Chapter 3

Pre-Therapeutic Dosimetry Employing Scandium-44 for Radiolabeling PSMA-617

Elisabeth Eppard

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79157

Abstract

In recent years, the positron emitter scandium-44 moved into the focus of research providing favorable nuclide properties for an application in nuclear medicine. Radiolabeling of PSMA-617 with scandium-44 as diagnostic match for [^{177}Lu]Lu-PSMA-617 instead of gallium-68 would enable pre-therapeutic dosimetry in clinical setting. Due to the chemical similarities of scandium and lutetium, the in vitro and in vivo characteristics of [^{177}Lu]Lu-PSMA-617 are more similar to [^{44}Sc]Sc-PSMA-617 than to the ^{68}Ga-compounds [^{68}Ga]Ga-PSMA-617 or [^{68}Ga]Ga-PSMA-11. [^{44}Sc]Sc-PSMA-617 showed its potential in a clinical setting as a PET imaging agent of prostate cancer providing several advantages over gallium-68 labeled tracers. The longer half-life of the nuclide would allow, for example, an optimized patient management and treatment, long-term or late time point imaging as well as transportation to more distant PET centers. However, especially clinical applications like individual dosimetry or intraoperative applications are still under investigation.

Keywords: scandium-44, PSMA-617, dosimetry, theranostic, castrate-resistant prostate cancer

1. Introduction

Prostate carcinoma is the fourth most common cancer in both sexes combined, the second most common cancer in men, and with an estimated 307,000 deaths in 2012, it is the fifth leading cause of death from cancer in men [1]. While prognosis of prostate carcinoma is good at an early stage, the 5-year survival of patients in advanced stages decreases to 31% [2, 3]. Consequently, a number of studies were conducted developing new strategies against the disease.

As the prostate-specific membrane antigen (PSMA) is overexpressed on prostate carcinoma and the neovasculature of most of the solid tumors but not of normal tissue, it is an attractive target for imaging and therapy [4]. Consequently, the development and the evaluation of small ligands targeting PSMA are the objectives of various studies.

With the introduction of PSMA-617, a further development of PSMA-11, a highly potent theranostic agent found its way into clinical routine where it is used as [^{68}Ga]Ga-PSMA-617 for PET and as [^{177}Lu]Lu-PSMA-617 for therapy of metastatic castrate-resistant prostate cancer (mCRPC). In the last few years, several studies proved the therapeutic efficacy of [^{177}Lu]Lu-PSMA-617 in mCRPC patients [2, 3, 5]. Although [^{177}Lu]Lu-PSMA-617 exhibited a favorable safety profile in mCRPC patients [2, 3, 5–9], adverse effects were due to physiologic expression of PSMA in small intestine, proximal renal tubules and salivary glands are observable [2, 10, 11]. Correspondingly, organs at risk are kidneys as well as salivary and lacrimal glands. First experiences showed that pre-therapeutic dosimetry might support pre-selection of patients as well as improvement of individualized therapy planning [7, 9, 12–15]. In this context, pre-therapeutic estimation of dose delivered to PSMA expressing tissue as well as whole body would be useful to predict therapeutic effect of a certain administered therapeutic activity and facilitate individual dose adjustment [16]. For this purpose, [^{177}Lu]Lu-PSMA-617 planar ± SPECT imaging, employing small amounts of tracer, or [^{68}Ga]Ga-PSMA-617 PET were considered [10–14, 17–19] but both tracers have disadvantages and limitations for dosimetry in a clinical setting.

Current studies on radiolabeling PSMA-617 with the positron emitter scandium-44 demonstrated its similar in vitro and in vivo properties compared with [^{177}Lu]Lu-PSMA-617 [20, 21]. As it is combining the similar pharmacokinetics to [^{177}Lu]Lu-PSMA-617 with more appropriate nuclide characteristics than [^{68}Ga]Ga-PSMA-617, it is assumed to improve pre-therapeutic dosimetry [20, 21].

2. Part I: Radiochemistry

Currently, [^{68}Ga]Ga-PSMA-11 is the most frequently used PET tracer, targeting the prostate-specific membrane antigen, worldwide [22, 23]. Gallium-68 has for PET imaging appropriate decay properties; nevertheless, its disadvantages limit its application.

Its high positron energy compared to fluorine-18 (cf. **Table 1**) leads to images tending to be noisier while its short physical half-life only covers imaging periods of a few hours. Moreover, the differences in coordination chemistry between gallium-68 and lutetium-177 lead to deviations in pharmacokinetics [20]. As a consequence, gallium-68 is not the nuclide of choice for late time imaging, extended dosimetric evaluations as well as intraoperative applications several hours post-injection (p.i.).

From this point of view, scandium-44 is a genuine alternative to gallium-68 and is in the focus of current research [20, 25–30].

Scandium-44 (β^+ = 94%, $\tilde{E}_\beta$ = 0.632 MeV) has a physical half-life of 3.97 h and can be produced on two different ways, via ^{44}Ti/^{44}Sc-generator or cyclotron [30–36]. Another potential advantage of scandium(III) in nuclear medicine is its radioisotope scandium-47 (β^-, primary ◎-ray of

http://dx.doi.org/10.5772/intechopen.79157

Positron emitter	Half-life	$\tilde{E}_{\beta}$	$E_{\beta, max}$
		(MeV)	
^{68}Ga	67.71 min	0.829	1.899
^{44}Sc	3.97 h	0.632	1.474
^{15}O	2.04 min	0.735	1.732
^{18}F	109.77 min	0.250	0.634

Table 1. Comparison of mean ($\tilde{E}_{\beta}$) and maximum ($E_{\beta, max}$) positron energies of scandium-44 with gallium-68, fluorine-18 and oxygen-15 [24].

159 keV and t½ = 3.3 d) which is suitable for therapeutical application. Constituting a matched pair of radioisotopes real Sc-labeled theranostic radiopharmaceuticals are applicable [28, 31, 37–40].

Scandium-44 can be quantitatively detected via its 511 keV emission. High radioactivities of scandium-44 can be measured in a dose calibrator applying the ^{18}F-setting. But due to different radionuclide characteristics, a multiplication factor has to be used, which is depending on the dose calibrator.

Since the 1980s, several radiolabeling studies with scandium radionuclides have been published [20, 21, 25, 28, 38, 41–44]. Chemically, scandium is similar to Y^{3+} and lanthanides. However, the ionic radius of Sc^{3+} is smaller than that of lanthanides for the coordination number 6 while at the same time, it is larger than any trivalent 3d transition metal cation. The most common coordination number of Sc^{3+} is six; nevertheless, examples for coordination numbers between three and nine exist [45, 46].

In vivo stability of a radiopharmaceutical is a crucial factor for clinical application; macrocyclic ligands are the ligands of choice forming thermodynamically and kinetically stable complexes with trivalent hard metal cations. Chemical and, at the end, biological behavior of the complex and consequently of the radiopharmaceutical depend on structural factors, for example, rigidity, cavity size and nature and number of the donor atoms chelating the metal cation [47]. Due to the similarity between Sc^{3+} and Ga^{3+}, Y^{3+} or trivalent lanthanides, DOTA, a common ligand in nuclear medicine, was evaluated with regard of its usability [48]. The study revealed that the stability constant of [Sc-DOTA] is comparable with those for Y^{3+} or the heaviest lanthanides and higher than those for In^{3+} and Ga^{3+} as well as the eight-coordination geometry of the complex in solution [48].

Together with its four times longer half-life than gallium-68 and its coordination chemistry similar to lutetium-177, scandium-44 enables longer imaging periods covering up to 24 h post injection as well as improved pre-therapeutic dosimetry.

2.1. Production of scandium-44

Scandium-44 can be produced via ^{44}Ti/^{44}Sc-generator [30, 31, 40]. Despite the advantages of the radionuclide generator system prevents the availability of titanium-44 the production

of this generator. Titanium-44 with its half-life of 60 years is only producible with limited yields and at high costs by a small number of facilities [49]. Accordingly, accessibility of the daughter scandium-44 by cyclotron production is an alternative as it provides scandium-44 in sufficiently high yields with radionuclidic purities >99% avoiding the problem of ^{44}Ti-waste management.

