

Gallium-68 or Fluorine-18 for prostate cancer imaging?

Claudia Kesch¹, Clemens Kratochwil³, Walter Mier³, Kopka Klaus², Frederik L. Giesel^{3§}

(1) Department of Urology, University Hospital Heidelberg, Germany

(2) Division of Radiopharmaceutical Chemistry, German Cancer Research Center (DKFZ) Heidelberg, Germany.

(3) Department of Nuclear Medicine, University Hospital Heidelberg, Germany

§ Corresponding author:

Frederik L. Giesel

Department of Nuclear Medicine

University Hospital Heidelberg

Im Neuenheimer Feld 110

69120 Heidelberg

Tel: +49-6221-56-39461

Fax: +49-6221-56-8672

Email: frederiek@egeisel.com

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ABSTRACT:

The introduction of prostate specific membrane antigen (PSMA)-positron emission tomography (PET) using ^{68}Ga revolutionized prostate cancer imaging. Outperforming standard imaging, it allows complete staging of the local tumor and possible lymph nodes, visceral or bone metastases with high accuracy in only one examination (1,2). Sensitivities of 66% and specificities of 99% were observed for primary lymph node staging (2). Moreover, it has become an excellent staging tool for recurrent prostate cancer even at early stage and low PSA levels (1,3). PSMA-positive detection rates of 50%-58% were reported for serum PSA values less than <0.5 ng/mL, 58%-73% for PSA values of 0.5 - <1 ng/mL and up to $>90\%$ at higher PSA values (1,3). Considering the high incidence of prostate cancer worldwide, the possibility of large scale batch production capacity of the novel ^{18}F -labelled PSMA-tracers ^{18}F -PSMA-1007 and ^{18}F -DCFPyL offers a promising advantage. Furthermore, the nuclear decay characteristics of ^{18}F , such as optimal positron energy and a half-life enabling delayed PET-acquisition, may also translate into refined imaging quality.

PSMA is a type II transmembrane glycoprotein with enzymatic carboxypeptidase activity. Expression is seen at low levels i.a. in the brain, kidneys, salivary glands, small intestines and normal prostatic tissue (4,5). However, until today the function of this enzyme, also called glutamate carboxypeptidase II (GCP II), in prostate cancer is still unclear (4). Compared to its normal expression, PSMA is highly overexpressed in prostate cancer cells and the level of PSMA expression rises with increasing tumor dedifferentiation as well as in metastatic and hormone refractory cancer (5–7). This makes PSMA an ideal imaging and therapeutic target for the treatment of prostate cancer.

By now several radiolabelled small-molecule inhibitors of PSMA have been designed (8). Currently, the low-molecular weight PSMA inhibitor ^{68}Ga -PSMA-11 is the most widely used PET tracer (9), but might have some disadvantages with respect to production capacity and nuclear decay properties. Anyhow, its main advantage is the commercial availability of gallium-68 (^{68}Ga) via germanium-68 (^{68}Ge) generators which allows the convenient batch production of approximately 2-4 patient doses per generator elution. For centers without access to a cyclotron and moderate examination numbers these generators present a reasonable priced upfront investment. PSMA-11 contains the chelator HBED-CC which allows labeling with kit-formulations at ambient temperature without critical demands regarding radiochemistry (10,11). At the same time, ^{68}Ga has a physical half-life of only 68 min. Therefore, ^{68}Ga -PSMA-PET scans are preferably performed in house but delivery of sufficient tracer activities to remote centers is challenging. Consequently, in large centers with high patient numbers several productions per day are required (12) or operating multiple generators simultaneously multiplies costs. To meet the quantitative demand of those centers, the use of ^{18}F -labelled PSMA tracers could overcome these limitations. PET radiopharmacies with an on-site cyclotron can produce high activities of ^{18}F at moderate costs. The physical half-life (110 min) of ^{18}F -labelled PSMA tracers such as PSMA-1007 and DCFPyL could also enable centralized production and delivery to more distant center by a satellite concept. At the same time ^{18}F has a lower positron energy than ^{68}Ga (0.65 MeV vs. 1.90 MeV),

which theoretically results in an increased maximum spatial resolution (13). Figure 1 shows a schematic comparison of PET tracers labeled with ^{18}F and ^{68}Ga .

But does ^{18}F really live up to its promises?

