PSMA PET/CT in primary prostate cancer diagnostics: an overview of the literature

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Published online: 7 September 2020
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Abstract Imaging with radiotracers targeting the prostate-specific membrane antigen (PSMA) receptor is identified as a promising novel technique in prostate cancer (PCa) detection. In this paper we aim to summarize the current knowledge derived from the literature as well as the authors' experiences on PSMA PET/CT in initial staging of PCa. PSMA PET/CT lesion- and template-based sensitivity and specificity respectively ranged from 35.1–96.1% and 96–100%. Patient-based sensitivity and specificity respectively ranged from 33.3–100% and 95–100%. Accuracy was 92% (95% CI 88–95) versus 65% (95% CI 60–69) compared to conventional imaging (CT and skeletal scintigraphy). PSMA PET/CT is superior for detection of metastases in primary PCa compared to conventional imaging. Also, PSMA PET/CT has a high specificity and moderate sensitivity for lymph node detection in primary PCa. For adequate initial staging, extended pelvic lymph node dissection (ePLND) will still be required, however, PSMA PET/CT can induce important management changes.

Keywords PSMA PET/CT · Primary prostate cancer · Staging · Sensitivity · Specificity

PSMA PET/CT in de diagnostiek van primaire prostaatkanker: een samenvatting van de huidige literatuur

Samenvatting Diagnostiek middels radiotracers die gericht zijn op de prostaatspecifiek membraanantigeen (PSMA) receptor zijn veelbelovend voor de detec-

tie van prostaatkanker. In dit artikel worden de kennis uit de literatuur met betrekking tot primaire stadiëring van prostaatkanker middels PSMA PET/CT en de ervaringen van de auteurs samengevat. De op patiënt-informatie gebaseerde sensitiviteit en specificiteit van PSMA PET/CT was 33,3–100% en 95–100%. De op laesie en template gebaseerde sensitiviteit en specificiteit was 35,1–96,1% en 96–100%. De accuratesse was 92% (95%-BI 88–95) versus 65% (95%-BI 60–69) in vergelijking met conventionele beeldvorming (CT en skeletscintigrafie). Concluderend is PSMA PET/CT in vergelijking met conventionele beeldvorming superieur voor de detectie van metastasen bij primair prostaatkanker. PSMA PET/CT heeft weliswaar een hoge specificiteit, maar slechts een matige sensitiviteit voor de detectie van lymfekliermetastasen. Daarmee blijft een lymfeklierdissectie nog steeds vereist, hoewel een positieve PSMA PET/CT kan leiden tot beleidsverandering.

Trefwoorden PSMA PET/CT · primaire prostaatkanker · stadiëring · sensitiviteit · specificiteit

Introduction

Globally, prostate cancer (PCa) is the most commonly diagnosed cancer, affecting 1 in 9 men. With 31,620 estimated deaths in 2019, PCa represents the second-ranked cause of cancer mortality [1]. In the Netherlands, approximately 12,420 patients were newly diagnosed in 2018 [2]. Due to aging of the population, this proportion is expected to increase even further in 2025.

Since metastases of PCa are characterized as an adverse prognostic factor [3], accurate staging is essential to select the most effective treatment strategy. To define TNM-stage, current international guidelines recommend intermediate- and high-risk PCa patients

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to undergo X-ray computed tomography (CT) or magnetic resonance imaging (MRI) of the lower abdomen [4]. However, to detect lymph node metastases conventional modalities (CT, MRI) rely on morphologic features: e.g. nodal size and shape. Lymph nodes larger than 8–10 mm. are considered suspicious, while over 80% of lymph node metastases in PCa are smaller than 8 mm [5].

To detect pelvic lymph node metastases, a bilateral extended pelvic lymph node dissection (ePLND) is currently considered the gold standard. This surgical procedure is performed if the estimated risk for positive lymph nodes exceeds a locally determined threshold (in the Netherlands 5–15%) according to the Memorial Sloan Kettering Cancer Center (MSKCC)-nomogram [4]. Since an ePLND is an invasive procedure with possible complications such as lymphedema, nerve injury and thrombosis, reliable imaging modalities for newly diagnosed PCa patients are desirable as an alternative for surgical lymph node staging [4, 6].

