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Seminars in
NUCLEAR
MEDICINE

Molecular Imaging for Primary Staging of Prostate Cancer

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According to SEER Cancer Statistics Review there are around 165,000 new prostate cancer cases estimated in 2018 accounting for 9.5% of all newly diagnosed cancers. Accurate staging of primary prostate cancer is important for therapy selection (local vs systemic). Recent developments in molecular imaging may significantly impact staging procedures and management. Accordingly, this article addresses the current clinical standard, discusses the areas of unmet clinical need for imaging and then summarizes the most commonly used molecular imaging probes. Finally, the authors dare an outlook to the short-term future role of molecular imaging in primary staging of prostate cancer.
Semin Nucl Med 49:271-279

Prostate cancer is the most common cancer type in males with an incidence of 112.6 per 100,000 persons in the United States.[1] The incidence ranges from as low as 54.8 for American Indian/Alaska Native up to 178.3 for Black men per 100,000 persons. The 5 year overall survival rate is 98.2%. However, the corresponding rates are 100% for localized and regional disease at primary diagnosis and only 30% in case of multiple distant disease manifestations. Depending on the current clinical standard for primary staging, disease is localized in 78% (confined to primary site), regional in 12% (spread to regional lymph nodes), and distantly spread in 5% (4% unstaged patients). Treatment options and prognosis significantly differ depending on disease stage at initial manifestation. Thus, there is great need for accurate and reliable primary staging to best tailor treatment strategies.

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Current Clinical Standard

According to the current clinical practice, prostate cancer risk stratification is used to determine which imaging modalities will be included in a patient's primary staging.[2] The National Comprehensive Cancer Network (NCCN) differentiates patients with a low, intermediate, or high risk for distant metastases accounting for the clinical stage, the PSA level at diagnosis and the histopathological Gleason score (Table 1). Favorable intermediate risk patients (clinical stage of T2b-T2c or prostate-specific antigen (PSA) of 10-20 ng/mL or Gleason score of 3 + 4 = 7 and percentage of positive biopsy scores <50%) should undergo pelvic with or without abdominal imaging if a nomogram predicts greater than 10% probability of pelvic lymph node involvement. Bone imaging is not recommended for this group. Unfavorable intermediate risk patients (clinical stage of T2b-T2c or PSA of 10-20 ng/mL or Gleason score of 3 + 4 = 7 or 4 + 3 = 7) should undergo pelvic with or without abdominal imaging if a nomogram predicts greater than 10% probability of pelvic lymph node involvement and bone imaging if the patient has a clinical stage of T2 and PSA > 10 ng/mL.[3] Patients with clinical stage greater than or equal to T3a or Gleason score greater than or equal to 8, or PSA greater than or equal to 20 ng/mL are considered high-risk and pelvic with or without abdominal imaging is recommended again if a nomogram predicts greater than 10% probability of pelvic lymph node involvement and bone imaging is always recommended. A nomogram is a predictive tool that requires input variables to calculate a prediction about an

https://doi.org/10.1053/j.semnuclmed.2019.02.004
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Table 1 Recommended Imaging for Staging of Prostate Cancer

	Intermediate-Risk	Recommendation	High-Risk	Recommendation
NCCN	T2b-T2c OR Gleason score 7 OR PSA 10-20 ng/mL	Pelvic ± abdominal imaging if nomogram predicts >10% probability of pelvic lymph node involvement Bone imaging if T2 and PSA >10 ng/mL and percentage of positive biopsy scores is >50%	T3a-T4 OR Gleason score ≥ 8 OR PSA > 20 ng/mL	Pelvic ± abdominal imaging if nomogram predicts >10% probability of pelvic lymph node involvement Bone imaging
EAU	T2b OR Gleason score 7 OR PSA 10-20 ng/mL	Abdominopelvic imaging and bone scan if predominately Gleason pattern 4	T2c or higher OR Gleason score >7 OR PSA 20 ng/mL	Abdominopelvic imaging and bone scan

outcome. The NCCN Guidelines Panel recommends that the NCCN risk groups should be used as a starting point for discussing staging and treatment options and nomograms be used to provide more individualized information.

