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Advances in PSMA Positron Emission Tomography (PET) of Prostate Cancer

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Abstract

Purpose of review—In recent years, a large number of reports have been published on PSMA/PET in prostate cancer (PCa) This review highlights advances in PSMA PET in PCa during the past year.

Recent findings—PSMA PET/CT is useful in detection of biochemical recurrence, especially at low PSA values. The detection rate of PSMA PET is influenced by PSA level. For primary PCa, PSMA PET/CT shows promise for tumor localization in the prostate, especially in combination with multiparametric MRI (mpMRI). For primary staging PSMA PET/CT can be used in intermediate and high risk PCa. Intraoperative PSMA radioligand guidance seems promising for detection of malignant lymph nodes. While the use of PSMA PET/MRI in primary localized disease is limited to high and intermediate risk patients and localized staging, in the recurrence setting PET/MRI can be particularly helpful when the lesions are subtle. PSMA PET/CT is superior to choline PET/CT and other conventional imaging modalities.

Summary—Molecular imaging with PSMA PET continues to pave the way for personalized medicine in PCa. However, large prospective clinical studies are still needed to fully evaluate the role of PSMA PET/CT and PET/MRI in the clinical workflow of PCa.

Keywords

Prostate cancer; PSMA; PET/CT; PET/MRI; personalized medicine

INTRODUCTION

Prostate cancer (PCa) is the most common cancer worldwide in men, with large numbers of patients dying due to the malignancy[1]. Imaging plays an increasingly important role in the clinical management of PCa patients. In recent years much attention has been focused on prostate specific membrane antigen (PSMA) as a target for PET imaging in PCa[2]. PSMA,

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a glutamate carboxypeptidase II enzyme, is a cell membrane bound metallopeptidase[2–5]. Nearly all PCa demonstrate PSMA expression in the majority of primary and metastatic cancers[6,7]. PSMA expression increases in de-differentiated, metastatic, or hormone-refractory disease, and the expression level is prognostic for disease outcome[8–9,••10]. Normally, variable physiological PSMA expression is seen in the lacrimal glands, salivary glands, liver, spleen, small intestine, colon and kidneys[••10]. However, PSMA is also expressed in other neoplasms and malignancies, and in infections and inflammation[2,11,12]. PSMA is an excellent target for both imaging and therapy with radionuclides because of high expression, suitable binding affinity, and internalization of PSMA ligands[2,••13,14–15]. Usually tumor lesions both inside and outside the prostate gland demonstrate a strong tumor to background ratio [16,••17]. Several small molecule PSMA agents for imaging and therapy have been explored, and some of these have already been translated into the clinic[3–5,18,19]. An increasing number of publications focusing on PSMA imaging and therapy in PCa have been published, including a joint EANM and SNM procedure guideline for PCa PSMA imaging[••10]. Furthermore, a new molecular imaging basedTNM classification for the interpretation of PSMA PET/CT has been proposed recently[20]. In this review, we focus on recent developments in PSMA PET in PCa published in the last year.

PSMA PET/CT in localized disease

Although PSMA PET/CT is most useful in patients with biochemical recurrence after definitive therapy, there is an important role for it in staging primary disease after initial diagnosis. Currently, the major role for PSMA PET/CT in localized disease is in initial staging and therefore it is reserved for patients with intermediate or high risk cancers based on PSA and Gleason scores, where there is a reasonable likelihood of extraprostatic disease. The most common workup for staging PCa consists of a CT or MRI of the abdomen and pelvis, and a ^{99m}Tc-based bone scan. Additional imaging, such as sodium fluoride PET, may be more sensitive for non-organ-confined disease[21–24]. PSMA-based scanning may provide added sensitivity for extraprostatic disease. Since many of these patients go on to surgery, tissue validation of PSMA PET/CT has been most readily accomplished in localized disease compared to other states of PCa.

On a per patient basis the results of PSMA PET/CT in identifying intraprostatic disease are very impressive, with sensitivities typically ranging from 87–98% and specificities from 91–96% for detecting intraprostatic disease[25,•26,27–28,••29]. While these results are encouraging, it is important to understand that they may not be indicative of disease in later states since most intermediate-high risk PCa going on to surgery tend to be larger and higher grade and thus easier to detect. This may result in inflated sensitivities and specificities compared to prospective studies in more generalized risk populations, but particularly may not apply to recurrent or metastatic disease. What information that does exist from incidentally discovered tumors in pathology specimens suggests that smaller and lower grade tumors are more difficult to identify on PSMA PET/CT.