2.1.1. Cyclotron production

Growing interest in scandium-44 as alternative to gallium-68 predicated research for production routes providing scandium-44 in the GBq range. Recent intermediate cyclotrons allow an economic production of the radionuclide utilizing p, d or α-particle-induced reactions (cf. **Table 2**) [26, 27, 33, 50–57]. The isomer scandium-44m ($T_{1/2}$ = 58 h) has also nuclide characteristics, which can be useful in nuclear medicine [26, 43].

Recently, the accessibility of scandium-44 via proton irradiation of natural calcium targets was described [53] as well as the employment of enriched calcium targets optimizing radionuclidic purity of the radionuclide produced [52].

Similar experiments performed by bombarding natural calcium targets with protons were reported [53, 55], yielding more than 650 MBq scandium-44 with 95.8% radionuclidic purity [53]. As this method leads to co-production of long-living radionuclidic impurities accounting for unnecessary doses for the patient its usability is limited. To obtain scandium-44 of higher radionuclidic purity enriched [^{44}Ca]$CaCO_3$ target material was found to be optimal [59]. This study also confirmed an optimal ratio of scandium-44m to scandium-44 by irradiating the targets with 9 MeV protons and the possibility to achieve yields in the GBq range utilizing this method [59]. Further refinement leads to reproducible production of GBq-activities of scandium-44 at a cyclotron in excellent quality [56]. As a result of all these investigations towards scandium-44 production, the basis for the introduction of scandium-44 into clinical routine for PET imaging may have been created.

Nuclide production via cyclotron is in need for an efficient separation strategy of the produced radionuclide from the target material. This is necessary to remove bulk metal, which disturbs eventual radiolabeling of PET tracers, to reduce the volume and to recover target material. For this purpose, different methods such as filtration [53] or ion exchange employing chelating resins were investigated [26, 55, 56, 59].

	Reaction	**Q (MeV)**	**E_{th} (MeV)**
p	^{44}Ca(p,n)^{44}Sc	−4.43	4.53
d	^{44}Ca(d,2n)^{44}Sc	−6.65	6.96
	^{44}Ca(d,n)^{44}Sc	0.0	0.0
α	^{44}Ca(α,3np)^{44}Sc	−32.73	35.71
	^{43}Ca(α,2np)^{44}Sc	−21.59	23.61
	^{42}Ca(α,np)^{44}Sc	−13.67	14.97

Table 2. Nuclear reaction data for the formation of scandium-44 [58].

http://dx.doi.org/10.5772/intechopen.79157

2.1.2. The ^{44}Ti/^{44}Sc-generator

Radionuclide generators are an alternative production route to reactors and cyclotron. They exploit radiochemical equilibria (transient or secular) between mother and daughter isotope. This means that the mother isotope has a half-life much greater than or approximately equal to 10 times longer than the half-life of the daughter usable for imaging. As mother and daughter are isotopes of different elements, they are present in different chemical forms and can be relatively easily separated chemically.

Beside the ^{99}Mo/^{99m}Tc-generator, which is still the working horse in nuclear medicine, the relevance of the ^{68}Ge/^{68}Ga-generator continues to increase with recent developments of new potent ^{68}Ga-radiopharmaceuticals for PET imaging. Apart from the cyclotron, scandium-44 can also be produced via ^{44}Ti/^{44}Sc-generator system. Just like the ^{68}Ge/^{68}Ga-generator, there is a secular equilibrium between the long-living mother and the short-living daughter nuclide. Titanium-44 decays via electron capture ($t_{1/2}$ = 59 ± 2 a) [60] into the ground state of scandium-44 which transforms to the stable calcium isotope calcium-44 emitting a positron.

First studies on the design of a ^{44}Ti/^{44}Sc-generator were conducted in the 1960ies and 70ies excluding pharmaceutical aspects [32, 35, 61, 62]. A first 185 MBq ^{44}Ti/^{44}Sc-generator designed for radiopharmaceutical use was described in the last decade [31] as well as a suitable post-processing [40]. An initial preclinical proof of concept study could show that scandium-44 is able to radiolabel a clinical relevant precursor (DOTA-TOC) leading to a stable radiopharmaceutical in good yields as well as the suitability of the generator and post-processing for this purpose [38]. Furthermore, a first clinical application of [^{44}Sc]Sc-DOTA-TOC, radiolabeled with generator-derived scandium-44, was conducted to proof the high potential of the radionuclide for PET imaging [30].

First challenge in the development of the ^{44}Ti/^{44}Sc-generator is the high-yield production of titantium-44 via accelerated particles. Up to now, all attempts building a ^{44}Ti/^{44}Sc-generator described in the literature use the ^{45}Sc(p,2n)^{44}Ti-process, although cyclotrons of high positron flux are necessary, to obtain titanium-44 in relatively low radioactivity yields [31, 32, 35, 61–63]. Before titanium-44 can be used separation from the target material and subsequent purification from residual metallic contaminants is mandatory.

Generally, for the design of a radionuclide generator, several critical radiochemical parameters have to be considered, such as separation strategy, stability of the generator and type of eluate. In context with the ^{44}Ti/^{44}Sc-generator, this means a separation strategy is needed which provides high ^{44}Sc-elution yields combined with low ^{44}Ti-breakthrough employing an eluate which is suitable for subsequent radiolabeling in terms of pH, volume and purity. Additionally, this separation strategy should guarantee high long-term stability of the generator. This is of particular importance for the ^{44}Ti/^{44}Sc-generator compared for example to the ^{99}Mo/^{99m}Tc- or ^{68}Ge/^{68}Ga-generators as usage for many years due to the long physical half-life of titanium-44 is possible.

The ^{44}Ti/^{44}Sc-generator system developed by Filosofov et al. uses the properties of Sc^{III} in oxalic as well as hydrochloric acid as basis of an anion-exchange separation strategy [31]. This concept leads to ^{44}Sc elution yields of 180 MBq in 20 ml 0.005 M $H_2C_2O_4$/0.07 M HCl accompanied by a ^{44}Ti breakthrough of 90 Bq representing a separation factor of 2×10^6 [31]. Long-term stability of the generator is ensured by a reverse elution mode which is needed to

provide high retention of titanium-44 on the column [31]. This concept leads to a generator design providing scandium-44 in stable yields without significant ^{44}Ti-breakthrough since approximate 10 years.

As volume, pH and eluent composition of the 180 MBq ^{44}Ti/^{44}Sc generator are not suitable for subsequent radiolabeling, for example, peptides for clinical application, an efficient post-processing strategy in analogy to the post-processing approach of ^{68}Ge/^{68}Ga generators was developed [40, 64, 65]. This post-processing includes reduction of the volume of ^{44}Sc solution, optimization of pH for subsequent radiolabeling as well as further purification from metal contaminants disturbing the complex formation by utilizing a cation exchange column. Finally, ~ 90% of chemically and radiochemically highly pure scandium-44 can be recovered in 3 ml 0.25 M ammonium acetate (pH = 4) with less than 7 Bq ^{44}Ti-breakthrough within 10 min ready for following radiolabeling reactions [21, 38, 40].

2.2. Synthesis of [^{44}Sc]Sc-PSMA-617

DOTA is used as bifunctional chelator in PSMA-617 (cf. **Figure 1**) requiring elevated temperatures for complex formation. Commonly DOTA-based radiopharmaceuticals are prepared using 95°C; therefore, it was evident to choose this as radiolabeling temperature for generator as well as for cyclotron produced scandium-44 [21, 25].

Due to the low activity obtained from the ^{44}Ti/^{44}Sc-generator, evaluation of the influence of precursor amount and reaction time on radiochemical yield resulted in apparent molar activities of 6.50 ± 0.76 MBq/nmol [21] while values of 5–10 MBq/nmol using cyclotron produced scandium-44 are possible [20].