To detect metastatic bone lesions, skeletal scintigraphy is recommended in intermediate-risk, International Society of Urological Pathology (ISUP) grade 3 (Gleason 4+3) PCa patients and high-risk PCa patients (prostate-specific antigen (PSA) levels >20 ng/mL, ISUP grade 4/5 (Gleason Score >7), >cT2c, or cN+) [4]. However, because of the origin of bone metastases in bone marrow, negative skeletal scintigraphy in patients with primary PCa does not exclude presence of bone metastases. Hence, lesions early in the metastatic process, are likely to be missed [7].

During the last decennium, positron emission tomography/computed tomography (PET/CT) emerged as an important new imaging modality, in which morphologic (CT) and molecular (PET) information are merged. The initially used radiotracers (fluor-18 (^{18}F)-Choline and carbon-11 (^{11}C)-Choline) however, appeared inadequate to detect metastases of PCa, because of their low sensitivity [8]. Past years, imaging with radiotracers targeting the prostate-specific membrane antigen (PSMA) receptor, was identified as a promising novel technique in PCa detection [9]. Consequently, imaging with PSMA PET/CT has been (inter)nationally implemented in the diagnostic work-up of PCa [4, 10]. In this paper, we aim to summarize the current literature as well as the authors' experience on PSMA PET/CT imaging in initial staging of PCa.

Prostate specific membrane antigen

PSMA is a type II transmembrane glycoprotein, expressed by the apical side of benign prostate epithelium. The PSMA receptor is significantly overexpressed in 90% of the PCa cells and its expression tends to increase 100–1000 times with the aggressiveness of the tumor (e.g. Gleason score or extent of metastases) [11]. Since labeled PSMA tracers bind

Fig. 1 Frontal image of ^{68}Ga -PSMA Maximal Intensity Projection (MIP) representing the uptake of PSMA in healthy tissue in a patient suspected for PCa metastases. All numbers represent healthy tissue. Non-specified areas with high activity are suspected for PCa metastases. 1. Right lacrimal gland, 2. Left lacrimal gland, 3. Right parotid gland, 4. Left parotid gland, 5. Right submandibular gland, 6. Left submandibular gland, 7. Liver, 8. Spleen, 9. Right kidney, 10. Left kidney, 11. Duodenum, 12. Urine bladder

with a high affinity to the PSMA receptor, they represent an attractive target for nuclear (PET) imaging. Although its specific role has not been clarified yet, the protein contributes to glutamatergic neurotransmission and folate absorption [12]. PSMA is also physiologically expressed in the salivary and lacrimal glands, kidneys, central nervous system, duodenum and colon as shown in Fig. 1 [13].

Clinical practice

Different PSMA tracers

To date, two types of PSMA tracers are used in the Netherlands, i.e. Gallium-68 (^{68}Ga)-labelled PSMA tracers (i.e. ^{68}Ga -PSMA-HBED-CC/ ^{68}Ga -PSMA-11, ^{68}Ga -PSMA-617 and ^{68}Ga -PSMA I&T) and ^{18}F Fluorine (^{18}F)-labelled PSMA tracers (i.e. ^{18}F -DCFpYL, ^{18}F -DCFBC and ^{18}F -PSMA-1007) as shown in Figs. 2 and 3. These radiotracers have different characteristics. Firstly, ^{68}Ga -PSMA can be produced on site if a Germanium-68 generator is available; ^{18}F -PSMA is a cyclotron product and must be purchased. Secondly, ^{18}F has a longer half life (110 minutes) compared to ^{68}Ga (68 minutes), which allows for transportation to surrounding hospitals. Thirdly, in absence of a positron range effect, ^{18}F -PSMA has a higher image resolution compared to ^{68}Ga -PSMA. Also, ^{18}F -PSMA has a lower positron emission energy of 0.65 MeV compared to ^{68}Ga -PSMA (1.90 MeV), which is assumed to result in higher imaging quality [14–16].

