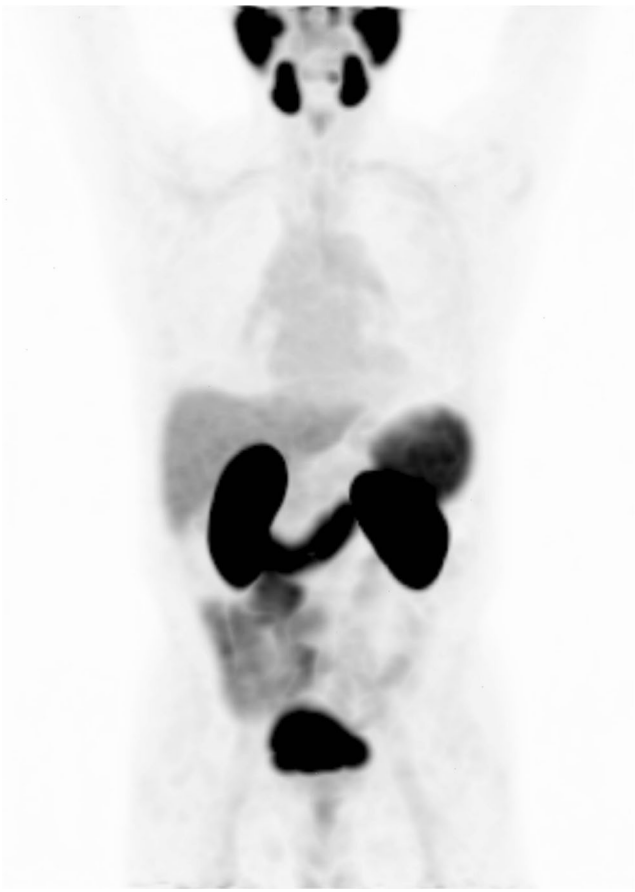

Fig. 2 Normal body distribution of ^{68}Ga-PSMA-11. Maximum intensity projection of a 78-year-old male patient after injection of 217 MBq ^{68}Ga-PSMA-11

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 [22, 44]. 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 ^{68}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 tumours, as well as in benign tissue [1, 45–49]. So far, a variety of mainly case reports exists 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 is prone to be misinterpreted as retroperitoneal lymph node metastases [50]. Moreover, uptake in Paget's bone disease, in stellate, and other ganglia as well as in ribs (without morphologic correlation on CT) may cause misinterpretation of findings [51].

Complementary information: Comparison with previous examinations should be part of the ^{68}Ga-PSMA PET/CT report. ^{68}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: ^{68}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 examinations.

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 second-generation AR-targeted therapies (e.g. enzalutamide, abiraterone). Caution has to be taken when interpreting an increase (or potentially a 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 tumours to ADT and needs further validation. Regarding taxane-based chemotherapy, preclinical data indicate that intensity of PSMA expression can serve as a surrogate parameter for therapy response [52]. In judging the effect of PSMA-directed therapy (e.g. radionuclide therapy) the tumour sink effect has to be taken into account. Hereby, in parallel to data from neuroendocrine tumours, 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 [53].

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

Summary and diagnosis/impression

The study should be clearly identified as normal or abnormal. Alternatively, an estimate of the likelihood of a diagnosis and the differential diagnoses should be given. The reason for study referral should be directly addressed. 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. Whenever possible the report should provide TNM stage including a statement 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 [54].

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 tumour 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. 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 ^{68}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 ^{68}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 ^{68}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.

Based on the available studies (Table 2), the coefficient for effective dose from ^{68}Ga-PSMA averages is 2.0×10^{-2} mSv/MBq, resulting in an average effective radiation dose of 3 mSv for an administered activity of 150 MBq. The radiation

Table 2 Data available for radiation dosimetry for ^{68}Ga-PSMA

		^{68}Ga-PSMA HBED-CC Pfob C et al. [55]	^{68}Ga-PSMA HBED-CC Afshar-Oromieh et al. [56]	^{68}Ga-PSMA 617 Afshar-Oromieh et al. [9]	^{68}Ga-PSMA-I&T 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

exposure related to a CT scan carried out as part of an ^{68}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 ^{68}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

^{nat}Ga-PSMA-I&T was tested in a single-dose toxicology study in male and female mice for 14 days. ^{nat}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, and gross- and histopathologic findings between control groups and those receiving the test article. There were no observable toxic effects of ^{nat}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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Compliance with ethical standards