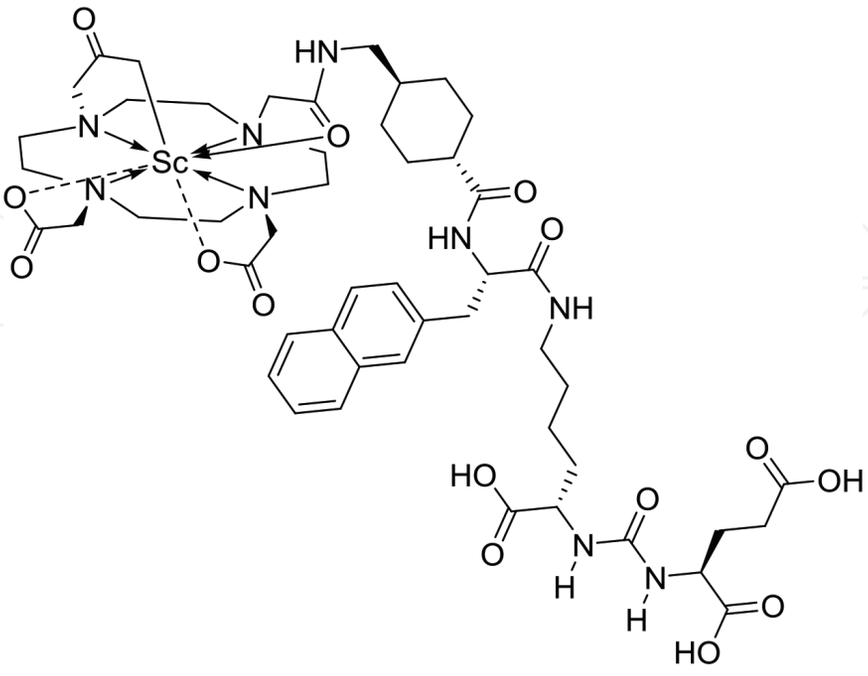

Figure 1. Putative structure of [^{44}Sc]Sc-PSMA-617.

With regard to the reported radiochemical yields of >97% [20, 21], it seems not necessary to evaluate a purification method. Nevertheless, removal of unwanted ions (e.g., acetate ions, uncomplexed $^{44}Sc^{3+}$) from the crude product solution is of interest especially with a view to clinical application. The purification method of choice is solid phase extraction. This cheap and easy method is commonly used when it is necessary to purify radiopharmaceuticals. Solid phase extraction with C-18 cartridges was suitable for further purification. After equilibration of the cartridge, almost quantitative retention of [^{44}Sc]Sc-PSMA-617 on the cartridge and product recovery with >90% efficacy is possible [21].

2.3. Preclinical evaluation

The evaluation of the logD values of the ^{68}Ga-, ^{44}Sc- and ^{177}Lu-complexes and [^{68}Ga]Ga-PSMA-11 revealed that the values are in the same range for the PSMA-617 complexes and reduced for [^{68}Ga]Ga-PSMA-11(cf. **Table 4**) [20].

The presence of metal cations like Fe^{3+} or other chelators can cause a release of the radionuclide from PSMA-617. As this is a crucial factor for later use as a radiopharmaceutical stability of [^{44}Sc]Sc-PSMA-617 against transmetallation, transchelation as well as its stability in human serum and in final formulation was investigated. To determine the stability in the presence of relevant metal cations, those typically present in vivo (Ca^{2+}, Fe^{3+}, Mg^{2+}), at levels significantly higher compared to normal in vivo levels, were chosen. Transchelation was determined against DTPA and EDTA, two chelators forming scandium complexes already at room temperature. In all stability experiments more than 95% of [^{44}Sc]Sc-PSMA-617 remained intact even after 24 h incubation [21]. (cf. **Table 3**).

Eppard et al. as well as Umbricht et al. determined the binding affinity of ^{nat}Sc-PSMA-617 but by different methods and cell lines [20, 21]. Due to the differences in the experimental set up, the results are not directly comparable. Nevertheless, there are similarities. Binding affinity to the target were for [^{44}Sc]Sc-PSMA-617 and [^{177}Lu]Lu-PSMA-617 in the same range cf. (**Table 4**). Similar results could be observed for the internalization of the radioligands. Uptake was comparable for all compounds without any significant differences within the

Time (h)	% intact [^{44}Sc]Sc-PSMA-617 ± SD						
	Ca^{2+}	Mg^{2+}	Fe^{3+}	EDTA	DTPA	NaCl	Human serum
0.5	98.0 ± 0.0	98.7 ± 0.5	97.3 ± 0.9	96.7 ± 0.1	96.7 ± 1.2	98.7 ± 0.5	98.7 ± 0.5
1	98.3 ± 0.5	98.3 ± 0.5	98.0 ± 0.8	97.3 ± 0.1	97.7 ± 0.5	98.0 ± 0–8	98.0 ± 0.8
2	97.0 ± 0.1	98.0 ± 0.8	98.0 ± 0.8	97.3 ± 0.1	97.0 ± 0.8	97.7 ± 1.3	98.0 ± 0.4
4	97.0 ± 1.4	97.7 ± 0.5	96.7 ± 0.5	97.3 ± 0.1	96.7 ± 0.5	97.3 ± 0.5	97.0 ± 0.8
24	96.7 ± 0.8	97.2 ± 0.8	95.0 ± 1.4	95.9 ± 1.2	95.1 ± 0.8	96.0 ± 0.8	96.3 ± 0.9

Table 3. Stability of [^{44}Sc]Sc-PSMA-617 at 37°C in the presence of different metal cations and in the presence of DTPA and EDTA, at 10^{-2} M concentration respectively (n = 3).

	Log D	Relative PSMA-binding affinity	
		LNCaP cells	PC-3 PIP cells
[^{44}Sc]Sc-PSMA-617	−4.21 ± 0.04	1.47	1.18
[^{177}Lu]Lu-PSMA-617	−4.18 ± 0.06	1	1
[^{68}Ga]Ga-PSMA-617	−4.30 ± 0.10	1.08	0.54
[^{68}Ga]Ga-PSMA-11	−4.82 ± 0.07	0.58	0.45

Table 4. Log D (n = 3–5) and relative PSMA-binding affinity as the inverse molar ratio of the average K_D values as determined in cell studies with LNCaP cells [21] and PC-3 PIP cells [20] according to Reddy et al. [66].

experimental set up [20, 21]. Additionally, it was possible to prove PSMA-specific uptake/internalization for all radioligands used employing a PC-3 PIP/flu tumor model [20, 21].

Umbricht et al. performed biodistribution and small animal imaging studies in PC-3 PIP and PC-3 flu tumor-bearing mice directly comparing [^{44}Sc]Sc-PSMA-617 with [^{177}Lu]Lu-PSMA-617, [^{68}Ga]Ga-PSMA-617 and [^{68}Ga]Ga-PSMA-11 under the same in vivo conditions [20]. The study confirmed comparable in vitro behavior, which was expected due to similar coordination behavior of scandium-44 and lutetium-177 [20, 48]. The similar chemical behavior of the two nuclides is also evident in vivo in the pharmacokinetics of the radiopharmaceuticals. [^{44}Sc]Sc-PSMA-617 and [^{177}Lu]Lu-PSMA-617 revealed a largely identical biodistribution within in the investigated period of time [20]. Along with the advantage of the longer half-life of scandium-44, enabling late-time imaging, the increasing tumor-to-background ratio over time can be exploited [20]. Additional comparison with the [^{68}Ga]Ga-PSMA-617 confirmed small differences in the pharmacokinetics of [^{68}Ga]Ga-PSMA-617 and [^{177}Lu]Lu-PSMA-617 explainable with the different coordination chemistry of gallium and lutetium [20].