Fig. 2 Different Gallium-68 (^{68}Ga)-labelled PSMA tracer structures

PSMA PET/CT acquisition

Internationally, Gallium-68 (^{68}Ga)-labelled PSMA tracers are most commonly used. The PSMA-PET/CT is usually performed with low-dose CT from head to upper thigh. Image acquisition starts 50–60 minutes after injection of 1.8–2.2 MBq/kg ^{68}Ga -PSMA in accordance with the European Nuclear Medicine guidelines [17]. Radiation dose is approximately 2–4 mSv. Patients do not need to fast or temporarily stop intake of their medication, however, they need to be well hydrated (e.g. oral intake of 500 ml of water during a 2 hour period prior to acquisition). Furosemide administration (20 mg i.v. shortly before or after i.v. administration of the radiopharmaceutical) may be used to reduce the high residual activity in the urinary system, which may lead to artefacts or even false positive findings.

PSMA/PET in primary staging prostate cancer

Gallium-68-labelled PSMA tracers

In 2011, Afshar-Oromieh et al. reported on PET/CT images obtained with ^{68}Ga -PSMA-HBED-CC in a 67-

year-old PCa patient with an increased PSA level and a history of radiotherapy to prostate and hormone therapy. Whereas the performed ^{18}F -FECH PET/CT did not detect any lesions, ^{68}Ga -PSMA-HBED-CC showed a lesion adjacent to the urinary bladder [18]. This publication marked the start of the ^{68}Ga -labelled PSMA PET/CT usage for PCa diagnostics. Subsequently, studies focusing on the setting of biochemical recurrence, showed high diagnostic value of ^{68}Ga -PSMA PET/CT for Pca [19, 20]. Additionally, a vast number of initial studies demonstrated promising results of ^{68}Ga -PSMA PET/CT in primary PCa detection (Tab. 1 and 2; [21–24]).

Hope et al. performed a meta-analysis to clarify detection rate of ^{68}Ga -PSMA PET/CT for lymph node detection in the setting of primary staging of PCa [20]. The study comprised five studies, including one prospective study [24], involving 266 patients mostly classified as having intermediate to high risk PCa. In all studies, PET results were compared to histopathology as a reference. A lesion-based sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and an accuracy of respectively; 74% (95% CI 51–89), 96% (95% CI

Fig. 3 Different ^{18}F (labeled PSMA tracer structures

85–99), 93% (95% CI 86–99), 85% (95% CI 75–93) and 86% (95% CI 72–92) was observed.

After the publication of this meta-analysis, Luiting et al. recently also reviewed diagnostic performance of ^{68}Ga -PSMA PET/CT for lymph node detection in primary staging in men with PCa [25]. In this review, 11 studies were included: two prospective studies [24, 25] ($n=63$ patients) with one using ^{68}Ga -PSMA PET/MRI as diagnostic scan ($n=33$) and nine retrospective studies ($n=696$ patients). In all studies, histopathology was referred to as the gold standard. Patient-based sensitivity and specificity ranges of respectively 64–100% and 90–95% were found in the prospective studies. Lesion-based sensitivity and specificity ranges were 50–58% and 96–100%, respectively. In the retrospective studies, the sensitivity and specificity range was 33.3–100% and 80–100%, respectively. With regard to the lesion-based analysis, they found a sensitivity and specificity range of 24.4–96.1% and 98.6–100%, respectively [26]. Especially sensitivity was lower in comparison with the previously discussed meta-analysis by Hope et al. [20] who included significantly less studies.

The PEPPIER-study initiated by the University Medical Center Utrecht in the Netherlands was neither included in the review of Luiting et al. [26], nor in the systematic review of Hope et al. [20]. This was a prospective study evaluating the diagnostic accuracy of ^{68}Ga -PSMA PET/CT for lymph node detection in primary staging in men with PCa with histopathology as a reference. Patients were included if they had newly diagnosed prostate cancer, negative skeletal scintigraphy, >10% risk for lymph node metastasis fol-