The European Association of Urology (EAU) risk stratification groups are similar to NCCN with intermediate-risk patients with a clinical stage of T2b or PSA of 10-20 ng/mL or Gleason score of 7 and high-risk patients with a clinical stage of T2c or PSA greater than 20 or Gleason score greater than 7 (Table 1).[4] The EAU recommends that patients in the intermediate-risk group with predominately Gleason pattern 4 and high-risk patients undergo cross-sectional abdominopelvic imaging and bone scan as well as multiparametric MRI for local staging.

In summary, neither NCCN or EAU recommend in the current versions any kind of next generation molecular imaging for primary staging of prostate cancer.

Clinical Unmet Needs in Primary Prostate Cancer Staging Providing Opportunities for Molecular Imaging

Primary staging of prostate cancer is crucial for adequate treatment planning and prognostication. It requires a correct local staging, the assessment of regional and distant lymph nodes as well as the status of potential distant metastases. The importance of local staging is to assess the presence or absence of extracapsular extension and regional lymph node metastases that may affect surgical and radio-therapeutic planning.[5] Local staging is completed with transrectal ultrasound guided biopsy and multiparametric magnetic resonance imaging (mpMRI).[6-10] However, when staging for extraprostatic disease, it has been shown that computed tomography (CT) cross-sectional imaging is limited in detecting lymph node metastases in normal sized lymph nodes[11-16] opening up the opportunity for molecular imaging to contribute.

Specifically, a paper reviewing 27 studies that examined the role of CT in evaluating lymph nodes in patients with prostate cancer found that out of 4264 patients who underwent CT and pelvic nodal dissection, 654 (15.3%) had pathology proven prostate cancer metastasis, while CT only detected disease in 105 patients (2.5%).[13] A meta-analysis of 24 studies compared the diagnostic accuracy of CT and MRI in the diagnosis of lymph node metastasis and found that the pooled sensitivity of CT was 0.42 (0.26-0.56 95% CI) and pooled specificity of 0.82 (0.8-0.83 95% CI) and the pooled sensitivity of MRI was 0.39 (0.22-0.56 95% CI) and pooled specificity was 0.82 (0.79-0.83 95% CI).[12] Another study evaluated 980 prostate cancer patients after prostatectomy and lymph node dissection and found that 74% of metastatic nodes had an axial size of less than 1 cm and 26% had an axial size less than 5 mm.[14] Another report analyzed 1542 prostate cancer patients who underwent prostatectomy and extended pelvic lymph node dissection and found that sensitivity, specificity, and accuracy of CT for detecting lymph node metastases were 13.0%, 96.0%, and 54.6%, respectively.[15] The poor overall performance of morphological imaging techniques for the assessment primary lymph node metastases encouraged many groups to evaluate molecular imaging techniques in this clinical setting.

Molecular Imaging for Primary Staging

A wide range of different nuclear imaging probes for positron emission imaging are available addressing a variety of different metabolic processes and cell receptors. Especially in the last 2 decades, numerous metabolic PET probes imaging the glucose (18F-FDG), the phospholipid (11C- and 18F-Choline), the amino acid (11C-Acetatate, 18F-FACBC) or the fluoride (18F-fluoride) metabolism have been introduced. More recently, specific receptor ligands e.g. for androgen receptor (18F-FDHT) and prostate specific membrane antigen (68Ga-/18F-Prostate-Specific Membrane Antigen [PSMA]) have been also developed and investigated for primary prostate cancer staging. The most common PET tracers are separately discussed below and summarized in Table 2.

Table 2 PET/CT Imaging Tracers Studied for Prostate Cancer

Tracer	Half-life (min)	Mechanism of action	Excretion	Sensitivity (%)	Specificity (%)	Role in prostate cancer imaging
F-18 FDG	110	Glucose metabolism	Renal	4-52	76	Limited role in patients with a Gleason score of 8 or 9 or castrate-resistant prostate cancer, prognostic information
C-11 choline	20	Cell membrane synthesis	Hepatic	49-62	92-98	FDA approved for BCR
F-18 fluciclovine	110	Amino acid transport	Renal	30-65	97-100	FDA approved for BCR
F-18 NaF	110	Adsorption within bone matrix	Hepatic	87-100	80-100	FDA approved for detecting bone metastases
C-11 Acetate	20	Lipid synthesis	Lung	73	79	Limited use for BCR as part of INDs
Ga-68 PSMA	68	PSMA ligand	Renal	33-92	74-100	High-risk patients before surgery or radiation therapy when detection of radiologically occult nodal or bone metastases would affect patient management and BCR. Not yet FDA approved.