Conflict of interest Matthias Eiber has a research grant from Siemens. Mohsen Beheshti is a member of the Oncology Committee of the EANM. Thomas Hope has research grants from GE Healthcare. Hans-Jürgen Wester is a shareholder of SCINTOMICS. Stefano Fanti is an advisory board member of BED, Bayer, and ANMI, receives travel support from Bayer, GE Healthcare, and Sanofi, and has grants from Movember and BED. All other authors declare no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997;3:81–5.
2. Bostwick DG, Pacelli A, Blute M, Roche P, Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer. 1998;82:2256–61.
3. Mannweiler S, Amersdorfer P, Trajanoski S, Terrett JA, King D, Mehes G. Heterogeneity of prostate-specific membrane antigen (PSMA) expression in prostate carcinoma with distant metastasis. Pathol Oncol Res. 2009;15:167–72.
4. Ghosh A, Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. J Cell Biochem. 2004;91:528–39.
5. Ross JS, Sheehan CE, Fisher HA, Kaufman Jr RP, Kaur P, Gray K, et al. Correlation of primary tumor prostate-specific membrane antigen expression with disease recurrence in prostate cancer. Clin Cancer Res. 2003;9:6357–62.

6. Banerjee SR, Pullambhatla M, Byun Y, Nimmagadda S, Green G, Fox JJ, et al. 68Ga-labeled inhibitors of prostate-specific membrane antigen (PSMA) for imaging prostate cancer. J Med Chem. 2010;53:5333–41.
7. Eder M, Schafer M, Bauder-Wust U, Hull WE, Wangler C, Mier W, et al. 68Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Bioconjug Chem. 2012;23:688–97.
8. Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, et al. PET imaging with a [68Ga]gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. Eur J Nucl Med Mol Imaging. 2013;40:486–95.
9. Afshar-Oromieh A, Hetzheim H, Kratochwil C, Benesova M, Eder M, Neels OC, et al. The Theranostic PSMA ligand PSMA-617 in the diagnosis of prostate cancer by PET/CT: biodistribution in humans, radiation dosimetry, and first evaluation of tumor lesions. J Nucl Med. 2015;56:1697–705.
10. Herrmann K, Bluemel C, Weineisen M, Schottelius M, Wester HJ, Czernin J, et al. Biodistribution and radiation dosimetry for a probe targeting prostate-specific membrane antigen for imaging and therapy. J Nucl Med. 2015;56:855–61.
11. Busemann Sokole E, Plachcinska A, Britten A. Acceptance testing for nuclear medicine instrumentation. Eur J Nucl Med Mol Imaging. 2010;37:672–81.
12. Thie JA. Understanding the standardized uptake value, its methods, and implications for usage. J Nucl Med. 2004;45:1431–4.
13. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42:328–54.
14. Perera M, Papa N, Christidis D, Wetherell D, Hofman MS, Murphy DG, et al. Sensitivity, specificity, and predictors of positive 68Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol. 2016;70:926–37.
15. Eiber M, Maurer T, Souvatzoglou M, Beer AJ, Ruffani A, Haller B, et al. Evaluation of hybrid (6)(8)Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med. 2015;56:668–74.
16. Ceci F, Uprimny C, Nilica B, Geraldo L, Kendler D, Kroiss A, et al. (68)Ga-PSMA PET/CT for restaging recurrent prostate cancer: which factors are associated with PET/CT detection rate? Eur J Nucl Med Mol Imaging. 2015;42:1284–94.
17. Rauscher I, Maurer T, Fendler WP, Sommer WH, Schwaiger M, Eiber M. (68)Ga-PSMA ligand PET/CT in patients with prostate cancer: How we review and report. Cancer Imaging. 2016;16:14.
18. Afshar-Oromieh A, Zechmann CM, Malcher A, Eder M, Eisenhut M, Linhart HG, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2014;41:11–20.
19. Afshar-Oromieh A, Avtzi E, Giesel FL, Holland-Letz T, Linhart HG, Eder M, et al. The diagnostic value of PET/CT imaging with the (68)Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42:197–209.