lowing (MSKCC)-nomogram and were eligible for an ePLND. A total of 103 patients were included. In six patients ePLND was canceled, because of ^{68}Ga -PSMA PET/CT findings (i.e. PET positive distant lesions) illustrated in Fig. 4. A patient-based sensitivity and specificity of respectively 41.5% (95% CI 26.7–57.8) and 90.9% (95% CI 79.3–96.6) was found for detecting lymph node metastasis, and positive and negative predictive values of 77.3% (95% CI 54.2–91.3) and 67.6% (95% CI 55.6–77.7), respectively. Furthermore, a template-based (i.e. left/right and lateral/medial of the external iliac artery) sensitivity, specificity, PPV and NPV of 35.1% (95% CI 23.2–48.9), 96.4% (95% CI 93.5–98.1), 64.5% (95% CI 45.4–80.2) and 89.0% (95% CI 85.0–92.0), respectively, was observed [27].

Hofman et al. recently published the first prospective, randomized, multi-center phase 3 study, evaluating accuracy for metastases detection with PSMA PET/CT compared with conventional imaging (CT and skeletal scintigraphy) [28]. A total of 302 patients with high risk features, being considered for radical prostatectomy or radiotherapy with curative intent, were included. The patients were randomly assigned for staging with either conventional imaging ($n=152$) or ^{68}Ga -PSMA PET/CT ($n=150$). The cases were considered positive if they met one hard criterion (histopathology showing PCa, or change of a bone lesion to a sclerotic or blastic state on follow-up imaging) or three from the soft criteria as not all the patients underwent prostatectomy ($n=126$) and/or ePLND ($n=83$). These soft criteria included: (1) typical appearance of multi-focal metastatic disease; (2) a metastatic lesion on an imaging modality

Table 1 Lesion-based sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)

Author	Sensitivity	Specificity	PPV	NPV
Hope et al. [20]	74% (95% CI 51–89)	96% (95% CI 85–99)	93% (95% CI 86–99)	85% (95% CI 75–93)
Luiting et al. pros. [25]	50–58%	96–100%	–	–
Luiting et al. retr. [25]	24.4–96.1%	98.6–100%	–	–
Van Kalmthout et al. [26] ^a	35.1% (59% CI 23.2–48.9)	96.4% (95% CI 93.5–98.1)	64.5% (95% CI 45.4–80.2)	89.0% (95% CI 85.0–92.0)

pros. prospective, retr. retrospective

^aUsed operation templated-based (i.e. left/right and lateral/medial of the external iliac artery)

Table 2 Patient-based sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)

Author	Sensitivity	Specificity	PPV	NPV
Luiting et al. pros. [25]	64–100%	90–95%	–	–
Luiting et al. retr. [25]	33.3–100%	80–100%	–	–
Van Kalmthout et al. [26]	41.5% (95% CI 26.7–57.8)	90.9% (95% CI 79.3–96.6)	77.3% (95% CI 54.2–91.3)	67.6% (95% CI 55.6–77.7)
Hofman et al. [27]	85% (95% CI 74–96)	98% (95% CI 95–100)	–	–

other than the one done as the index scan; (3) increase in size or number of lesions from one imaging exam to the next; (4) decrease in size or number of lesions from one imaging exam to the next, following appropriate treatment; (5) lesion associated with clinical symptoms suggesting malignancy; (6) patient received localized treatment for imaging finding; (7) increase in PSA in keeping with clinical scenario of progression, or decrease in response to treatment; and (8) unequivocal persistence of positive finding on repeated imaging at 6 months in patients with a PSA concentration of >0.2 ng/mL at least three weeks following prostatectomy. It was found that PSMA PET/CT had a significant ($p < 0.0001$) greater accuracy than conventional imaging; 92% (95% CI 88–95) versus 65% (95% CI 60–69). They also found a lower patient-based sensitivity of 38% (95% CI 24–52) versus 85% (95% CI 74–96) and specificity of 91% (95% CI 85–97) versus 98% (95% CI 95–100) for conventional imaging compared to PSMA PET/CT. Compared to the PEPPER-study, Hofman et al. (2020) found a much higher patient-based sensitivity: 41.5% (95% CI 26.7–57.8) versus 85% (95% CI 74–96). An explanation for this is that Hofman et al. [27] did not only use histopathology as reference and therefore may have overestimated true positive lesions.