BCR, biochemical recurrence; INDs, investigational new drug applications.

18F-FDG

18F-Fludeoxyglucose (FDG) PET/CT is not commonly used to assess prostate cancer patients. The main reason is the low glycolytic activity of well differentiated prostate cancer and accordingly the low sensitivity and specificity of 18F-FDG PET/CT for detecting primary disease.[17,18] Most prostate cancers use other metabolic pathways such as fatty acid metabolism[19] or fructose rather than glucose.[20,21] Additionally, FDG uptake is not specific for prostate cancer and can be seen in cases of benign hyperplasia and inflammatory pathologies.[22] However, generally there is high FDG uptake in prostate tumors that are poorly differentiated. Additionally, glucose metabolism in prostate tumors is modulated by androgen, therefore it may be able to show response to androgen deprivation therapy.[23] FDG PET/CT can be useful in limited resource settings for patients with a Gleason score of 8 or 9 or castrate-resistant prostate cancer[5,24,25] (Fig. 1). A study of 54 prostate cancer patients with a Gleason score of 8 or higher who underwent FDG/PET prior to surgery found 11 patients with lymph node metastases by histopathology and only three (27%) of these patients had positive lymph nodes on the FDG PET/CT. Nevertheless, the presence or absence of intra-prostatic FDG uptake presented prognostic information concerning cancer-free survival.[26]

Choline

Choline is necessary for the synthesis of cell membranes during cell growth and is metabolized by choline kinase, an enzyme that is overexpressed in certain tumors, including prostate cancer.[27,28] There are three choline tracers: 11C-choline (Fig. 2), 18F-fluoroethylcholine, and 18F-fluoromethylcholine. The 11C isotope has a short half-life (20 minutes) and requires an onsite cyclotron, while 18F has longer half-life (110 minutes) and can be transported to various clinics.

Regarding intraprostatic lesion detection, combined choline PET/MRI had a very high sensitivity for the detection of the dominant malignant lesion in the prostate compared to MRI or PET alone.[29] Additionally, Choline PET is specific and has been shown in previous studies to be more sensitive than MRI for detecting lymph node metastases. A study of 28 patients who underwent 11C-choline PET/CT prior to pelvic lymph node dissection reported a sensitivity of 51.9% for PET/CT and 18.5% for MRI and a specificity of 98.4% for PET/CT and 98.7% for MRI.[30]

A meta-analysis combining 11C-choline and 18F-choline PET/CT studies discovered the pooled sensitivity for pelvic lymph node metastases to be 0.62 (0.51-0.66 95% CI) and the pooled specificity to be 0.92 (0.89-0.94 95% CI). Additionally, more patients had positive findings with choline

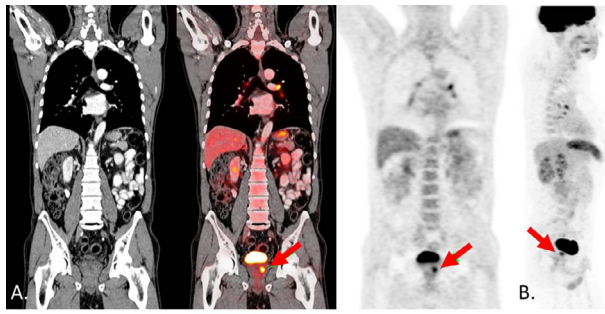

Figure 1 FDG PET/CT of 61-year-old male with prostate cancer (GS 8) presenting for initial staging, found to have intense FDG activity in the left prostate gland (red arrow). FDG uptake in hilar lymph nodes are reactive in the setting of granulomatous disease. Coronal images of CT, PET, and fused PET/CT are shown in image (A) PET Maximum intensity projection (MIP) image is shown in image (B).

