PET/CT imaging of prostate cancer in the era of small molecule prostate specific membrane antigen targeted tracers

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Keywords: Biochemical failure - Staging - Theragnostics - Conventional imaging

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Received:
7 August 2020
Accepted revised:
18 October 2020

Abstract
Staging and restaging of prostate cancer is crucial for treatment planning and prognosis. Accurate localization is of high relevance for a tailor-made therapy and an early detection of unknown metastatic spread can lead to a survival benefit. Evidence based guidelines that are currently in use were established using data from conventional imaging (such as magnetic resonance imaging (MRI), computed tomography (CT) and bone scintigraphy). Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) is rapidly evolving with promising results. However, up to now there is little consensus about the usefulness of this method, especially since different guidelines are "biased" depending on the association that shapes them. Firstly, little data exists on the staging of low risk tumors and probably PSMA PET/CT should be avoided in this setup for most patients. On the other hand, it has been recently proven that PSMA PET/CT can replace CT and bone scintigraphy (combined) in staging of advanced prostate cancer. Furthermore, the examination gained general acceptance through its excellent performance in biochemical recurrence, both for castration naïve and castration resistant tumors, and should be implemented where available. It is undisputed that PSMA PET/CT provides a more accurate picture of prostate cancer patients and can lead to both upstaging and downstaging, thus affecting therapeutic management. Though it is not clear yet if the more accurate staging will lead to better therapeutic decisions and improve patient outcomes, PSMA PET/CT appears as the next imaging standard for prostate cancer for the years to come.

Hell J Nucl Med 2020; 23(3): 339-345 *Epub ahead of print: 14 December 2020* *Published online: 28 December 2020*

Introduction

Prostate cancer (PC) is the most common type of cancer in men and the third leading cause of cancer death worldwide [1]. Staging, and restaging, of PC is crucial for treatment planning and prognosis as the accurate localization is of high relevance for a tailor-made salvage therapy (e.g. salvage radiotherapy or salvage lymph node dissection) and an early detection of unknown metastatic spread can provide a survival benefit.

Various studies have shown that the standard of care (i.e. that which has been used up to now) for PC suffers from various limitations. Computed tomography (CT) and magnetic resonance imaging (MRI) rely primarily on size for detection of lymphogenous spread. However, up to 80% of nodal metastases in PC are smaller than 8mm in size, and thus morphological imaging fails to recognize most of them [2]. Furthermore, the additional information gained from diffusion-weighted images (DWI) on MRI in many cases fails to distinguish between benign and malignant lymph nodes [3]. Thus, when using anatomical imaging a high number of false-negative results are generated, especially when it comes to nodal staging in intermediate-to-high risk or metastatic PC. Besides that, high false-positive results are produced due to enlarged lymph nodes representing other pathologies (reactive, granulomatous disease, nodal metastases from a synchronous primary). Bone scintigraphy, that detects the increased osteoblastic activity earlier than CT, is also hampered from a high number of false positive findings. Similarly, visceral findings detected with conventional imaging have a range of differential diagnoses and do not offer the specificity provided by molecular imaging, which targets the tumour cells directly.

Consequently, a lot of effort has been carried out in recent years in developing new molecular imaging techniques in tackling these problems, with small-molecule prostate specific membrane antigen targeted (PSMA) tracers being the most promising agents. In addition, these molecules can be labeled in many cases with a therapeutic counterpart (of the diagnostical radiopharmacon) using alpha or betta emitters for therapeutic pur-

purposes (i.e. theragnostics). An indirect sign of the intensive efforts carried out is that about 130 prospective clinical studies registered are currently investigating PSMA-positron emission tomography (PET) in PC (as of October 15th, 2020).