2.4. Synthesis and quality control for human use

The pharmacopeia contains recognized pharmaceutical rules on the quality, testing, storage and labeling of medicinal products and the substances, materials and methods used in their manufacture and testing. It is legally binding [21].

As scandium-44 is a new isotope for human PET application, there is no monograph in the European or another pharmacopeia available for the preparation of scandium-44 or ^{44}Sc-radiopharmaceuticals. Therefore, quality control was performed based on the monograph for [^{68}Ga]Ga-DOTATOC of the European Pharmacopeia [67].

With respect to the use of generator-derived scandium-44, special attention has to be paid to the quality control of the titanium-44 content in the final formulation.

To ensure the quality of [^{44}Sc]Sc-PSMA-617, the radiolabeling procedure was modified for patient application. Since only a maximum of 180 MBq scandium-44 is available via the generator per elution and the time from the beginning of the generator elution to the injection to the patient is 3–4 h, it was necessary to guarantee high and stable radiochemical yields. To achieve this, the amount of precursor was increased to 38.4 nmol, and 9 vol% ethanol

was added to the radiolabeling mixture. Ethanol has two tasks: to improve radiolabeling efficacy [68] and to prevent radiolysis in the initial radiolabeling mixture. Its use as scavenger is very important to ensure radiochemical purity as radiolysis by-products can cause undesired and serious side effects while their removal is time-consuming and complicated. Additionally, C-18 purification was performed by default. This step removes potentially remaining ^{44}Ti-breakthrough, uncomplexed scandium-44 as well as ammonium acetate buffer prior to final formulation of the radiopharmaceutical. Although this step extends synthesis time, its contribution to ensure radiochemical and especially radionuclidic purity is very important. With respect to the use of generator-derived scandiuim-44, the ^{44}Ti-breakthrough was of major interest. During process set-up, it was even tested twice, in the radiolabeling mixture and final formulation. It was measured not earlier than 120 h after synthesis in a γ-spectrometer at 67.9 and 78.3 keV. Titanium-44 was not traceable in any of the quality control samples.

Due to the limited activity derived from the ^{44}Ti/^{44}Sc-generator system, the apparent molar activity was 3.05 ± 0.36 MBq/nmol at time of calibration (end of synthesis) which is considerably lower compared to [^{68}Ga]Ga-PSMA-11 (14–355 MBq/nmol) or [^{68}Ga]Ga-DOTA-TOC (4–72 MBq/nmol).

Parameters checked during the quality control procedure were listed in **Table 5**.

Due to the nature of radiopharmaceuticals sterility, breakthrough and content of long living radionuclides could not be determined before release of the final radiopharmaceutical. Therefore, only a preliminary release was possible. Final release of the respective batch was performed with receipt of the last test results.

	Method	**Acceptance criteria**
Volume activity	Dose calibrator	5–15 MBq/ml
Visual appearance	Optical	Clear, colorless
Drug Identity	Radio-HPLC	11.3 ± 0.4 min
Nuclide identity	γ-Spectroscopy	511 ± 25 keV
	Decay measurements	3.97 ± 0.2 h
pH	Indicator strip	4–8.5
Apparent molar activity	Calculation	0.7–8 MBq/nmol
Radiochemical purity	Radio-HPLC/Radio-TLC	≥ 95%
Long living nuclides	γ-Spectroscopy	Yes/No
Breakthrough	γ-Spectroscopy	< 0.001%
Filter integrity	Bubble point	> 3447 mbar
Endotoxins	LAL-test	< 17.5 IU/ml
Sterility	According Ph. Eur.	Sterile

Table 5. Parameters checked during quality control with acceptance criteria and average value measured.

3. Part II: Dosimetry

Theranostics and personalized medicine in oncology are in need for highly sensitive and specific diagnostic PET probes that may be radiolabeled with therapeutic radionuclides [18]. It is assumed that diagnostic PET agent distribution is more appropriate for prediction of therapeutic dose increasing therapeutic outcome [18]. Among the several matched pairs for imaging and therapy used in nuclear medicine, focus is on the PET nuclides gallium-68 and scandium-44 as imaging counterpart for lutetium-177.

3.1. Methodology

For the first clinical application, five men with progressive mCRPC enrolled for [^{177}Lu]Lu-PSMA-617 therapy received [^{44}Sc]Sc-PSMA-617 for PET imaging (cf. **Table 6**) [21, 69, 70].

The study protocol stipulates PET/CT imaging starting with a dynamic PET scan of abdomen with kidneys in the field of view (FOV) followed by a low dose CT scan and three static whole-body scans from skull to mid-thigh acquired 45 minutes, 2 h and 19.5 h post injection with preceding low-dose CT. Quantitative analysis was performed visually to identify organs of increased tracer uptake as source organs for further dosimetric calculations. Residence times, organ-absorbed doses (mSv/MBq) as well as effective doses were calculated during quantitative analysis [21, 69, 70] and the maximum permissible activity as well as the maximum number of therapy cycles (6 GBq per cycle) which can be administered were determined [70].

3.2. First in-human studies

Following the promising preclinical results, Eppard et al. conducted a first-in-human application [21, 69, 70].

In all patients, PSMA-positive metastases were detectable by [^{44}Sc]Sc-PSMA-617 PET/CT applying a single dose of 50.45 ± 9.25 MBq. Visual comparison with images from previous [^{68}Ga]Ga-PSMA-11-PET/CT those from [^{44}Sc]Sc-PSMA-617 PET/CT were found to

Patient no.	Age	Weight (kg)	Hematocrit	Injected activity (MBq)	Injected activity (MBq/kg)	PSA (ng/ml)
1	70	78	0.33	50.00	0.64	453.00
2	72	80	0.30	62.23	0.78	26.00
3	67	70	0.39	39.61	0.57	7.20
4	70	80	0.30	50.00	0.63	139.00
5	67	104	0.29	48.95	0.47	3000.0
Mean	69	82.4	0.32	50.16	0.62	
SD	2.2	12.76	0.04	8.04	0.11	

Table 6. Details of study population [21, 69, 70].

http://dx.doi.org/10.5772/intechopen.79157

be at least equal at a significantly reduced dose. Direct comparison of [^{68}Ga]Ga-PSMA-11 and [^{44}Sc]Sc-PSMA-617 PET/CT images as well as planar scintigraphy and SPECT/CT of [^{177}Lu]Lu-PSMA-617 in one patient is depicted in **Figure 2**.

Due to the longer half-life of scandium-44, patient management could become more flexible through its use allowing PET/CT imaging several hours post injection (**Figure 3**) [20]. Indeed using low doses still and late time point imaging still enables detection of lesions while accumulated activity in urinary tract or kidney is no longer observed [21]. Qualitative detection of PSMA-positive lesions is feasible due to increased tumor-to-background ratios and resulting improved image contrast [21].