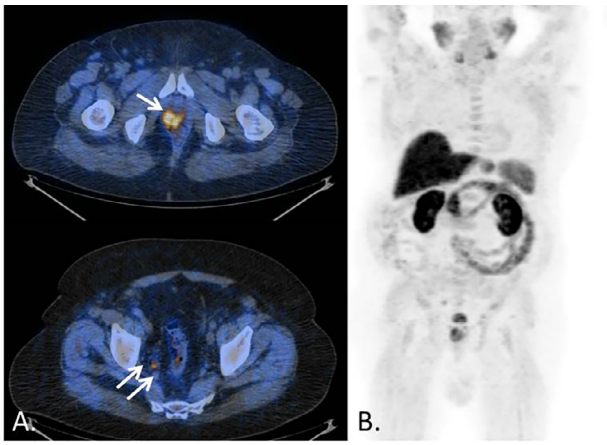

Figure 2 A 72-year-old male with biopsy proven prostate cancer (Gleason 4 + 4; iPSA 16.1 ng/mL) and PIRADS 5 lesion on the mpMRI underwent 11C-PET/CT prior to radical prostatectomy. Corresponding fused transaxial 11C-Choline PET/CT images (A) display intense uptake in the right prostate lobe (SUVmax 8.6; white arrow) and focal moderate to intense uptake in a right obturator lymph node (SUVmax 3.6; white double arrow). Corresponding MIP is also shown in image B.

PET/CT than with bone scanning.[31] Another meta-analysis however found a lower pooled sensitivity of 0.49 (0.40-0.58 95% CI) but a similar pooled specificity of 0.95 (0.92-0.97 95% CI).[32] A third meta-analysis comparing choline PET/CT, MRI, bone SPECT, and bone scintigraphy, found that choline PET/CT had the highest specificity and MRI had the highest sensitivity.[33] Overall, choline PET/CT does not have an adequate sensitivity for primary lymph node staging, ranging from 49 to 62%, and therefore is not recommended in current guidelines.

18F-Fluciclovine

18F-Fluciclovine (anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid [18F-FACBC]) is a synthetic nonmetabolized leucine amino acid analog that is taken up by sodium-dependent amino acid transporters which are associated with aggressive tumors.[34] There are limited studies investing primary staging with 18F-Fluciclovine (Fig. 3). One study of 68 patients found the sensitivity and specificity of 18F-Fluciclovine PET/CT for primary prostate lesions to be 92.5 and 90.1%, respectively. When compared to contrast-enhanced CT, 18F-Fluciclovine PET/CT had similar accuracy (87% vs 86%), sensitivity (65% vs 65%), and specificity (100 vs 97%). For detection of bone metastases, 18F-Fluciclovine PET/CT and combined bone scintigraphy and CT were concordant 83% of the time, and 7 of 18 patients with bone metastases were only positive with 18F-Fluciclovine PET/CT.[35] Regarding lymph node staging, a recently published study investigated 28 high-risk prostate cancer patients with 18F-Fluciclovine PET/MRI prior to surgery. Corresponding patient- and region-based sensitivities were low for both MRI (40% and 35%) and 18F-Fluciclovine PET (40% and 30%), respectively while corresponding specificities were high (MRI: 87.5% and 95.7%; PET: 100% and 100%).[36] Accordingly, the FDA approval label of 18F-Fluciclovine was not for primary staging but only for detection of biochemical recurrence.[37]

18F-Sodium Fluoride

18F-Sodium Fluoride (NaF) is an analog of the hydroxyl group in hydroxyapatite bone crystals. Fluorine is directly absorbed onto the surface of the bone matrix.[21] Tracer uptake correlates with bone remodeling, osteoblastic activity, as well as bone blood flow.[38] Compared to 99m-Tc-labeled phosphonates used for conventional bone scintigraphy (Fig. 4), 18F-NaF has a faster plasma clearance, shorter uptake time, and a 2-fold higher bone uptake,[39] allowing shorter scanning time with better image quality. Unfortunately, however, both of the tracers reflect osteoblastic activity and are not specific for malignancy. Increased uptake is also seen in degenerative disease.