At the moment two promising ^{18}F -labelled PSMA-tracers are under clinical investigation: ^{18}F -DCFPyL and ^{18}F -PSMA-1007. Few studies evaluated ^{18}F -DCFPyL in the setting of recurrent prostate cancer or biochemical relapse (14–16) but until now there are no data published on primary prostate cancer and only in a subgroup of patients the imaging results were confirmed by histopathological evaluation. For ^{18}F -PSMA-1007 one proof of concept study examined the tracer in 10 patients with primary high-risk prostate cancer and in majority with LN metastases, which were systematically evaluated histopathologically (17). Only, nevertheless interesting, case reports have been published in the setting of biochemical relapse (17) and for tailoring an advanced stage patient to PSMA-RLT (18). ^{18}F -PSMA-1007 was reported favorable for primary tumors and local relapse due to low clearance via the urinary tract (1.2% ID over 2 h). In contrast urinary excretion of ^{18}F -DCFPyL, ^{68}Ga -PSMA-11 and ^{68}Ga -PSMA-617 is remarkable higher (>10% ID over 2h) (1,16,19). However, this improvement is less related to the radiolabelling moiety but rather to the optimized structure of the overall molecule. Thus, today the published overall experience with ^{18}F -PSMA-ligands is still limited to about 100 patients which also diversify into different clinical settings. In contrast, confirmative publications from different centers, in sum now reporting several thousand patients examined with ^{68}Ga -PSMA-11, present a robust basis about the value and limitation of these radionuclide/ligand-combination (3,20).

Experience regarding intra-individual comparisons between ^{68}Ga - and ^{18}F -PSMA ligands is limited to 25 patients (21). A separate cohort of 62 patients with biochemical relapse examined with ^{18}F -DCFPyL performed comparable to literature values of ^{68}Ga -PSMA-11 and even slightly better than the intra-institutional ^{68}Ga -PSMA controls (21). As promising as these preliminary results are, they also demonstrate that larger, prospective clinical trials evaluating ^{18}F -labelled PSMA tracers in different clinical settings are mandatory.

Therefore, for now it is too early to answer the question “Gallium-68 or Fluorine-18 for prostate cancer imaging?”. Both should be considered widely exchangeable for the majority of clinical indications (Figure-1). Today it is rather the perspective of “decentralized” or “centralized” production to achieve adequate coverage for the clinical demand of examination capacity.

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Physical Difference or Practical demand	Gallium-68	Fluorine-18
Half-Life	<p>68 min</p> <ul style="list-style-type: none"> less radiation burden to relatives (complete decay within few hours after examination) only shippable to close satellite centers. 	<p>110 min</p> <ul style="list-style-type: none"> satellite shipping possible delayed imaging after longer incubation time
Positron energy	<p>1.90 MeV</p> <ul style="list-style-type: none"> the theoretical higher penetration depth of the positron (most pronounced in lungs) is widely negligible in solid tissues using standard reconstruction algorithms and adjusted filtering 	<p>0.65 MeV</p> <ul style="list-style-type: none"> lower radiation burden despite longer half-life theoretically higher resolution
Labelling	<p>Chelator molecules</p> <ul style="list-style-type: none"> Dedicated environment required, but Kit-formulation (One vial, room temperature) also possible 	<p>Prosthetic group molecules</p> <ul style="list-style-type: none"> requires dedicated environment (hot cells, remotely controlled radiosynthesizers)
Theranostic approach	<ul style="list-style-type: none"> One molecule approach: radiolabelling with diagnostic (e.g. ⁶⁸Ga) and therapeutic radionuclides (e.g. ¹⁷⁷Lu, ²²⁵Ac, ²¹³Bi) possible (please note: PSMA-11 can only be radiolabelled with diagnostic radionuclide) 	<ul style="list-style-type: none"> Tandem approach: different chemical structure of diagnostic and (more or less structurally related) therapeutic tracer (e.g. PSMA-1007 / PSMA-617, DCFPyL / MIP-1095)
Upfront investment /Running costs	<ul style="list-style-type: none"> generators (~50t USD/EUR, ~2 generators per year) Radiosynthesizer or Kit-production 	<ul style="list-style-type: none"> cyclotron (~1000t to 3000t USD/EUR) Radiosynthesizers connected to a cyclotron; 18O-water as target material per production run
Scalability	<ul style="list-style-type: none"> Defined generator capacity 	<ul style="list-style-type: none"> Production demand well scalable to adapt requested examination numbers