¹⁸Fluorine-labelled PSMA tracers

As an alternative for ⁶⁸Ga-PSMA, ¹⁸Fluorine-labelled PSMA tracers were developed, most notably ¹⁸F-DCF-PyL and ¹⁸F-PSMA-1007 [29]. The radiotracer ¹⁸F-DCF-PyL was first described in literature by Chen et al. in 2011 [30]. The first clinical experience in humans was obtained four years later, consisting of nine hormone-naïve and castration-resistant patients. As no severe adverse events occurred in these nine men, this study not only demonstrated the tumor uptake of ¹⁸F-DCF-PyL, but also its safety [31]. Studies evaluating diagnostic performance of ¹⁸F-DCF-PyL PET/CT in recur-

rent PCa showed promising results [32]. With regard to diagnostic performance of ¹⁸F-labelled PSMA tracers in primary PCa however, only a small number of studies was published and initial results of prospective studies are awaited.

In 2018, Gorin et al. prospectively evaluated diagnostic performance of preoperative ¹⁸F-DCF-PyL PET/CT in 25 men with high risk PCa being eligible for prostatectomy and ePLND. When compared to histopathology findings patient-based sensitivity and specificity was respectively 71.4% (95% CI 29.0–96.3) and 88.9% (95% CI 65.3–98.6). Lesion-based sensitivity and specificity was 66.7% (95% CI 29.9–92.5) and 97.7% (95% CI 80.1–98.5), respectively [33].

At present, the diagnostic performance of ¹⁸F-DCF-PyL and ¹⁸F-PSMA-1007 in the setting of initial staging of PCa with histopathology reference are currently under investigation in prospective trials conducted at the Amsterdam UMC, location VUmc (the SALT-study; NL6754), and the Canisius Wilhelmina Ziekenhuis in Nijmegen (the MINT-study; NL7428). The results of these studies are expected soon.

Discussion

In this paper, we aimed to summarize the current knowledge derived from the literature as well as the authors' experiences on PSMA PET/CT in initial staging of PCa. Overall, the diagnostic accuracy of PSMA PET/CT for lymph node detection in primary staging in men with PCa appears to be very promising with a high lesion- and patient-based specificity [19, 20, 26, 28, 33]. The superiority of PSMA PET/CT for the detection of PCa metastases in primary setting compared to conventional imaging (CT and skeletal scintigraphy) has been shown by the recent randomized-controlled trial by Hofman et al. [28]. These results support the (inter)national implementation of PSMA PET/CT as a first-line diagnostic modality for primary PCa stag-

Fig. 4 Case description. Transversal (a) and frontal (c) fused ^{68}Ga -PSMA-PET/CT and transversal (b) and frontal (d) PET images of a 80-years old man with cT3a, Gleason 4+4=8 PCa (initial PSA-level of 33ng/ml) and considered candidate for ePLND (MSKCC-nomogram: 77% risk of lymph node involvement). ^{68}Ga -PSMA-PET/CT showed PSMA avid disease in the prostate region (a,b), as well as extensive bilateral (extra-) pelvic lymph node involvement (c,d). During the post-PET tumor board meeting, it was decided to cancel ePLND and start androgen deprivation therapy, followed by a PSA-decline to 0.24 ng/ml

ing instead of conventional imaging (CT and skeletal scintigraphy).

However, despite its high specificity, PSMA PET/CT had a moderate to low patient-, and lesion-based sensitivity [19, 20, 26, 28, 33] indicating that a negative PSMA PET/CT cannot rule out lymph node metastasis and therefore is not able to replace ePLND for lymph node detection. Nevertheless, because of the high specificity, a positive PSMA PET/CT can change treatment management. In the PEPPER-study, an ePLND was avoided in 5.8% of the patients because of distant metastases on PSMA PET/CT [27]. Therefore, an invasive and expensive intervention could be prevented.