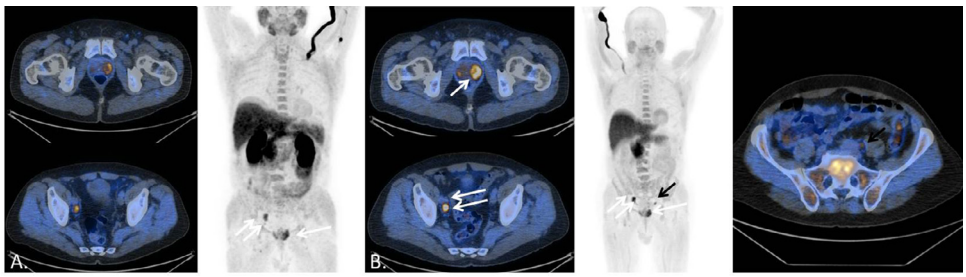

Figure 3 A 68-year-old male with iPSA 31.3 ng/ml with biopsy proven prostate cancer (13/13 positive cores, Gleason Score 4 + 3; EAU high risk patient) prior to scheduled surgery. (A) 11C-Choline and 18F-FACBC (B) were performed within 2 weeks confirming the intense uptake predominately in the left prostate lobe (white single arrow) and in a right external iliac lymph node (white double arrow). Additionally there was increased 18F-FACBC uptake perceived (not visible on the 11C-Choline scan) in a left common iliac lymph node (SUVmax = 3.8; black single arrow). The consecutive robotic-assisted radical prostatectomy confirmed pT3b (left seminal vesicle invasion), pN1 (1/41 in right external iliac region), perineural diffuse invasive Gleason 4 + 3 prostate cancer. The common iliac lymph nodes were not removed. Image B is provided as a courtesy of Dr Lucia Zanoni (Nuclear Medicine Division, Policlinico S Orsola, University of Bologna, Bologna, Italy) and her project "18F-FACBC PET/CT for staging high risk prostate cancer" granted by Programma di ricerca Regione-Università Area 1- Bando Giovani ricercatori "Alessandro Liberati" 2013.