How well does PSMA PET/CT define the extent of intraprostatic tumor compared with histopathology?

When comparing the results of PET/CT with histology it is important to remember that PET has a resolution at least 100-fold lower than histopathology. When PET scans are compared to digital pathology on a voxel wise basis[30], then sensitivity of PSMA PET ranges from 67–79%[31,32]. This has implications for the guidance of focal therapies as it demonstrates that PSMA PET/CT tends to underestimate the tumor volume. Additionally, PSMA expression is not universal; in PSMA positive tumors only 20–80% of the individual PCa cells within the tumor will stain positively on immunohistochemistry[28,31].

How well does PSMA uptake correlate with Gleason scoring?

PSMA PET/CT scans show that the SUVmax increases with increasing grade of the tumor. For instance, lower grade tumors (Gleason 3+3 and 3+4) typically have SUVs ranging from 5.9–9.6[•26,33,••29]. Higher grade tumors (>Gleason 7) typically demonstrate much higher SUVmax, ranging from 16–21[•26,••29]. Intermediate grade tumors (e.g. Gleason 4+3) have intermediate SUVs, ranging from 8.2–8.8[••29]. However, there do not appear to be distinct cutoffs between these tumor grades so that considerable overlap exists for any Gleason category. Thus, while PSMA uptake, as measured by SUVmax, correlates with Gleason score it cannot be considered a surrogate for Gleason score.

Can PSMA be used to distinguish benign from malignant tissue in the prostate?

This question arises in patients with elevated PSA but no distinct lesion on MRI or for those in whom a biopsy carries increased risk. Thus, PSMA PET/CT could play a role in sparing biopsies in selected cases. Investigators have found that SUVmax values below 3.15–6.5 are strongly associated with benign tissue such as benign prostatic hyperplasia[28,30]. This could be a useful concept that will require further exploration. However, the routine use of PSMA PET/CT prior to biopsy is not justified at present but is reserved for special circumstances when biopsy is relatively contraindicated (e.g. bleeding disorders, absence of rectum). It is clear that patients with lower grade (Gleason score <7) tumors and PSA <5 ng/ml are unlikely to benefit from PSMA scanning in this setting. This population exhibits a lower sensitivity (73% sensitivity) compared to intermediate and high risk cancers[27,34]. In this latter group of patients, PSMA PET/CT may be helpful in identifying the more aggressive tumors, however, the value compared to MRI-guided biopsy is unclear at this point[31,35,36]. One potential use for PSMA PET/CT is to limit the number of biopsies to the high uptake lesions, however, this idea must be tested. If PSMA-PET/CT is to be used prior to biopsy it should be reserved for higher risk patients (Gleason score>7 or PSA >10ng/ml).[••29]. In general, PSA levels correlate with the likelihood of a positive PSMA scan and with the SUVmax[•26,35]. For instance, comparing patients with mean PSA values below and above 10ng/ml, the mean SUVmax for tumors increases from 7.7 to 17.6[35].

Staging of primary lesions by PSMA PET/CT can be important in guiding treatment decisions. In patients with positive nodes, a more extensive lymph node (LN) dissection may be performed. In the case of radiotherapy, the fields may be extended to encompass the additional pathology found by PSMA. If widespread metastases are disclosed by PSMA PET/CT systemic therapy may be favored. Although the long term benefits of these

approaches to therapeutic decision making are unknown, it is logical to conclude that earlier and more complete therapy of PCa could result in better outcomes, both in terms of overall survival and quality of life.

PSMA PET/MRI

While PET/CT is a very useful hybrid technology, the CT component does not increase sensitivity in PCa. In contrast, MRI plays a very important role in identifying PCa. It is used to help identify suspicious prostate lesions which can then be biopsied under transrectal ultrasound (TRUS) using image fusion hardware and software. Fusion biopsies have become commonplace. In patients experiencing biochemical,, MRI is used to identify sites of local recurrence and LN metastases. In the metastatic setting whole body MRI is being used to document the extent of disease and response to therapy, although this latter application is limited to research settings. One common theme of MRI, however, is that by itself it is nonspecific for PCa and identified lesions must be biopsied.

PET/MRI devices offer the opportunity to more accurately diagnose the extent of disease in all phases of the disease. The primary advantage of these devices is that they take the guesswork out of fusing PET images to MRI images, thus improving co-registration of imaging. While their use in primary localized disease is limited to high risk patients, in the recurrence setting PET/MRI can be particularly helpful when the lesions are very subtle. A number of studies have recently documented the superiority of PET/MRI compared to PET/CT [34,37–38,•39]. The combination of PET and MRI increased the cancer detection rate from 66% for MRI alone and 92% for PSMA PET to 98% for the combined PET/MRI[••17]. Moreover, PET/MRI improved intraprostatic cancer localization[••17].