Spectrum of PET radiopharmaca in PC

The workhorse of PET/CT imaging is (still) fluorine-18-fluorodeoxyglucose (^{18}F-FDG), a radiolabeled glucose that takes advantage of the elevated anaerobic metabolism of most malignant cells as compared to the surrounding tissues to make them detectable. Furthermore, in oncology, the Warburg effect is a form of modified cellular metabolism found in cancer cells, which tend to favor a specialized fermentation over the aerobic respiration pathway that most other cells of the body prefer. Yet the use of ^{18}F-FDG PET/CT is of limited value for PC as only adenocarcinoma with neuroendocrine differentiation, neuroendocrine tumors of the prostate or patients with advanced disease experience an increased glucose metabolism. Hence, novel radiopharmaca for imaging of PC have rapidly emerged over the last decades.

Radiolabelled choline derivatives such as carbon-11 (^{11}C)-Choline or ^{18}F-Fluorocholine have been investigated and used throughout the world for more than a decade, mainly for restaging of PC after biochemical failure and for the primary staging of high-risk PC patients. Both have shown promising results in terms of sensitivity, but they have limited sensitivity [4]. Several other PET radiopharmaceuticals such as ^{11}C acetate or ^{18}F-fluorocyclobutane-1-carboxylic acid (FACBC) have been developed and evaluated in the past, but none of these gained clinical acceptance due to absence of superiority over the choline derivatives. The most important radiopharmacon developed and used in the U.S.A. for PC is ^{18}F-fluciclovine (Axumin®), however after a prospective head-to-head comparison with gallium-68 (^{68}Ga)-PSMA-11 PET/CT in patients with early biochemical recurrence showed inferior results, its use remains limited [5]. The U.S. Food and Drug Administration approved Axumin®, since 2016 in men with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment.

Currently, by far the most promising candidates for PC imaging are radiolabelled small molecules that bind with high affinity to the PSMA. This is a cell surface protein strongly overexpressed in PC cells and is imaged preferably with positron-emission tomography (Figure 1).

PSMA ligands

The identification and use of PSMA as a target structure for PC imaging gave great thrust to the imaging of PC and nuclear medicine in general, as it is a target molecule suitable for theragnostics. The most commonly used ligands for PET/CT imaging are ^{68}Ga-PSMA-11 (known as ^{68}Ga-HBED-CC or ^{68}Ga-HBED-PSMA), ^{68}Ga-PSMA-I&T and ^{68}Ga-PSMA-617. Advantages of ^{68}Ga-chemistry is that having a ^{68}Ge/^{68}Ga generator is an excellent solution for sites not having an in-house cyclotron (or access to ^{18}F labelled compounds) and, with a generator half-life of 271 days, that they can remain "autonomous" for ^{68}Ga labeling. Additionally, the theragnostic experiences with lutetium-177 (^{177}Lu)-labeled PSMA inhibitors are based on adequate uptake in a preceding ^{68}Ga-PSMA PET/CT scan, as the PSMA molecule is identical for both imaging and therapy [6]. Nevertheless, a lot of effort has been made to shift from ^{68}Ga- to ^{18}F-labeled PSMA-targeted compounds such as ^{18}F-N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-F-fluorobenzyl-L-cysteine (DCFBC), 2-(3-{1-carboxy-5-[(6-[(18)F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (^{18}F-DCFPyL), ^{18}F-