Khawar et al. reported estimated residence times (MBq-h/MBq) to be prolonged in the liver followed by the kidneys, urinary bladder, bone marrow and rest of organs compared with [^{68}Ga]Ga-PSMA-617 [69]. Also, the study revealed that kidneys (3.19E-01 mSv/MBq;

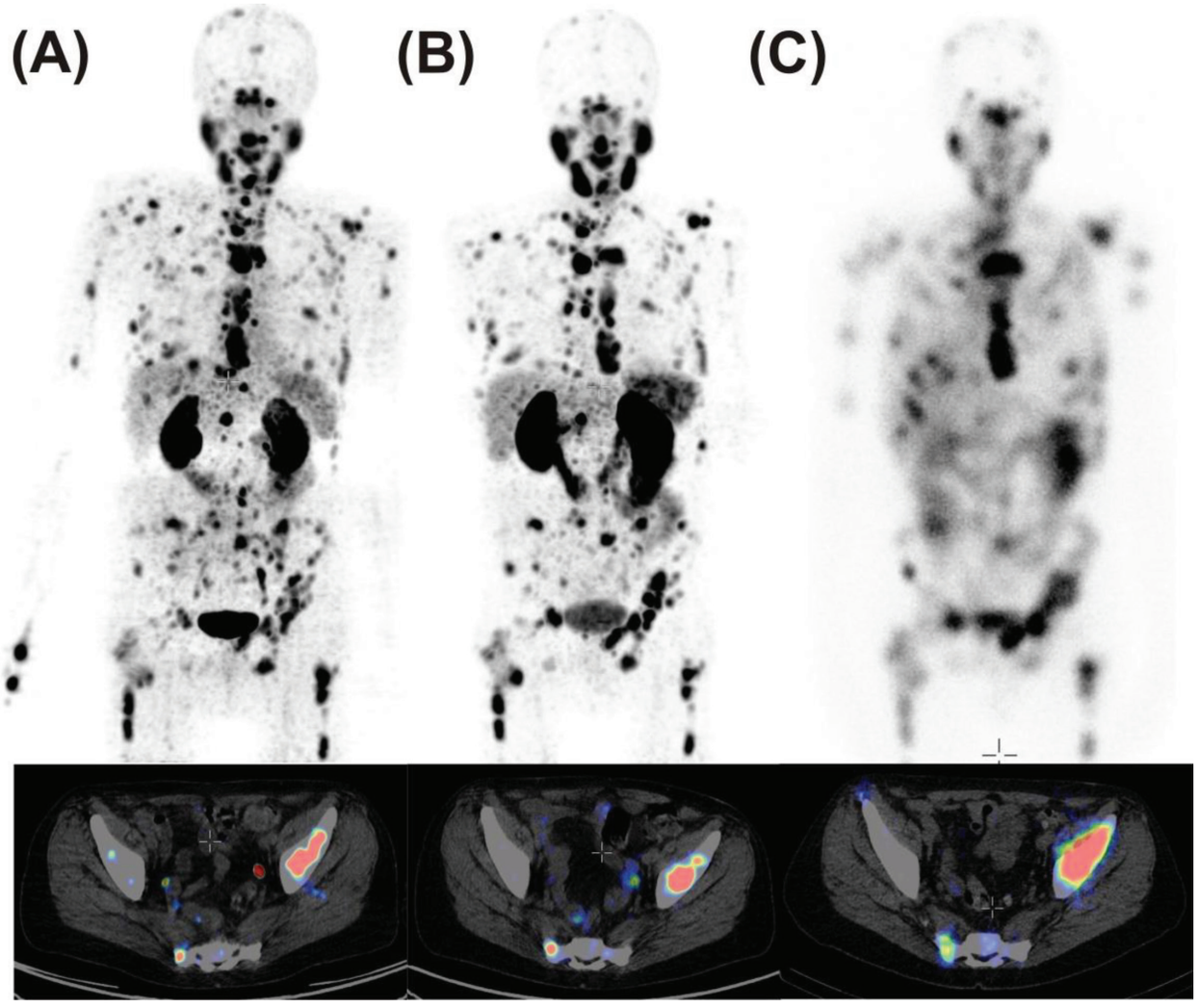

Figure 2. Maximal intensity projection (top) and representative slice (bottom) of PET/CT examination of a 70-year-old patient suffering of mCRPC with high tumor load using (A) [^{44}Sc]Sc-PSMA-617 (50 MBq, 60 min p.i.), and (B) [^{68}Ga]Ga-PSMA-11 (120 MBq, 60 min p.i.). (C) On the right-hand side, the planar scintigraphy (top) and a representative slice of the post-therapy SPECT/CT scan, about 24 h after application of 6.7 GBq of [^{177}Lu]Lu-PSMA-617 are shown [21].

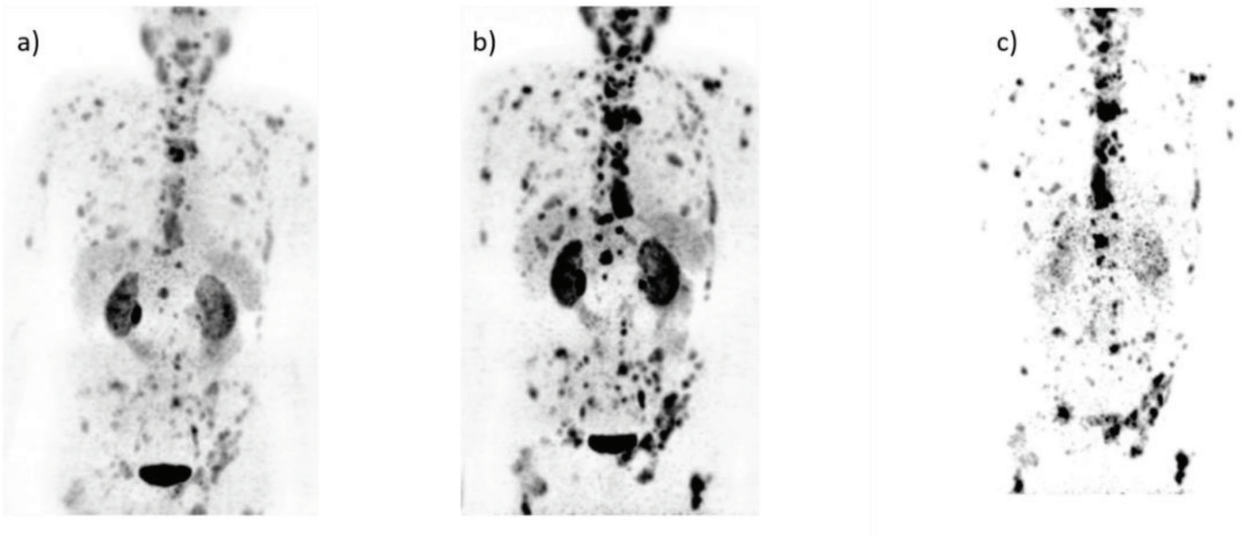

Figure 3. PET/CT whole body images at different time points p.i. using [^{44}Sc]Sc-PSMA-617: (A) 30 min, (B) 120 min, and (C) 19 h [21].

range: 1.78 E-01-4.88E-01 mSv/MBq) are the critical organs at risk receiving the highest dose followed by the urinary bladder wall, spleen, salivary glands, liver and small intestine while bone marrow dose was less and consequently not included in organs at risk for therapeutic application [69]. These findings are consistent with the results for small PSMA ligands of previous studies [71, 72]. Overall, the study confirmed absorbed doses to be higher for [^{44}Sc]Sc-PSMA-617 than for [^{68}Ga]Ga-PSMA-617, [^{68}Ga]Ga-PSMA-11, [^{68}Ga]Ga-PSMA-I&T but less than [^{124}I]I-PSMA [69]. Also the mean effective dose was found to be higher than [^{68}Ga]Ga-PSMA-617, [^{68}Ga]Ga-PSMA-11, [^{68}Ga]Ga-PSMA-I&T but less than [^{124}I]I-PSMA [69, 72].

In a follow-up study, Khawar et al. used [^{44}Sc]Sc-PSMA-617 PET/CT for pre-therapeutic dosimetry estimating the organ doses of [^{177}Lu]Lu-PSMA-617 administered [70]. This was performed by mathematical exploration of pharmacokinetics of [^{44}Sc]Sc-PSMA-617 to that of [^{177}Lu]Lu-PSMA-617. As preclinical in vitro and in vivo studies proofed better correlation between [^{44}Sc]Sc-PSMA-617 and [^{177}Lu]Lu-PSMA-617 as compared to ^{68}Ga-PSMA agents, the authors assumed that dosimetric analysis from 19.5 h imaging data of [^{44}Sc]Sc-PSMA-617 could be converted into 6.7 d imaging data for [^{177}Lu]Lu-PSMA-617 [20, 70]. Total activity (MBq) in source organs and whole body from reconstructed images of dynamic data, and three static whole body PET/CT images were decay corrected back to time of injection using scandium-44 half-life and then forward decay corrected using half-life of lutetium-177 for calculation [70].