This implies that the implementation of PSMA PET/CT could be cost-effective. A recent study from the Netherlands evaluated the cost-effectiveness of PSMA PET/CT in primary staging of Pca- versus ePLND-based staging on an interactive model [34]. Effectiveness (Quality Adjusted Life Year's (QALYs) combining utility score and survival) and the cost analysis (from a healthcare perspective) were mod-

elled over lifetime. Healthcare states were either: no evidence of disease, biochemical recurrence, salvage treatment, palliative care or death. They found a cost saving with PSMA PET/CT of €3074 (95% CI -3515—2330), but at the possible expense of a small QALY loss of 0.07 (95% CI -0.13—0.02) when ePLND was considered the gold standard with a sensitivity and specificity of 100%. However, this study evaluated the total replacement of ePLND with PSMA PET/CT and did not include the ability of PSMA PET/CT to detect distant metastases. If accounted for the detection of distant metastases, more cost-savings and better effectiveness can be expected due to earlier treatment of distant metastases detected by PSMA PET/CT. As mentioned before, due to low sensitivity an ePLND is still required in patients with negative PSMA PET/CT, but ePLND may possibly be omitted in patients with positive PSMA PET/CT findings. Therefore prospective cost-effectiveness studies are needed.

In this paper, we focused on the radiotracers that are commonly used in the Netherlands. There is no study that compared diagnostic accuracy of ^{68}Ga -labelled PSMA to ^{18}F -labelled PSMA radiotracers in patients with newly diagnosed PCa. However, there are some studies that compared the diagnostic accuracy in relapse PCa. Dietlein et al. compared the clinical use of ^{68}Ga -PSMA-HBED-CC tracer and ^{18}F -DCFPyL tracer for PSMA PET imaging in 14 patients with relapse PCa [15]. All the suspicious lesions identified by the ^{68}Ga -PSMA-HBED-CC tracer were also identified by the ^{18}F -DCFPyL tracer. However, the ^{18}F -DCFPyL tracer identified additional lesions in three patients. Also a higher maximal Standardized Uptake Value (SUV_{max}) in PSMA positive lesions and higher mean tumor to background ratios (when using kidney, spleen or parotid as reference organ) were found in ^{18}F -DCFPyL PET/CT compared to ^{68}Ga -PSMA-HBED-CC PET/CT. The higher detection rate of the ^{18}F -DCFPyL tracer in this study can be explained by the higher injected dose (mean dose of $318.4 \text{ Mbq} \pm 59.0 \text{ MBq}$ versus $128.3 \text{ MBq} \pm 35.9 \text{ MBq}$) of ^{18}F -DCFPyL. A consecutive study from Dietlein et al. confirmed the non-inferiority of the ^{18}F -DCFPyL tracer compared to the ^{68}Ga -PSMA-HBED-CC tracer in the diagnostic performances of relapse PCa [14]. They retrospectively included 62 patients who underwent ^{18}F -DCFPyL- and 129 patients who underwent ^{68}Ga -PSMA-HBED-CC PET/CT, subdivided by previous therapy (i.e. prostatectomy or radiotherapy). They found a higher detection rate in ^{18}F -DCFPyL imaging with PSA levels between $0.5\text{--}3.5 \mu\text{g/L}$ in prostatectomy patients.

Based on these studies and due to the logistic features of ^{18}F -labelled PSMA tracers, we expect that these tracers will ultimately be preferred over ^{68}Ga -PSMA. A prospective comparison in newly diagnosed PCa with histopathologic reference is needed.

Conclusion

Overall, we can conclude that regarding primary PCa, the accuracy of PSMA PET/CT is superior to that of conventional imaging (CT and skeletal scintigraphy). PSMA PET/CT has a high specificity but a moderate sensitivity for lymph node detection in primary PCa. Therefore, an ePLND is still required for initial PCa staging in PSMA PET/CT negative patients. However, a positive PSMA PET/CT may induce management changes.

In the current Dutch oncology guidelines, PSMA PET/CT is recommended for two indications: (1) metastasis detection in primary PCa when indicated (i.e. $\text{PSA} \geq 20 \text{ ng/mL}$, cT3 PCa, Gleason score ≥ 8 , or bone pain) and (2) for the detection of biochemical recurrent PCa in patients with a history of prostatectomy or radiotherapy with a PSA value of $>0.2 \text{ ng/mL}$. For adequate local staging, MRI is still recommended.

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