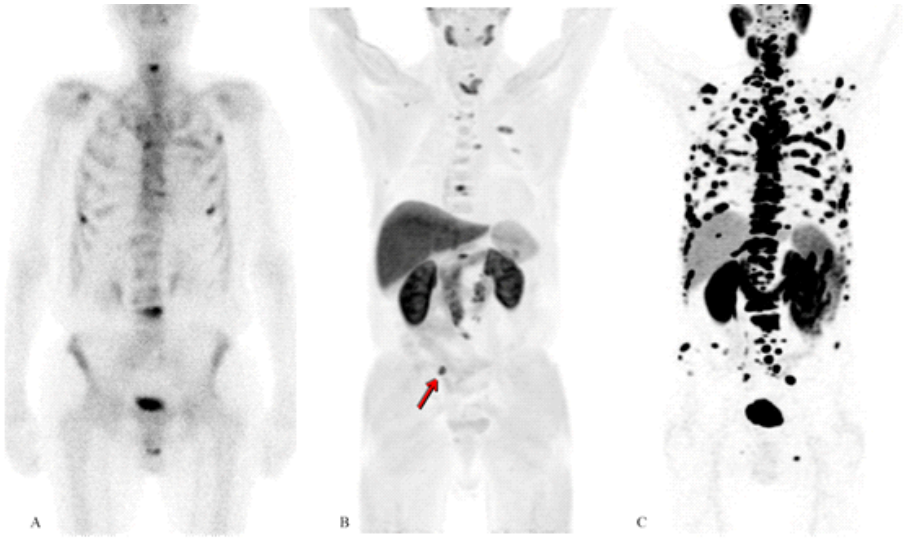

Figure 1. Patient with prostate cancer referred for bone scintigraphy due to biochemical failure, which demonstrates a multifocal increased osteoblastic activity compatible with multifocal osseous spread (A). Within one week the patient also underwent a ^{11}C-Choline PET/CT in order to exclude visceral spread (B) for treatment planning. Due to the different mechanism and the direct visualization of the upregulated choline kinase additional to some bone metastasis, a common iliac lymph nodal metastasis right (arrow) is depicted (maximum intensity projection (MIP); B). However, the true spread of the disease is much more extended if the ^{68}Ga-PSMA PET/CT is utilized (MIP; C).

PSMA-1007 and the newest ^{18}F-CTT1057, ^{18}F-FSU-880, ^{18}F-JK-PSMA-7 and ^{18}F-AlF-PSMA-11. This is driven mainly from the fact that imaging with ^{68}Ga has multiple drawbacks as compared to ^{18}F [6]:

I The lower positron yield (89.1% vs. ^{18}F, 96.9%) and higher positron energy of ^{68}Ga (1,899keV vs. ^{18}F, 633keV) may negatively impact image quality, also contributing counterproductively to the partial volume effect, and subsequently to quantification.

ii. A large variety of commercially available ^{68}Ge/^{68}Ga generators with different properties are available in the market that may add to the complexity of labeling, due to different properties. Furthermore, delays are observed in the delivery times of certified ^{68}Ge/^{68}Ga generators, depending on the authorities of each country.

iii. In terms of economics a relatively high throughput of patients is needed to reduce the cost per injected dose for ^{68}Ga generators, due to the more limited "shipping range" of ^{68}Ga-labeled PSMA-targeted radiotracers to remote PET/CT facilities (because of the shorter half-life of ^{68}Ga over ^{18}F and lower capabilities of generators for starting activity).

iv. The longer half-life of ^{18}F (110 minutes for ^{18}F vs 68 minutes for ^{68}Ga) is logistically less demanding for delayed imaging protocols, which may be advantageous in terms of lesion detection rate and tumor-to-background ratios. This also applies to increased acquisition times, which improves overall imaging quality by reducing image noise.

v. Additionally, slightly different pharmacokinetics (e.g. the preferable significantly reduced renal elimination of ^{18}F-PSMA-1007 as compared ^{68}Ga-PSMA-11) could play an important role for lesion detectability, especially when it comes to local assessment (Figure 2).

Staging

In a retrospective analysis published recently by Ferraro et al. (2020) the results of 116 patients who underwent ^{68}Ga-PSMA-11 PET/CT or MRI scans for staging of their intermediate or high-risk PC were presented. The primary tumour was false negative only in 3 patients (2.6%). Additionally, nodal metastases were detected in 28 patients (24%) and bone metastases in 14 patients (12%). Compared with clinical staging and conventional imaging, ^{68}Ga-PSMA-11 PET/CT resulted in additional/unknown information in approximately one third of the patients (42/116; 36%), of which 32 patients would most likely have received a change in their management, either to a different therapy modality or adjusted treatment details (e.g. radiation planning) [7].