Table 7 shows the mean residence times (MBq-h/MBq) for [^{44}Sc]Sc-PSMA-617 and based on [^{44}Sc]Sc-PSMA-617 pharmacokinetics for [^{177}Lu]Lu-PSMA-617 [69, 70].

Also for [^{177}Lu]Lu-PSMA-617, kidneys appeared to be the organ at risk (mean absorbed dose 0.44 mSv/MBq) followed by the salivary glands, liver, small intestine, spleen and urinary bladder wall [70]. The mean bone marrow absorbed dose was reported to be 0.05 mSv/MBq,

http://dx.doi.org/10.5772/intechopen.79157

PT No	[44Sc]Sc-PSMA-617		[177Lu]Lu-PSMA-617	
	Mean±	SD	Mean±	SD
Organs				
Salivary glands	0.03±	0.027	0.24	0.21
Kidneys	0.24±	0.109	1.51	0.48
Liver	0.35±	0.263	4.46	1.72
Spleen	0.07±	0.031	0.18	0.07
Small Intestine	0.05±	0.029	0.63	0.37
Bone marrow	0.09±	0.047	0.52	0.69
Urinary bladder contents	0.18±	0.195	0.33	0.32
Remainder of body	1.82	0.684	46.58	16.04

Table 7. Mean residence times (MBq-h/MBq) for [44Sc]Sc-PSMA-617 and estimated for [177Lu]Lu-PSMA-617 on basis of [44Sc]Sc-PSMA-617 pharmacokinetics [69, 70].

and the mean whole body dose was 0.08 mSv/MBq [70]. These findings are comparable with literature [11, 13, 17, 19]. Total dose (Gy) per cycle administered lies in a range from 2 till 3.26 Gy although applying the same therapeutic activities [70]. Due to the use of 3D instead of usual 2 D dosimetric analysis, it was found that it is possible to administer a mean dose of 52 Gy to reach a dose limit of 23 Gy [70] which is significantly higher than reported before with 30 Gy [13].

All together both studies proved that dosimetry using [44Sc]Sc-PSMA-617 PET/CT is possible applying a protocol which could be implemented in clinical daily routine.

4. Conclusion

Recent studies demonstrated the high potential of [44Sc]Sc-PSMA-617 for PET imaging in a preclinical as well as a clinical setting where it revealed more similar characteristics to [177Lu]Lu-PSMA-617 than the routinely used [68Ga]Ga-PSMA-11 [20, 21].

While images at early time points are comparable with those of [68Ga]Ga-PSMA-11, the advantages of scandium-44 over gallium-68 show up at late time points due to its longer half-life. Enabling delayed image acquisition would simplify patient management at improved image quality and allows improved pre-therapeutic dosimetry for therapy with [177Lu]Lu-PSMA-617. Especially for pre-therapeutic dosimetry scandium-44 would be beneficial as implementation in the clinical setting is uncomplicated, and there is no need for patient hospitalization. Together with the possibility transporting scandium-44 and 44Sc-radiopharmaceuticals further routes to radiopharmaceutical institutions without option for in-house production scandium-44 could make a significant contribution to patient care even in remote areas.

Author details

Elisabeth Eppard

Address all correspondence to: e.eppard@web.de

Johannes Gutenberg-University Mainz, Mainz, Germany

References

[1] UNPB. World Health Organization. International Agency for Research on Cancer. May 15, 2018. http://gco.iarc.fr/today/fact-sheets-cancers?cancer=19&type=0&sex=1

[2] Ahmadzadehfar H, Eppard E, Kürpig 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**:12477-12488. DOI: 10.18632/oncotarget.7245

[3] Rahbar K, Ahmadzadehfar H, Kratochwil C, Haberkorn U, Schäfers M, Essler M, et al. German Multicenter study investigating 177Lu-PSMA-617 Radioligand therapy in advanced prostate Cancer patients. Journal of Nuclear Medicine. 2017;**58**:85-90. DOI: 10.2967/jnumed.116.183194

[4] Ghosh A, Heston WDW. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. Journal of Cellular Biochemistry. 2004;**91**:528-539. DOI: 10.1002/jcb.10661

[5] Ahmadzadehfar H. Targeted therapy for metastatic prostate cancer with radionuclides. In: Mohan R, editor. Prostate Cancer - Leading-Edge Diagnostic Procedures and Treatments. Croatia: InTech; 2016. DOI: 10.5772/64016

[6] Pfestroff A, Luster M, Jilg CA, Olbert PJ, Ohlmann CH, Lassmann M, et al. Current status and future perspectives of PSMA-targeted therapy in Europe: Opportunity knocks. European Journal of Nuclear Medicine and Molecular Imaging. 2015;**42**:1971-1975. DOI: 10.1007/s00259-015-3186-3

[7] 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. Journal of Nuclear Medicine. 2015;**56**:914-920. DOI: 10.2967/jnumed.114.147413

[8] Ahmadzadehfar H, Wegen S, Yordanova A, Fimmers R, Kurpig S, Eppard E, et al. Overall survival and response pattern of castration-resistant metastatic prostate cancer to multiple cycles of radioligand therapy using 177LuLu-PSMA-617. European Journal of Nuclear Medicine and Molecular Imaging. 2017;**44**:1448-1454. DOI: 10.1007/s00259-017-3716-2

[9] Ahmadzadehfar H, Rahbar K, Kurpig S, Bogemann M, Claesener M, Eppard E, et al. Early side effects and first results of radioligand therapy with (177)Lu-DKFZ-617 PSMA

of castrate-resistant metastatic prostate cancer: A two-Centre study. EJNMMI Research. 2015;**5**:114. DOI: 10.1186/s13550-015-0114-2

[10] Yordanova A, Becker A, Eppard E, Kurpig S, Fisang C, Feldmann G, et al. The impact of repeated cycles of radioligand therapy using 177LuLu-PSMA-617 on renal function in patients with hormone refractory metastatic prostate cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2017;**44**:1473-1479. DOI: 10.1007/s00259-017-3681-9

[11] Fendler WP, Reinhardt S, Ilhan H, Delker A, Böning G, Gildehaus FJ, et al. Preliminary experience with dosimetry, response and patient reported outcome after 177Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer. Oncotarget. 2017;**8**:3581-3590. DOI: 10.18632/oncotarget.12240

[12] 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. Journal of Nuclear Medicine. 2016;**57**:1006-1013. DOI: 10.2967/jnumed.115.168443

[13] Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: A new radiopharmaceutical for the treatment of metastatic prostate cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2016;**43**:42-51. DOI: 10.1007/s00259-015-3174-7

[14] Kabasakal L, AbuQbeitah M, Aygun A, Yeyin N, Ocak M, Demirci E, Toklu T. Pre-therapeutic dosimetry of normal organs and tissues of (177)Lu-PSMA-617 prostate-specific membrane antigen (PSMA) inhibitor in patients with castration-resistant prostate cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2015;**42**:1976-1983. DOI: 10.1007/s00259-015-3125-3

[15] 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. Journal of Nuclear Medicine. 2016;**57**:1334-1338. DOI: 10.2967/jnumed.116.173757

[16] Zechmann CM, Afshar-Oromieh A, Armor T, Stubbs JB, Mier W, Hadaschik B, et al. Radiation dosimetry and first therapy results with a (124)I/ (131)I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. European Journal of Nuclear Medicine and Molecular Imaging. 2014;**41**:1280-1292. DOI: 10.1007/s00259-014-2713-y

[17] Kratochwil C, Giesel FL, Stefanova M, Benešová M, Bronzel M, Afshar-Oromieh A, et al. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate Cancer with 177Lu-Labeled PSMA-617. Journal of Nuclear Medicine. 2016;**57**:1170-1176. DOI: 10.2967/jnumed.115.171397

[18] Kulkarni HR, Singh A, Schuchardt C, Niepsch K, Sayeg M, Leshch Y, et al. PSMA-based radioligand therapy for metastatic castration-resistant prostate cancer: The bad Berka experience since 2013. Journal of Nuclear Medicine. 2016;**57**:97S-104S. DOI: 10.2967/jnumed.115.170167