20. Morigi JJ, Stricker PD, van Leeuwen PJ, Tang R, Ho B, Nguyen Q, et al. Prospective comparison of 18F-Fluoromethylcholine versus 68Ga-PSMA PET/CT in prostate cancer patients Who have rising PSA after curative treatment and Are being considered for targeted therapy. J Nucl Med. 2015;56:1185–90.
21. Verburg FA, Pfister D, Heidenreich A, Vogg A, Drude NI, Voo S, et al. Extent of disease in recurrent prostate cancer determined by [(68)Ga]PSMA-HBED-CC PET/CT in relation to PSA levels, PSA doubling time and Gleason score. Eur J Nucl Med Mol Imaging. 2016;43:397–403.
22. Maurer T, Gschwend JE, Rauscher I, Souvatzoglou M, Haller B, Weirich G, et al. Diagnostic efficacy of (68)gallium-PSMA positron emission tomography compared to conventional imaging for lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. J Urol. 2016;195:1436–43.
23. Herlemann A, Wenter V, Kretschmer A, Thierfelder KM, Bartenstein P, Faber C, et al. Ga-PSMA positron emission tomography/computed tomography provides accurate staging of lymph node regions prior to lymph node dissection in patients with prostate cancer. Eur Urol. 2016;70:553–7.
24. Hijazi S, Meller B, Leitsmann C, Strauss A, Meller J, Ritter CO, et al. Pelvic lymph node dissection for nodal oligometastatic prostate cancer detected by 68Ga-PSMA-positron emission tomography/computerized tomography. Prostate. 2015;75:1934–40.
25. Pyka T, Okamoto S, Dahlbender M, Tauber R, Retz M, Heck M, et al. Comparison of bone scintigraphy and 68Ga-PSMA PET for skeletal staging in prostate cancer. Eur J Nucl Med Mol Imaging. 2016;43:2114–21.
26. Rahbar K, Schmidt M, Heinzel A, Eppard E, Bode A, Yordanova A, et al. Response and tolerability of a single dose of 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer: a multicenter retrospective analysis. J Nucl Med. 2016;57:1334–8.
27. Baum RP, Kulkarni HR, Schuchardt C, Singh A, Wirtz M, Wiessalla S, et al. 177Lu-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: safety and efficacy. J Nucl Med. 2016;57:1006–13.
28. Heck MM, Retz M, D'Alessandria C, Rauscher I, Scheidhauer K, Maurer T, et al. Systemic radioligand therapy with (177)Lu labeled prostate specific membrane antigen ligand for imaging and therapy in patients with metastatic castration resistant prostate cancer. J Urol. 2016;196:382–91.
29. Ahmadzadehfar H, Eppard E, Kurpig S, Fimmers R, Yordanova A, Schlenkhoff CD, et al. Therapeutic response and side effects of repeated radioligand therapy with 177Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. Oncotarget. 2016;7:12477–88.
30. Laidler P, Dulinska J, Lekka M, Lekki J. Expression of prostate specific membrane antigen in androgen-independent prostate cancer cell line PC-3. Arch Biochem Biophys. 2005;435:1–14.
31. Parimi V, Goyal R, Poropatich K, Yang XJ. Neuroendocrine differentiation of prostate cancer: a review. Am J Clin Exp Urol. 2014;2:273–85.
32. Yuan TC, Veeramani S, Lin MF. Neuroendocrine-like prostate cancer cells: neuroendocrine transdifferentiation of prostate adenocarcinoma cells. Endocr Relat Cancer. 2007;14:531–47.
33. Eiber M, Weirich G, Holzapfel K, Souvatzoglou M, Haller B, Rauscher I, et al. Simultaneous 68Ga-PSMA HBED-CC PET/MRI improves the localization of primary prostate cancer. Eur Urol. 2016;70:829–36.
34. Giesel FL, Sterzing F, Schlemmer HP, Holland-Letz T, Mier W, Rius M, et al. Intra-individual comparison of Ga-PSMA-11-PET/CT and multi-parametric MR for imaging of primary prostate cancer. Eur J Nucl Med Mol Imaging. 2016;43:1400–6.
35. Ahmadzadehfar H, Schlenkhoff CD, Rogenhofer S, Yordanova A, Essler M. 68Ga-PSMA-11 PET represents the Tumoricidal effect of 223Ra in a patient with castrate-resistant metastatic prostate cancer. Clin Nucl Med. 2016;41:695–6.
36. Donohoe KJ. THE SNM PROCEDURE GUIDELINE FOR GENERAL IMAGING 6.0. 2010. http://snmmi.files.cms-plus.com/docs/General_Imaging_Version_6.0.pdf
37. Murga JD, Moorji SM, Han AQ, Magargal WW, DiPippo VA, Olson WC. Synergistic co-targeting of prostate-specific membrane