Multiple studies have shown that PSMA PET/CT has a moderate sensitivity but very high specificity for detection of nodal metastasis in intermediate-to-high-risk prostate cancer. For example, Koerber and colleagues demonstrated that nodal metastases derived from prostate cancer could be detected reliably by PSMA PET/CT in a large cohort of treatment-naïve patients. PSMA-positive nodes were detected in 90 of 280 men (32.1%) with more than one third in extrapelvic sites [8]. In a very recent review for the use of ^{68}Ga-PSMA-11 for detecting lymph nodal disease in the primary staging, eleven studies were included [9]. Two prospective studies, including a total of 63 patients, showed a range of per-patient sensitivity and specificity of 64%-100% and 90%-95%, respectively. The per-node reported sensitivity and specificity were 50%-58% and 96%-100%, respectively. Nine

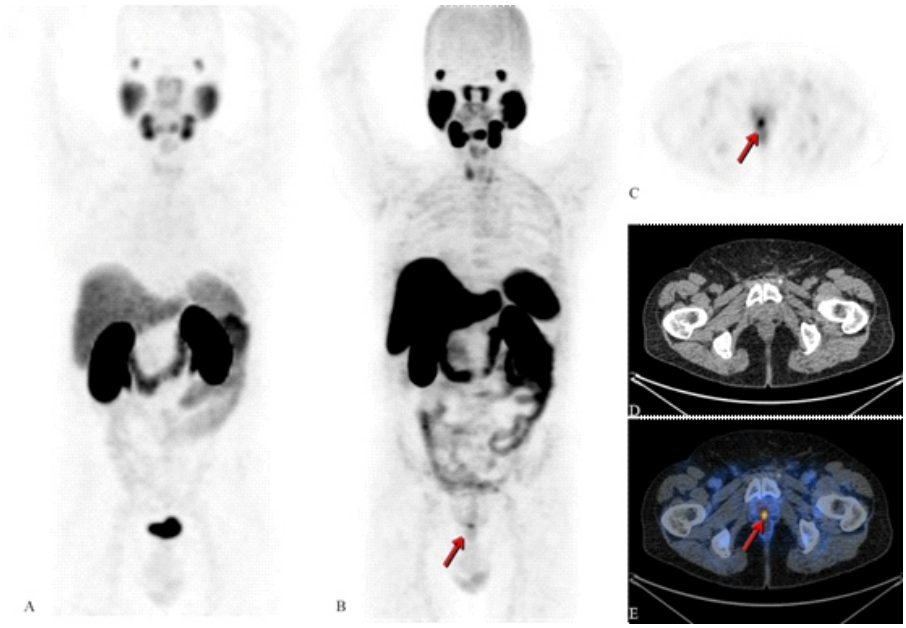

Figure 2. Patient treated with radical prostatectomy in 2004 due to adenocarcinoma of the prostate and salvage radiotherapy after biochemical relapse in 2007 with negative restaging. In 2013, new biochemical relapse with negative restaging (CT, MRI and bone scintigraphy, not shown) treated by intermittent androgen-deprivation therapy. Patient referred for ^{68}Ga-PSMA-11 PET/CT in 2016 (not shown) and 2017 (maximum intensity projection (MIP); A) without any findings (PSA levels at 0.8 and 1.0ng/mL, respectively). Due to further increase of PSA (1.1ng/mL) an ^{18}F-PSMA-1007 PET/CT examination was carried out in 2018. Images B - E show ^{18}F-PSMA-1007 PET/CT of the same patient (B: MIP, C: axial cross section PET, D: axial cross section CT, E: fused axial PET/CT image). Arrows show unequivocal focal uptake representing a local recurrence, with significant contrast, with no distracting ureteral or vesical excretion activity (as compared to A).