Interestingly, how MRI is combined with PET depends on the goal of the study. For instance, for improving sensitivity (i.e. detecting metastatic disease) the “union” of PET and MRI is the best way to use the modalities together. To improve specificity (limiting biopsies to the most likely lesions), the “intersection” of the two studies is superior[•39].

It should be noted that the necessity of performing MRI simultaneously with PET has not been documented. It is perfectly possible to achieve comparable results by obtaining PET scans separately from MRI and then fusing the images using anatomic fiducials (typically the CT scan obtained with the PET can be fused to the MRI and hence the PET to the MRI). The simultaneous acquisition of PET and MRI in PET/MRI scanners entails a very expensive device that requires the skills of two different types of technologists (technologists with both MRI and nuclear medicine training are still rare) and a potentially disruptive workflow as the MRI takes longer to obtain than the PET but the scanner must be occupied until both scans are completed. Thus, technical challenges remain for the implementation of PET/MRI devices in PCa.

PSMA PET/CT in primary staging

In PCa accurate pretreatment staging including evaluation of LN is crucial to guide the most appropriate treatment. This is especially important in patients with a high-risk for metastatic disease (T3a and/or Gleason score 8–10 and/or PSA > 20 ng/ml). Patients with intermediate-

risk disease (T2b-T2c and/or sum Gleason score 7 and/or PSA 10–20 ng/ml) may also have disease outside the prostate gland, and are often imaged in order to detect metastases. Therefore, preoperative accurate assessment of LN status is important in intermediate and high-risk PCa patients. Conventional imaging with CT and MRI are often used for primary LN staging. However, it is well-known that the LN status is largely underestimated with CT and MRI. A meta-analysis reported the pooled sensitivity and specificity of CT for LN detection to be 42% and 82%, respectively[40]. For MRI, the pooled sensitivity and specificity were 39% and 82%, respectively, essentially the same as CT as they both rely on the same LN size criteria[40]. Pelvic node lymph dissection (PLND) is still considered the most accurate method for assessment of LN involvement[40]. However, this technique is invasive and is associated with increased lymphocele/lymphedema rates and venous thromboembolism rates[41]. Therefore, novel and non-invasive techniques are being evaluated in clinical trials.

Can PSMA PET/CT be used for LN detection?

LN metastases from PCa overexpress PSMA, with positive immunoreactivity for PSMA detected in 98% of the metastases[42]. The first published results in PCa patients referred for primary LN staging with PSMA PET/CT were not very promising, with sensitivity of only 33.3% but specificity of 100%[43]. However, the study had several important limitations[44], and the low sensitivity has not been confirmed in other studies. In a large retrospective study (n=130), a much higher sensitivity for LN detection was reported[42]. On a patient-based and a template-based analysis, sensitivity was 65.9% and 68.3%, respectively, while specificity was 98.9%. Detection of LN metastases was superior with PSMA PET/CT compared to CT and MRI, which had patient-and template-based sensitivity of only 43.9% and 27.3%, respectively[42]. Other studies have reported similar results for PSMA PET/CT for detection of LN metastases [45–47], and confirmed PSMA PET/CT to be superior to conventional CT and MRI[48–50]. Importantly, PSMA PET/CT has also been reported to be superior to choline PET/CT for LN detection[14,51,52].

Recently, 2 studies have compared PSMA PET/CT and mpMRI for LN staging. In one study PSMA PET/CT detected higher numbers of patients with regional and non-regional LNs in comparison with mpMRI[49]. Additional sites of metastatic disease reported on PSMA PET/CT were to skeleton, lung and liver. In the second study, the diagnostic value of PSMA PET/CT was compared with mpMRI for LN staging in patients with intermediate- to high-risk PCa undergoing radical prostatectomy with PLND[25]. PSMA PET/CT demonstrated a patient-based sensitivity, specificity, PPV and NPV of 93.33, 96.30, 93.33 and 96.30%, respectively. On a LN region-based analysis the results of sensitivity, specificity, PPV and NPV were 96.08, 99.65, 96.08 and 99,65%, respectively. Multiparametric (mp)MRI demonstrated a patient-based sensitivity, specificity, PPV and NPV of 93.33, 96.30, 87.5 and 96.15%, respectively, while pelvic mpMRI showed a LN region-based sensitivity, specificity, PPV and NPV of 96.08, 99.47, 94.23 and 99.65%, respectively. Thus, the studies support the notion that PSMA PET/CT may be used for LN detection in intermediate and high risk PCa[25,49].