antigen and androgen receptor in prostate cancer. Prostate. 2015;75:242–54.
38. Evans MJ, Smith-Jones PM, Wongvipat J, Navarro V, Kim S, Bander NH, et al. Noninvasive measurement of androgen receptor signaling with a positron-emitting radiopharmaceutical that targets prostate-specific membrane antigen. Proc Natl Acad Sci U S A. 2011;108:9578–82.
39. Wright Jr GL, Haley C, Beckett ML, Schellhammer PF. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urol Oncol. 1995;1:18–28.
40. Thomsen H, Webb J. Contrast media safety issues and ESUR guidelines. 3rd ed. Berlin: Springer; 2014.
41. Media ACoDaC. ACR Manual on Contrast Media, Version 10.2. American College of Radiology 2016.
42. Benesova M, Schafer M, Bauder-Wust U, Afshar-Oromieh A, Kratochwil C, Mier W, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and Endoradiotherapy of prostate cancer. J Nucl Med. 2015;56:914–20.
43. Weineisen M, Schottelius M, Simecek J, Baum RP, Yildiz A, Beykan S, et al. 68Ga- and 177Lu-labeled PSMA I&T: optimization of a PSMA-targeted Theranostic concept and first proof-of-concept human studies. J Nucl Med. 2015;56:1169–76.
44. Budaus L, Leyh-Bannurah SR, Salomon G, Michl U, Heinzer H, Huland H, et al. Initial experience of (68)Ga-PSMA PET/CT imaging in high-risk prostate cancer patients prior to radical prostatectomy. Eur Urol. 2016;69:393–6.
45. Sawicki LM, Buchbender C, Boos J, Giessing M, Ermert J, Antke C, et al. Diagnostic potential of PET/CT using a 68Ga-labelled prostate-specific membrane antigen ligand in whole-body staging of renal cell carcinoma: initial experience. Eur J Nucl Med Mol Imaging. 2017;44:102–7.
46. Verburg FA, Krohn T, Heinzel A, Mottaghy FM, Behrendt FF. First evidence of PSMA expression in differentiated thyroid cancer using [(6)(8)Ga]PSMA-HBED-CC PET/CT. Eur J Nucl Med Mol Imaging. 2015;42:1622–3.
47. Demirci E, Ocak M, Kabasakal L, Decristoforo C, Talat Z, Halac M, et al. (68)Ga-PSMA PET/CT imaging of metastatic clear cell renal cell carcinoma. Eur J Nucl Med Mol Imaging. 2014;41:1461–2.
48. Chang SS, O'Keefe DS, Bacich DJ, Reuter VE, Heston WD, Gaudin PB. Prostate-specific membrane antigen is produced in tumor-associated neovasculature. Clin Cancer Res. 1999;5:2674–81.
49. Chang SS, Reuter VE, Heston WD, Bander NH, Grauer LS, Gaudin PB. Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature. Cancer Res. 1999;59:3192–8.
50. Krohn T, Verburg FA, Pufe T, Neuhuber W, Vogg A, Heinzel A, et al. [(68)Ga]PSMA-HBED uptake mimicking lymph node metastasis in coeliac ganglia: an important pitfall in clinical practice. Eur J Nucl Med Mol Imaging. 2015;42:210–4.
51. Artigas C, Alexiou J, Garcia C, Wimana Z, Otte FX, Gil T, et al. Paget bone disease demonstrated on (68)Ga-PSMA ligand PET/CT. Eur J Nucl Med Mol Imaging. 2016;43:195–6.
52. Hillier SM, Kern AM, Maresca KP, Marquis JC, Eckelman WC, Joyal JL, et al. 123I-MIP-1072, a small-molecule inhibitor of prostate-specific membrane antigen, is effective at monitoring tumor response to taxane therapy. J Nucl Med. 2011;52:1087–93.
53. Beauregard JM, Hofman MS, Kong G, Hicks RJ. The tumour sink effect on the biodistribution of 68Ga-DOTA-octreotate: implications for peptide receptor radionuclide therapy. Eur J Nucl Med Mol Imaging. 2012;39:50–6.
54. Husband JE, Padhani AR. Radiologists RCo. Recommendations for cross-sectional imaging in cancer management. London: Royal College of Radiologists; 2006.
55. Pfob CH, Ziegler S, Graner FP, Kohner M, Schachoff S, Blechert B, et al. Biodistribution and radiation dosimetry of 68Ga-PSMA HBED CC-A PSMA specific probe for PET imaging of prostate cancer. Eur J Nucl Med Mol Imaging. 2016;43:1962–70.
56. Afshar-Oromieh A, Hetzheim H, Kubler W, Kratochwil C, Giesel FL, Hope TA, et al. Radiation dosimetry of (68)Ga-PSMA-11 (HBED-CC) and preliminary evaluation of optimal imaging timing. Eur J Nucl Med Mol Imaging. 2016;43:1611–20.