retrospective studies, including 696 patients, showed a per-patient sensitivity and specificity of 33%-100% and 80%-100%. The per-node sensitivity and specificity were 24%-96% and 98%-100%, respectively. A further recent systematic search on primary lymph nodal staging included eighteen eligible clinical trials and 969 patients with a higher "inhomogeneity" regarding the radiopharmaceuticals, equipment used and risk profile of the patients [10]. Five trials were prospective, and nine trials had a consecutive patient enrolment. Most trials included patients with intermediate and high-risk. Sixteen studies used ^{68}Ga-PSMA-11, there was one study with copper-64 (^{64}Cu)-PSMA and one study with ^{18}F-DCDFPyL. Twelve studies used PET/CT, four trials used PET/MR. Diagnostic accuracy varied notably among the studies probably due to the "inhomogeneity" stated above; sensitivity ranged from 23% to 100%, specificity 67%-100%, positive predictive value 20%-100%, and negative predictive value 41%-100%. The reported weighted sensitivity was 59%, but the weighted specificity was excellent and reached 93%. Furthermore, in a comparison of PSMA PET with anatomical imaging; in all cases, sensitivity and specificity were superior with PSMA PET.

Prostate specific membrane antigen PET/CT also has the advantage of diagnosing distant metastatic spread as a one-stop procedure and further delineating equivocal visceral findings of CT or bone scintigraphy. This can spare valuable time and resources both for patients and health care systems. Absence of PSMA expression in suspicious morphological lesions, whilst the primary tumor is PSMA positive, excludes PC metastases with a high negative predictive value, while PSMA expression in those lesions confirms the presence of metastatic disease confidently [11].

In a multicenter Australian prospective study, 431 patients, of which 25% were for primary staging of intermediate- and high-risk PC, underwent ^{68}Ga-PSMA-11 PET/CT examinations and the primary outcome was a change in the management plan. Overall, ^{68}Ga-PSMA-11 PET/CT scanning led to a change in planned management in 21% of these patients as it revealed unsuspected disease in a proportion of these patients [12].

The most important study to date comes also from Australia in which, in a multicentre, two-arm, randomised set-up, Hofman et al. (2020) recruited men with biopsy-proven PC and high-risk features at ten hospitals in Australia. Patients were randomly assigned to first line imaging (CT and bone scintigraphy) or ^{68}Ga-PSMA-11 PET/CT. The primary outcome was accuracy of first-line imaging for identifying either pelvic nodal or distant-metastatic disease using histopathology, imaging, and biochemistry at 6-month follow-up as standards of reference. Overall, 302 men were randomly assigned 1:1 to the two groups. In all performed analyses ^{68}Ga-PSMA-11 PET/CT was proven statistically superior to first line imaging as it had an absolute 27% greater accuracy than that of conventional imaging for pelvic nodal or distant metastatic disease (92% vs 65%), a higher sensitivity (85% vs 38%) and specificity (98% vs 91%). Furthermore, management change was more frequent after ^{68}Ga-PSMA-11 PET/CT as compared to CT and bone scintigraphy (combined) (28% vs 15%) and had less equivocal findings (7% vs 23%). Even radiation exposure was >50% lower in the one-stop-shop imaging with ^{68}Ga-PSMA-11 PET/CT as compared to conventional imaging (8.4mSv vs 19.2mSv). Finally, there was a change in management in 39 (27%) of 146 patients that underwent ^{68}Ga-PSMA-11 PET/CT after CT and bone scintigraphy, and only in 5% that had the imaging vice versa [13]. Based on these results it is a matter of time that PSMA PET/CT will replace conventional imaging (CT and bone scintigraphy) for staging in this subset of patients.

This is partially in contrast, however, with a suggestion of the panel in a 2018 consensus meeting of experts from various disciplines (Focus 1), in which advanced PC patients, both those with non-castration and those with castration-resistant prostate cancer, should be studied with imaging and bone scintigraphy and CT should be considered as necessary [14]. Nonetheless, in the same panel, at the third round of the modified Delphi process, the majority of panelists (11 of 21) responded that they would recommend PSMA PET/CT for most patients to replace conventional imaging methods. On the other hand, in the Focus 1 group a consensus was reached (based on the available data in 2018) that PSMA PET/CT was considered necessary for staging only in a minority of low risk patients.