[19] Okamoto S, Thieme A, Allmann J, D'Alessandria C, Maurer T, Retz M, et al. Radiation dosimetry for 177Lu-PSMA I&T in metastatic castration-resistant prostate cancer: Absorbed dose in normal organs and tumor lesions. Journal of Nuclear Medicine. 2017;**58**:445-450. DOI: 10.2967/jnumed.116.178483

[20] Umbricht CA, Benesova M, Schmid RM, Turler A, Schibli R, van der Meulen, Nicholas P, Muller C. 44Sc-PSMA-617 for radiotheragnostics in tandem with 177Lu-PSMA-617-preclinical investigations in comparison with 68Ga-PSMA-11 and 68Ga-PSMA-617. EJNMMI Research. 2017;**7**:9. DOI: 10.1186/s13550-017-0257-4

[21] Eppard E, de La FA, Benešová M, Khawar A, Bundschuh RA, Gärtner FC, et al. Clinical translation and first in-human use of 44ScSc-PSMA-617 for PET imaging of metastasized castrate-resistant prostate cancer. Theranostics. 2017;**7**:4359-4369. DOI: 10.7150/thno.20586

[22] Schäfer M, Bauder-Wüst U, Leotta K, Zoller F, Mier W, Haberkorn U, et al. A dimerized urea-based inhibitor of the prostate-specific membrane antigen for 68Ga-PET imaging of prostate cancer. European Journal of Nuclear Medicine and Molecular Imaging Research. 2012;**2**:23

[23] Eder M, Schäfer M, Bauder-Wüst U, Hull W-E, Wängler C, Mier W, et al. 68 Ga-complex lipophilicity and the targeting property of a urea-based PSMA inhibitor for PET imaging. Bioconjugate Chemistry. 2012;**23**:688-697. DOI: 10.1021/bc200279b

[24] http://www.nndc.bnl.gov/chart. [Accessed: 16 May 2018]

[25] Domnanich KA, Müller C, Farkas R, Schmid RM, Ponsard B, Schibli R, et al. 44Sc for labeling of DOTA- and NODAGA-functionalized peptides: Preclinical in vitro and in vivo investigations. EJNMMI Radiopharmacy and Chemistry. 2017;**1**:2. DOI: 10.1186/s41181-016-0013-5

[26] Hernandez R, Valdovinos HF, Yang Y, Chakravarty R, Hong H, Barnhart TE, Cai W. (44)Sc: An attractive isotope for peptide-based PET imaging. Molecular Pharmaceutics. 2014;**11**:2954-2961. DOI: 10.1021/mp500343j

[27] Muller C, Bunka M, Reber J, Fischer C, Zhernosekov K, Turler A, Schibli R. Promises of cyclotron-produced 44Sc as a diagnostic match for trivalent beta--emitters: In vitro and in vivo study of a 44Sc-DOTA-folate conjugate. Journal of Nuclear Medicine. 2013;**54**:2168-2174. DOI: 10.2967/jnumed.113.123810

[28] Müller C, Bunka M, Haller S, Köster U, Groehn V, Bernhardt P, et al. Promising prospects for 44Sc-/47Sc-based theragnostics: Application of 47Sc for radionuclide tumor therapy in mice. Journal of Nuclear Medicine. 2014;**55**:1658-1664. DOI: 10.2967/jnumed.114.141614

[29] Singh A, Baum RP, Klette I, van der Meulen, Nicholas P, Muller C, Tuerler A, Schibli R. Scandium-44 DOTATOC PET/CT: First in-human molecular imaging of neuroendocrine tumors and possible perspectives for Theranostics. Journal of Nuclear Medicine 2015;**56**:267

[30] Rösch F. Scandium-44: Benefits of a long-lived PET radionuclides available from the 44Ti/44Sc generator system. Current Radiopharmaceuticals. 2012;**5**:187-201

[31] Filosofov DV, Loktionova NS, Rösch F. A 44Ti/44Sc radionuclide generator for potential application of 44Sc-based PET-radiopharmaceuticals. Radiochimica Acta. 2010;**98**:149-156

[32] Greene MW, Hillman M. A scandium generator. The International Journal of Applied Radiation and Isotopes. 1967;**18**:540-541

[33] Alliot C, Kerdjoudj R, Michel N, Haddad F, Huclier-Markai S. Cyclotron production of high purity (44m,44)Sc with deuterons from (44)CaCO3 targets. Nuclear Medicine and Biology. 2015;**42**:524-529. DOI: 10.1016/j.nucmedbio.2015.03.002

[34] Wittwer D, Dressler R, Eichler R, Gäggeler HW, Piguet D, Serov A, et al. The thermal release of scandium from titanium metal – A simple way to produce pure 44 Sc for PET application. Radiochimica Acta. 2011;**99**:193-196. DOI: 10.1524/ract.2011.1832

[35] Seidl E, Lieser KH. Die Radionuklidgeneratoren 113Sn/113mIn, 68Ge/68Ga und 44Ti/44Sc. Radiochimica Acta. 1973;**19**:196-199

[36] Radchenko V, Meyer CAL, Engle JW, Naranjo CM, Unc GA, Mastren T, et al. Separation of 44Ti from proton irradiated scandium by using solid-phase extraction chromatography and design of 44Ti/44Sc generator system. Journal of Chromatography. A. 2016;**1477**: 39-46

[37] Rösch F, Baum RP. Generator-based PET radiopharmaceuticals for molecular imaging of tumours: On the way to THERANOSTICS. Dalton Transactions. 2011;**40**:6104-6111. DOI: 10.1039/c0dt01398f

[38] Pruszyński M, Majkowska-Pilip A, Loktionova NS, Eppard E, Roesch F. Radiolabeling of DOTATOC with the long-lived positron emitter 44Sc. Applied Radiation and Isotopes. 2012;**70**:974-979. DOI: 10.1016/j.apradiso.2012.03.005

[39] Alenitzky YG, Novgorodov AF, Filosofov DV, Skripnik AV, Kaplun VG, Suzikov AG, Eliseev IA, Rösch F. ^{44}Ti: Investigation of Target Preparation, Irradiation and Yields in the 45Sc(p,2n) Process. Mainz; 2005. E:\1 - Bibliothek\Paper\2005 Jahresberich KC MZ.pdf

[40] Pruszynski M, Loktionova NS, Filosofov DV, Rösch F. Post-elution processing of 44Ti/44Sc generator-derived 44Sc for clinical application. Applied Radiation and Isotopes. 2010;**68**:1636-1641. DOI: 10.1016/j.apradiso.2010.04.003

[41] Nagy G, Szikra D, Trencsényi G, Fekete A, Garai I, Giani AM, et al. AAZTA: An ideal chelating agent for the development of 44 Sc PET imaging agents. Angewandte Chemie. 2017;**129**:2150-2154. DOI: 10.1002/ange.201611207

[42] Mausner LF, Joshi V, Kolsky KL, Meinken GE, Mease RC, Sweet MP, Srivastava SC. Evaluation of chelating agents for radioimmunotherapy with scandium-47. Journal of Nuclear Medicine. 1995;**36**:104

[43] Koumarianou E, Loktionova NS, Fellner M, Roesch F, Thews O, Pawlak D, et al. 44Sc-DOTA-BN[2-14]NH2 in comparison to 68Ga-DOTA-BN[2-14]NH2 in pre-clinical investigation. Is 44Sc a potential radionuclide for PET? Applied Radiation and Isotopes. 2012;**70**:2669-2676. DOI: 10.1016/j.apradiso.2012.08.004

[44] Anderson WT, Strand M. Stability, targeting, and biodistribution of scandium-46- and gallium-67-labeled monoclonal antibody in erythroleukemic mice. PubMed - NCBI. https://

www.ncbi.nlm.nih.gov/pubmed/?term=Cancer+Res.+45+(1985)+2154%E2%80%932158. [Accessed: 7 May 2018]