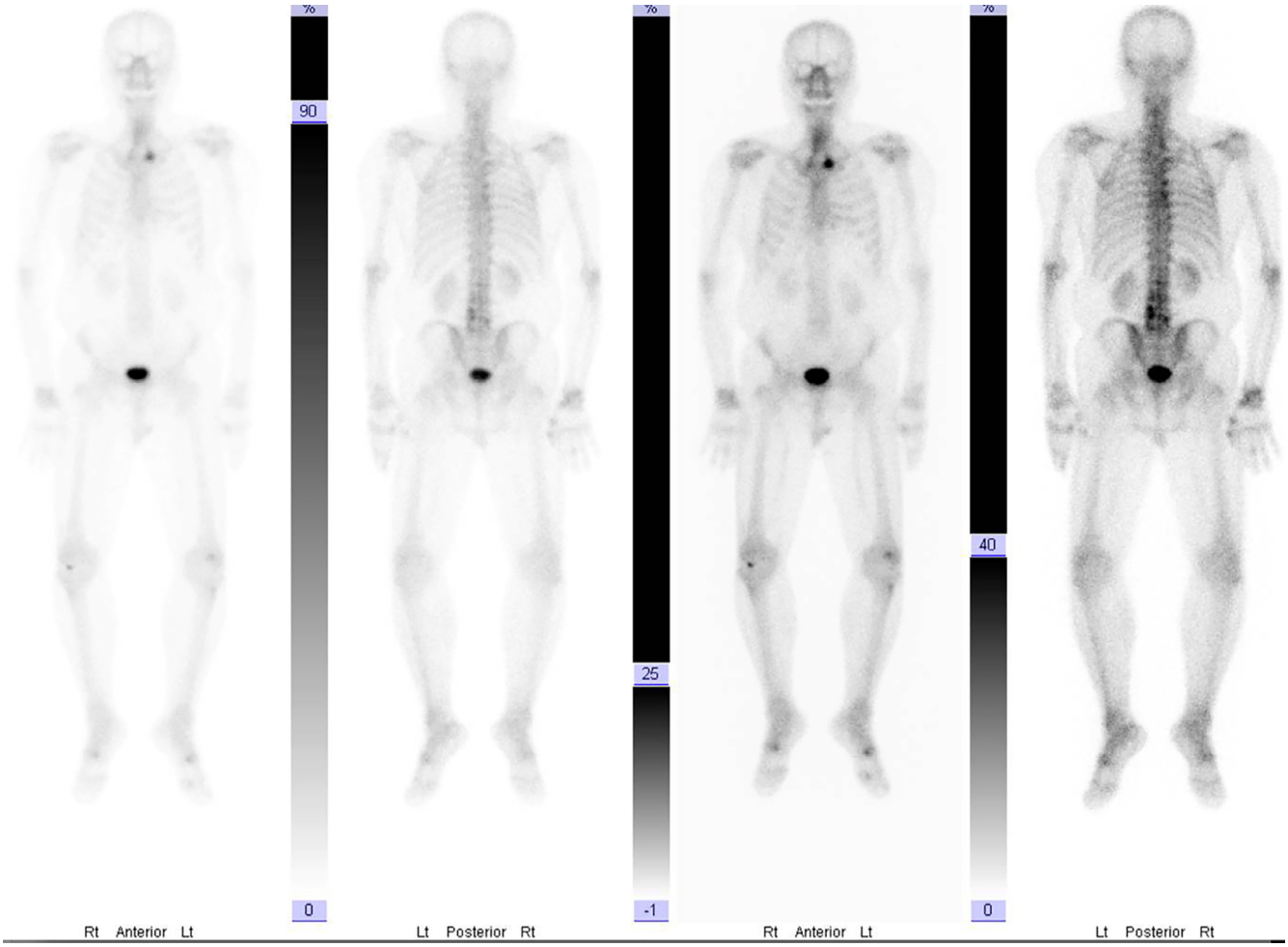

Figure 4 A 78-year-old male underwent Tc-99 m MDP whole body bone scan for primary staging of high-risk prostate cancer (GS 8), without evidence of osseous metastasis. Increased tracer uptake in the left sternoclavicular joint is degenerative.

Several studies suggest that NaF PET performs better than Tc-99 m methylene diphosphonate (MDP; Fig. 4). One notable study compared MDP planar bone scintigraphy, single and multi-field-of-view SPECT, NaF PET, and NaF PET/CT[40] in high-risk prostate cancer patients. The sensitivity and specificity for detecting bone metastases were significantly higher for NaF PET/CT (100% and 100%, respectively) than for planar scintigraphy (70% and 57%), SPECT (92% and 82%) or NaF PET alone (100% and 62%). A literature review of 18F-NaF PET/CT for detecting prostate cancer metastases to bone, found pooled sensitivities and specificities of 89% and 91%, respectively, on a per-lesion basis and 87% and 80%, respectively, on a per-patient basis.[41] Together these results support NaF PET/CT over conventional scintigraphy for the accurate detection of skeletal disease in prostate cancer; however, more studies are needed to compare NaF PET/CT to other prostate cancer tracers, especially if one tracer is accurate with detecting both lymph node and bone metastases. Additionally, another limitation of NaF PET/CT is that there is no independent lesion validation; there may be false positives.

A few studies have compared NaF to other PET/CT tracers,[42-44] including a study of 18F-NaF PET/CT and 18F-choline PET/CT in the staging of prostate cancer patients with negative or inconclusive findings with MDP planar bone scintigraphy.[42] Researchers found nodal or bone metastases in 39% (35 of 90 cases) with 18F-choline PET/CT and found bone metastases in 41% of cases with 18F-NaF PET/CT, showing a slight advantage to NaF. In a prospective study comparing 18F-choline and 18F-NaF PET/CT, investigators found no significant difference in site-based performance in the group of patients referred at initial staging.[43] In summary, NaF PET/CT demonstrates superior sensitivity and specificity when compared with MDP bone scintigraphy, but the results are mixed when comparing NaF and choline tracers for detecting bone metastases. Despite the encouraging results however, Centers for Medicare & Medicaid Services declined again in the spring of 2018 the coverage of NaF-PET scans.[45]

PSMA

Prostate-Specific Membrane Antigen (PSMA) is a transmembrane glycoprotein enzyme on the cell surface of normal prostate tissue. It is overexpressed in prostate cancer and has increased expression in high-grade tumors, and in