Restaging

In terms of restaging i.e. biochemical failure (BF) after definitive treatment (e.g. prostatectomy, brachytherapy etc.), the results of PSMA PET/CT imaging are even more promising than for those of initial staging. In the very recent review partially presented above for the use of ^{68}Ga-PSMA-11 PET/CT in eight retrospective studies [9], the positive predictive value of the examination in patients with BF before salvage lymph node dissection ranged from 70% to 100%. The detection rate of ^{68}Ga-PSMA-11 PET/CT in patients with BF after radical prostatectomy had also a correlation with the PSA levels. In the PSA subgroups <0.2ng/mL, 0.2-0.49ng/mL and 0.5 to <1.0 ng/mL the detection rate ranged from 11.3%-50.0%, 20.0%-72.7% and 25.0%-87.5%, respectively.

The multicenter Australian prospective study previously presented involved in a large proportion of patients (75% of 431) undergoing ^{68}Ga-PSMA-11 PET/CT for restaging/biochemical recurrence, with the primary outcome being a change in the management plan [12]. Overall, ^{68}Ga-PSMA-11 PET/CT led to a management change in 62% of cases, as it revealed unsuspected disease in the prostate bed in 27%, locoregional lymph nodes in 39%, and distant metastatic disease in 16% of the patients.

Müller et al. (2019) also published data on the clinical impact of ^{68}Ga-PSMA-11 PET/CT on patient management and outcome in patients with BF [15]. In the initial experience of the group with this novel (at the time) radiopharmacon, authors reported a positivity in 166 of the 223 patients (74%). To some extent this was consistent with other studies [9], with the detection rate for recurrent disease at PSA values of <0.5 ng/mL found to be 50%. The positivity of the examination led to a change in management in a more than half of the patients (122/203, 60%). A substantial increase in the use of metastasis-targeted treatment and a reduction in the use of sys-

Table 1. *Summary of strengths of conventional imaging (PCWG2/3) and advantages and limitations of PSMA PET/CT. Modified from Alipour R et al. (2019) [11].*

Advantages of conventional imaging (PCWG2/3)	Advantages of PSMA PET/CT	Limitations of PSMA PET/CT
• Widely available • Extended experience in reporting and standardization • Better reimbursement by healthcare providers	· Detection rate of primary or local relapse at least comparable to MRI · Detection of nodal metastasis not limited by size · Higher detection rate for metastatic disease · Lower FP (nodal, osseous and visceral) · High NPV for enlarged nodes · Therapy response · 'One-stop shop' imaging for (re)staging · Detection of marrow disease earlier · Can be used for therapy simulation (i.e. theragnostics)	• Lesions smaller than 4 mm could potentially be below PET resolution • No standardized criteria for reporting • Inconclusive evidence of impact of ADT on PSMA uptake • Complementary ^{18}F-FDG PET/CT is needed in very advanced disease as PSMA expression may be lost • High cost (but not necessarily higher than conventional imaging) / not yet funded by healthcare providers • Several similar but slightly different radiopharmaceuticals currently in use, thus harder to provide evidence-based data

FP, false positive; NPV, Negative predictive value; ADT, androgen-deprivation therapy; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; MRI, magnetic resonance imaging; PCWG2/3, Prostate Cancer Working Group 2/3; PET, positron-emission tomography; PSMA, prostate-specific-membrane antigen.

temic treatment were observed, with 29% of the patients undergoing targeted radiotherapy only and 10% undergoing radiotherapy with hormonal therapy, as the two most frequently selected therapy options. Consequently, the proportion of patients in whom systemic therapy was selected, on the basis of the information provided by the ^{68}Ga-PSMA-11 PET/CT, decreased from 60% (133 of 223 patients) to 34% (70 of 203 patients). However, a very important finding from the analysis was that, PSMA PET/CT-directed metastasis-targeted treatment led to a complete response after 6 months in 45% of patients, illustrating that the treatment change was in the right direction [15].