According to EANM and SNMMI guidelines published recently, a contrast enhanced PSMA PET/CT can replace abdomino-pelvic CT for the detection of LN metastases[••10]. The detection of radiologically occult LN metastases can significantly influence the management of PCa patients, although the impact of improved sensitivity of detection by PSMA PET/CT on overall survival remains to be established.

Is PSMA PET/CT superior to conventional bone scan?

^{99m}Tc-MDP whole-body bone scan is a highly sensitive imaging method that has been used for decades to evaluate PCa bone metastasis based on its availability and low cost; however, because of accumulation of this radiotracer in degenerative, inflammatory and traumatic lesions the specificity is relatively low. PSMA-PET/CT outperforms ^{99m}Tc-MDP-SPECT in detecting bone metastases in PCa patients although the two studies can be complementary in some patients[53,54]. ^{68}Ga-PSMA uptake is higher in osteolytic and bone marrow metastases compared to osteoblastic metastases[55]. Information derived from PSMA PET and CT complement each other for the reliable diagnosis of the different types of bone metastases in PCa patients[55]. Furthermore, PSMA PET/CT detects more bone metastases as compared to choline PET/CT[52].

PSMA PET/CT in recurrence

PSMA PET/CT has been most extensively studied in the context of biochemical recurrence following failed therapy (PSA≥0.2 ng/ml post radical prostatecmy, or a 2 ng/ml rise above the PSA nadir post radiation). Biochemical recurrence after radical prostatectomy occurs in up to 50% of the patients[56]. Detection of the recurrence site is of paramount importance in order to guide the optimal treatment, and avoid futile localized treatment in cases with systemic recurrence, and avoid the side effects of systemic treatments in cases of localized disease. Furthermore, there is much focus on detecting low volume disease in the recurrent setting because of newly available technologies, such as stereotactic radiotherapy. The most significant reason for failure of salvage therapy is undetected metastatic disease. This demonstrates the need for a more accurate monitoring tool for evaluation of biochemical recurrence.

Is PSMA PET/CT superior to conventional imaging?

Conventional imaging has low diagnostic yield for detection of local reccurrence, as well as LN and bone metastases. Bone scan has a detection rate of only 5% for PSA values < 7 ng/mL, and CT has a similar low sensitivity of 11–14% for detection of local recurrence and LN metastases in this group of patients[56]. In a recent meta-analysis, the detection rate of PSMA PET/CT in biochemical recurrence was 76% (66–85%)[57]. On per-patient analysis, the summary sensitivity and specificity were both 86%. On per-lesion analysis, the summary sensitivity and specificity were 80% and 97%, respectively[57]. A recent large retrospective study (n=1007) found a detection rate of 97.5% for PSMA PET/CT in biochemical recurrence[•58]. The detection rates in two other large retrospective studies (n=319 and n= 248) were reported to be 83–90%[59,60]. Several reports have demonstrated PSMA PET is superior to conventional imaging, including CT and MRI for detecting sites of recurrent disease[59–62,•63]. Sensitivity depends on the PSA value. It has been demonstrated that

patient prognosis is significantly improved with the initiation of salvage therapies before the PSA level exceeds 0.5 ng/ml[64]. For this group of patients, the detection rate by PSMA PET/CT is in the range of 50–60%[5,59,60,62,65], which is superior to any other currently available imaging modalities. Even very small soft tissue lesions can be detected with PSMA PET/CT with a high PPV and high specificity[66].

Does PSA level, PSA doubling time and Gleason score affect the detection rate of PSMA PET/CT?

In a meta-analysis, positivity on PSMA PET scans increased with PSA levels[57]. For PSA categories 0–0.2, 0.2–1, 1–2, and >2 ng/ml, PSMA PET/CT were positive in 42%, 58%, 76%, and 95% of patients, respectively. Shorter PSA doubling times also increased PSMA PET positivity. In a large retrospective study (n=1007), detection rates were clearly associated with PSA levels and ADT[•58]. A non-statistically significant trend between higher Gleason scores and detection rates was also observed. In contrast, another recent study (n=147) demonstrated correlation between Gleason score and positive LN on PSMA PET/CT[•63]. In this study (n=147) the dimensions, volume, localization and SUVmax of LNs identified by PSMA PET/CT correlated with the Gleason score (GS) at diagnosis. Mean SUVmax was 13.5, 12.4 and 17.8 with low, intermediate and high Gleason scores, respectively. The morphologic assessment of the PSMA positive LN demonstrated that the low Gleason score cohort had smaller PSMA positive LN, followed by intermediate and high Gleason score cohorts.