[45] Cotton SA. Recent advances in the chemistry of scandium. Polyhedron. 1999;**18**:1691-1715. DOI: 10.1016/S0277-5387(99)00039-X

[46] Meehan PR, Aris DR, Willey GR. Structural chemistry of Sc(III): An overview. Coordination Chemistry Reviews. 1999;**181**:121-145. DOI: 10.1016/S0010-8545(98)00214-8

[47] Marques F, Gano L, Paula Campello M, Lacerda S, Santos I, Lima LMP, et al. 13- and 14-membered macrocyclic ligands containing methylcarboxylate or methylphosphonate pendant arms: Chemical and biological evaluation of their (153)Sm and (166)Ho complexes as potential agents for therapy or bone pain palliation. Journal of Inorganic Biochemistry. 2006;**100**:270-280. DOI: 10.1016/j.jinorgbio.2005.11.011

[48] Majkowska-Pilip A, Bilewicz A. Macrocyclic complexes of scandium radionuclides as precursors for diagnostic and therapeutic radiopharmaceuticals. Journal of Inorganic Biochemistry. 2011;**105**:313-320

[49] Zhernosekov K, Bunka M, Hohn A, Schibli R, Türler A. Development and evaluation of (44)Ti production on high energy protons. Journal of Labelled Compounds and Radiopharmaceuticals 2011;**54**:S239. DOIL 10.1002/jlcr.1926

[50] Duchemin C, Guertin A, Haddad F, Michel N, Métivier V. Production of scandium-44 m and scandium-44 g with deuterons on calcium-44: Cross section measurements and production yield calculations. Physics in Medicine and Biology. 2015;**60**:6847-6864. DOI: 10.1088/0031-9155/60/17/6847

[51] Kamel A, Cydzik I, Federica S, Krajewski S, Kasparek A, Bilewics A. Cyclotron production of 44Sc - new radionuclide for PET technique. Journal of Labelled Compounds and Radiopharmaceuticals. 2011;**54**. DOI: S53. DOI:10.1002/jlcr.1925

[52] Krajewski S, Cydzik I, Kamel A, Bulgheroni A, Simonell F, Majakowska-Pilip A, Bilewicz A. Simple procedure of dotatate labelling with cyclotron produced 44SC and 43SC. Nuclear Medicine Review. 2012;**15**:22-46

[53] Severin GW, Engle JW, Valdovinos HF, Barnhart TE, Nickles RJ. Cyclotron produced 44gSc from natural calcium. Applied Radiation and Isotopes. 2012;**70**:1526-1530. DOI: 10.1016/j.apradiso.2012.04.030

[54] Szkliniarz K, Sitarz M, Walczak R, Jastrzębski J, Bilewicz A, Choiński J, et al. Production of medical Sc radioisotopes with an alpha particle beam. Applied Radiation and Isotopes. 2016;**118**:182-189. DOI: 10.1016/j.apradiso.2016.07.001

[55] Valdovinos HF, Hernandez R, Barnhart TE, Graves S, Cai W, Nickles RJ. Separation of cyclotron-produced 44Sc from a natural calcium target using a dipentyl pentylphosphonate functionalized extraction resin. Applied Radiation and Isotopes. 2015;**95**:23-29. DOI: 10.1016/j.apradiso.2014.09.020

[56] van der Meulen NP, Bunka M, Domnanich KA, Müller C, Haller S, Vermeulen C, et al. Cyclotron production of (44)Sc: From bench to bedside. Nuclear Medicine and Biology. 2015;**42**:745-751. DOI: 10.1016/j.nucmedbio.2015.05.005

[57] Walczak R, Krajewski S, Szkliniarz K, Sitarz M, Abbas K, Choiński J, et al. Cyclotron production of (43)Sc for PET imaging. EJNMMI Physics. 2015;**2**:33. DOI: 10.1186/s40658-015-0136-x

[58] Hassan HE, Al-Abyad M, Mohamed G. Production of 44Ti→44Sc generator in comparison with direct routes by cyclotrons: Cross section evaluation using nuclear models codes. Arab Journal of Nuclear Sciences and Applications. 2018;**51**

[59] Krajewski S, Cydzik I, Abbas K, Bulgheroni A, Simonelli F, Holzwarth U, Bilewicz A. Cyclotron production of 44 Sc for clinical application. Radiochimica Acta. 2013;**101**:333-338. DOI: 10.1524/ract.2013.2032

[60] Hashimoto T, Nakai K, Wakasaya Y, Tanihata I, Fulop Z, Kumagai H, et al. Half-life of Ti. Nuclear Physics A. 2001;**686**:591-599. DOI: 10.1016/S0375-9474(00)00566-2

[61] Hosain F, Syed I, Spencer RP. The Role of Positron Emitters in Nuclear Medicine with Special Reference to Scandium 44; 1977

[62] Mirza MY, Aziz A. A scandium generator. Radiochimica Acta. 1969;**11**:43-44

[63] Radchenko V, Engle JW, Medvedev DG, Maassen JM, Naranjo CM, Unc GA, et al. Proton-induced production and radiochemical isolation of 44Ti from scandium metal targets for 44Ti/44Sc generator development. Nuclear Medicine and Biology. 2017;**50**:25-32. DOI: 10.1016/j.nucmedbio.2017.03.006

[64] Asti M, Gd P, Fraternali A, Grassi E, Sghedoni R, Fioroni F, et al. Validation of 68Ge/68Ga generator processing by chemical purification for routine clinical application of 68Ga-DOTATOC. Nuclear Medicine and Biology. 2008;**35**:721-724. DOI: 10.1016/j.nucmedbio.2008.04.006

[65] Zhernosekov KP, Filosofov DV, Baum RP, Aschoff P, Bihl H, Razbash AA, et al. Processing of generator-produced 68Ga for medical application. Journal of Nuclear Medicine. 2007;**48**:1741-1748

[66] Reddy JA, Xu L-C, Parker N, Vetzel M, Leamon CP. Preclinical evaluation of (99m)Tc-EC20 for imaging folate receptor-positive tumors. Journal of Nuclear Medicine. 2004;**45**:857-866

[67] European Pharmacopoeia: 8.6 to 8.8. Strasbourg: Council Of Europe; 2015

[68] Eppard E, Pèrez-Malo M, Rösch F. Improved radiolabeling of DOTATOC with trivalent radiometals for clinical application by addition of ethanol. EJNMMI Radiopharmacy and Chemistry. 2017;**1**:314. DOI: 10.1186/s41181-016-0010-8

[69] Khawar A, Eppard E, Sinnes JP, Roesch F, Ahmadzadehfar H, Kürpig S, et al. 44ScSc-PSMA-617 biodistribution and dosimetry in patients with metastatic castration-resistant prostate carcinoma. Clinical Nuclear Medicine. 2018;**43**:323-330. DOI: 10.1097/RLU.0000000000002003

[70] Khawar A, Eppard E, Sinnes JP, Roesch F, Ahmadzadehfar H, Kürpig S, et al. Prediction of normal organ absorbed doses for 177LuLu-PSMA-617 using 44ScSc-PSMA-617 pharmacokinetics in patients with metastatic castration resistant prostate carcinoma. Clinical Nuclear Medicine. 2018. DOI: 10.1097/RLU.0000000000002102

[71] 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. Journal of Nuclear Medicine. 2015;**56**:1697-1705. DOI: 10.2967/jnumed.115.161299

[72] Pfob CH, Ziegler S, Graner FP, Köhner M, Schachoff S, Blechert B, et al. Biodistribution and radiation dosimetry of (68)Ga-PSMA HBED CC-a PSMA specific probe for PET imaging of prostate cancer. European Journal of Nuclear Medicine and Molecular Imaging. 2016;**43**:1962-1970. DOI: 10.1007/s00259-016-3424-3

IntechOpen