In a recently published prospective study of 197 patients, ^{68}Ga-PSMA-11 PET/CT had a profound impact on stage and management of PC patients due to an upstaging of 38% and downstaging of 30% of the patients. Management was affected in 104/182 (57%) patients. Specifically, ^{68}Ga-PSMA-11 PET/CT impacted the management of patients who were re-staged after radiotherapy or after other definitive local treatments without meeting the criteria for biochemical complete response in 13/18 (72%) and 8/12 (67%), respectively [16].

As ^{18}F-labeled PSMA is newer than ^{68}Ga labelled agents, data in the literature are more limited. However, in a recent meta-analysis Treglia et al. (2019) evaluated the detection rate of ^{18}F-labeled PSMA PET/CT in BF [17] and found this to be comparable to published results of ^{68}Ga-PSMA-11. In this work, 645 patients were included. Based on the results, the pooled detection rate of ^{18}F-labeled PSMA in BF was 81% (95% CI: 71%-88%). Furthermore, similar to the results published for ^{68}Ga-PSMA-11, the pooled detection rate was 49% for PSA <0.5ng/mL (95% CI: 23%-74%; Figure 3) and 86% for PSA ≥0.5ng/mL (95% CI: 78%-93%).

These data are line with the suggestions of the Focus 1 meeting, in which the panelists (20 of 22) would recommend PSMA imaging at biochemical recurrence to replace conventional imaging methods (bone scintigraphy or CT) [14]. The panelists suggested a PSA concentration of less than 0.5ng/mL at early relapse for patients with castration-naive prostate cancer presenting with biochemical recurrence after radical prostatectomy as a cut-off for starting imaging. No consensus was reached for a PSA cut-off concentration for castration-resistant prostate cancer patients at biochemical recurrence, but just over half of panelists (11 of 21 in round 3) were in favour of not using a cut-off.

Influence of androgen deprivation therapy on PSMA-ligand PET/CT imaging of PC

In a recent editorial from the European Journal of Nuclear Medicine and Molecular Imaging the authors try to enlighten the role of androgen deprivation therapy (ADT) on PSMA expression [18]. It is not uncommon that patients referred for PSMA-ligand PET/CT are under ADT. Despite the lack of consistency in literature, most studies suggest that short-term ADT increases PSMA expression so that imaging can be performed under these circumstances. On the other hand, there is evidence that long-term ADT decreases PSMA uptake. A hypothesis for the latter is that under ADT tumour lesions respond and get smaller and partial volume effects are more relevant. Since the updated European Association of Urology guidelines suggest PSMA-imaging in men with biochemical recurrence as early as at PSA-levels >0.2ng/mL, it should be avoided to start ADT before PSMA PET/CT imaging. On the other hand, and despite not being extensively validated, short-term ADT may help to increase tumour detection rates especially if the aim of the examination is to confirm the presence of recurrent disease in patients in the lower range of PSA values (<0.5ng/mL). From this partially controversial data it is clear that there is a need for more robust data in order to better understand ADT effects on PSMA expression and imaging.

Reporting system

At present, besides reimbursement, one of the major advantages of conventional imaging (bone scintigraphy and CT) is the extended experience of the healthcare providers and the standardization in reporting. As PSMA-PET/CT gains acceptance a unified language for image reporting is needed, in order also to minimize equivocal or false positive findings and