Is PSMA PET/CT superior to choline PET/CT?

Several studies have compared PSMA PET/CT with choline PET/CT for the detection of lesions in biochemical recurrence. All studies to date have reported a higher detection rate for PSMA PET/CT compared to choline PET/CT[52,61,62,67,68]. PSMA PET/CT demonstrated higher sensitivity and specificity as compared to choline PET/CT at all PSA values, especially at low values (< 1 ng/mL). The detection rate was higher both for local recurrence as well as LN and bone metastases. Additionally, PSMA PET/CT detected more lesions and demonstrated higher tumor to background ratio.

Can PSMA PET/CT guide salvage therapy?

PSMA PET/CT can change the clinical management in 40–60% of patients with biochemical recurrence[•63,65,69,70]. In a study including one hundred patients, PSMA PET/CT led to changes in staging in 43% of the patients and in radiotherapy planning in 59% of patients[71]. Due to the information provided by PSMA PET/CT, an additional simultaneous integrated boost (SIB) to the prostate bed or LNs was given to 32% and 63%, respectively. Ten patients received stereotactic body RT (SBRT) to single bone metastases. Other studies also reported a major impact of PSMA PET/CT on clinical management, especially in patients with low PSA levels[62,•72,73]. PET/CT may also be useful in guiding salvage extended LN dissection [74], radiotherapy[71,75,76], or planning of ^{223}Ra therapy in selected patients[••77]. However, it must be noted that the ultimate benefits of these treatment modifications are still unknown. When PSMA PET is used in addition to bone scanning, radionuclide therapy with ^{223}Ra may potentially be more effective[77].

Is PSMA radioguided salvage LN dissection feasible?

There are several challenges when performing salvage surgery procedures. Previous surgery and radiation treatment may result in scar tissue which may complicate soft tissue removal, with increased risk of injury to the ureter, vessels, intestine, bladder, among others. Furthermore, LN metastases after previous surgery are often located at atypical sites and are often very small. Thus, there has been much attention on PSMA radioguided LN surgery[78,79]. Recently, PSMA ligands labelled with ^{111}Indium and ^{99m}Technetium have been established. After preoperative injection of these novel PSMA agents, SPECT/CT imaging can be performed using the gamma-emitting properties. Although the diagnostic performance of these ligands seem inferior to PSMA PET/CT, intraoperative guidance using hand-held gamma-probes has been reported to facilitate detection and resection of sites of recurrence within soft tissues[78].

Can PSMA/PET be used for therapy assessment?

A few preliminary studies have recently begun to address the possible role of PSMA PET/CT for response assessment to systemic therapies or radiation in metastatic PCa[80–82]. Response assessment with PSMA PET/CT may be superior to conventional CT[82]. However, larger prospective trials are clearly needed to further evaluate and better define the role of PSMA PET/CT in assessing response to anti-cancer therapies.

CONCLUSION

Most of the studies involving PSMA PET/CT have been in the setting of PCa recurrence, where it has higher sensitivity than other imaging modalities for detecting sites of recurrence, even at very low serum PSA values. For primary PCa, PSMA PET/CT shows promise for tumor localization in the prostate, especially in combination with mpMRI. For primary staging, PSMA PET/CT can be used in intermediate and high risk PCa for detection of LN and bone metastases. Overall, it appears that PSMA PET/CT is superior to conventional imaging. Importantly, also PSMA PET/CT in a “theranostic” approach can identify patients who can benefit from PSMA targeted radiotherapy, which is increasingly being used in advanced PCa.

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KEYPOINTS

- PSMA PET/CT detects most intermediate and high risk primary prostate cancers with high sensitivity and specificity.
- PSMA PET/MRI is ideal for co-localizing PET findings with MRI in the setting of small primary tumors or subtle sites of local recurrence, allowing more accurate biopsy guidance.
- For primary staging PSMA PET/CT can be used in intermediate and high risk PCa.
- PSMA PET/CT is useful in detection of biochemical recurrence, especially at low PSA values.
- PSMA PET/CT is superior to choline PET/CT and other conventional imaging modalities.