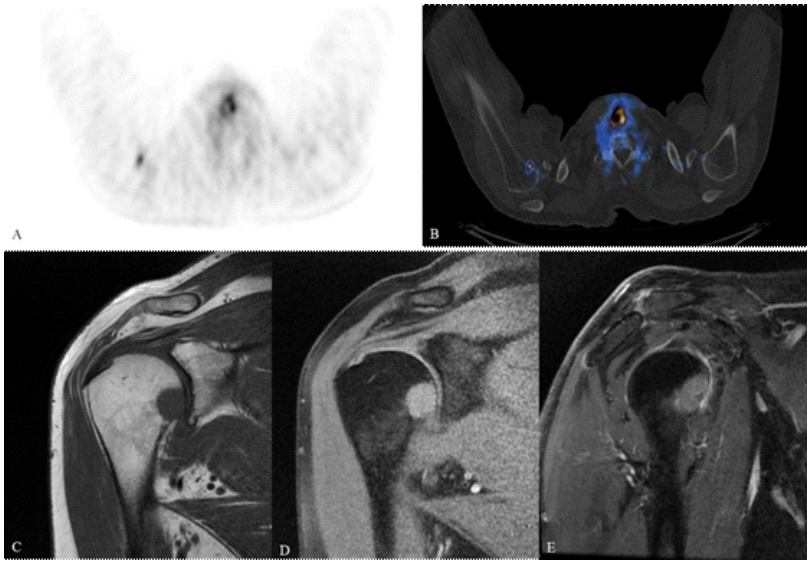

Figure 3. Patient with locally advanced prostate cancer diagnosed in 2015 and treated with androgen deprivation therapy (ADT). Subsequent brachytherapy in 07/2016 due to unwanted side effects of ADT. Patient was referred for an ^{18}F-PSMA-1007 PET/CT examination in 06/2018 due to minor increase of his PSA value (0.3ng/mL) and negative conventional imaging (CT, bone scintigraphy and Prostate-MRI; not shown). A moderate/equivocal PSMA uptake in the humeral head right (A: axial cross section PET, B: fused axial PET/CT image) without morphological correlative in the CT examination was judged as unspecific from the referring physician and watchful waiting was carried out. Unfortunately, 3 months later PSA value rose to 8.1 and 15.2ng/mL by 01/2019 without findings in the conv entional examinations (CT, bone scintigraphy and Prostate-MRI; not shown). The PET/CT images were re-assessed, and an MRI of the right humeral head was then performed confirming the presence of an osseous spread (B-E).

thus reduce unnecessary examinations/interventions. To date two different and highly sophisticated reporting systems have been contemporaneous published: the PSMA-RADS 1.0 and the molecular imaging TNM system (miTNM, version 1.0) [19, 20]. Prostate specific membrane antigen-RADS suggest categories of PSMA PET/CT findings with a likelihood for malignancy [19]. The miTNM system offers additional flowcharts integrating findings of PSMA-ligand PET/CT and morphologic imaging to guide image interpretation [20]. Both systems are a very pleasant step towards uniformity in reporting and interpreting PSMA PET/CT results, yet both need to be evaluated in the clinical setting and/or future trials.

Furthermore, radiomic features are gaining interest also on PSMA PET/CT imaging e.g. for intraprostatic tumor discrimination and non-invasive characterization of Gleason score and pelvic lymph node status with highly encouraging results [21]. However, additional research is demanded on further evaluation of the sensitivity and robustness of radiomic features.

Impediments to clinical applications

Despite the potential advantages of PSMA-based imaging for patients with PC, a number of limitations must be considered. Currently, PSMA-based imaging is not globally available, mainly owing to regulatory issues. Driven from data recently published from well-designed prospective studies, however, there is a very positive vibe regarding availability, regulations and reimbursement. It seems only as a matter of time that the evidence produced will enable implementation of this promising imaging technology into clinical guidelines [22]. A second issue that has to be considered is that, despite the advantages of PSMA PET/CT especially for "correction" of staging, its impact on patient outcome needs to be better understood. While it is logical to believe that more accurate staging will lead to better therapeutic decisions, it is not yet clear if this translates also to better patient outcomes and this requires better assessment in randomized, controlled, prospective trials [11].

In conclusion, the use of PSMA PET/CT in PC diagnostics has shown very promising results over the past few years and has a significant impact on the clinical management of PC patients. Currently, ^{68}Ga-PSMA ligands are increasingly being replaced by ^{18}F-labelled PSMA ligands due to various advantages, with data illustrating at least a non-inferiority of the latter. Prostate specific membrane antigen PET/CT is mostly used in PC recurrence, with excellent detection rates compared to conventional imaging modalities, even at low PSA levels. However, a significant shift is expected also in staging (at least) of high risk PC, based on the results of currently published prospective studies.

Acknowledgements
Special thanks to Dr. Paul Doolan for language editing.

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