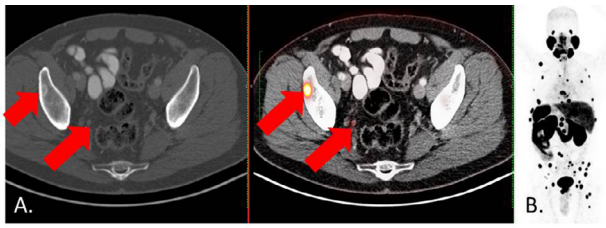

Figure 5 A 65-year-old male with prostate cancer and PSA of 190 ng/mL presents for primary staging, found to have primary tumor in the prostate, numerous bone metastases, and bilateral pelvic lymph node metastases. Axial images of CT and fused PSMA PET/CT are shown in image (A) with example pelvic lymph node and bone metastases. PSMA PET MIP image is shown in image (B).

castration-resistant disease.[46,47] PSMA ligands are frequently labeled with 68-gallium which has a half-life of 68 minutes (Fig. 5). Studies focusing on the localization and extent of primary prostate cancer lesions found that PSMA is not very sensitive for lesions within the prostate, especially for those with a lower Gleason score,[48,49] but can be very helpful when combined with MRI imaging,[50,51] where sensitivity increases to 76% from 64% with PET alone.[51]

Several studies have compared lymph node metastases detected by 68Ga-PSMA PET to lymph node histopathology.[52-56] Across the studies, median sensitivity on per-lesion analysis ranged from 33% to 92%, while median specificity ranged from 82% to 100%.[57] It is important to note, that one study[52] was correlating lymph node immunohistopathology results with outside PET/CT reports and produced a sensitivity of 33%. This same group published another report with updated data that found a sensitivity of 90% and specificity of 74% in side-based analysis and a sensitivity of 76% and specificity of 88% in lymph node field-based analysis.[58]

68Ga-PSMA PET/CT has been shown to be superior to that of planar bone scintigraphy for detection of bone metastases[59] (Fig. 6). Due to recent studies illuminating the diagnostic superiority of 68Ga-PSMA PET/CT over conventional imaging in the detection of nodal and bone metastases, recent guidelines recommend the use of 68Ga-PSMA PET/CT imaging in high-risk patients before surgery or external beam radiation therapy in cases in which detection of radiologically occult nodal or bone metastases would substantially affect patient management.[47]

More recently, 18F-labeled PSMA-targeted PET/CT tracers have been studied, including 18F-DCFBC (N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-(18)F-fluorobenzyl-L-cysteine),[60-62] 18F-DCFPyL (2-(3-{1-carboxy-5-[(6-18F-fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid),[63,64] 18F-PSMA-1007 (((3S,10S,14S)-1-(4-(((S)-4-carboxy-2-((S)-4-carboxy-2-(6-18F-fluoronicotinamido)butanamido)butanamido)methyl)phenyl)-3-(naphthalen-2-ylmethyl)-1,4,12-trioxo-2,5,11,13-tetraazahexadecane-10,14,16-tricarboxylic acid)),[64,65] and 18F-rhPSMA-7.[66] These tracers may be used more frequently in the future due to their longer half-life.[67] Especially the latter two tracers are particularly promising, as they are predominately excreted via the GI tract and therefore do not accumulate in the urinary bladder. This might significantly improve the performance of 18F-PSMA 1007 PET for T-staging and detection of local recurrence.[65,68] However, to date, none of the PSMA tracers are integrated into clinical guidelines for primary staging.

Other

There are additional molecular imaging tracers that have been studied less frequently, including acetate and tracers related to androgen receptors. Acetate is the most common building block for the biosynthesis of fatty acids and other structural cell compounds. Prostate cancer cells upregulate fatty acid synthesis.[28] Both 11C-labeled acetate and 18F-labeled acetate are available, and neither are specific to prostate cancer. Both tracers can be seen in the setting of inflammation, benign tumors, or other cancers. For the diagnosis of primary prostate cancer, 11C-acetate is inferior to MRI, especially because it can also be seen in benign prostatic hyperplasia.[69] Additionally, for detection of lymph node metastases, 11C-acetate also has suboptimal sensitivity (73%) and specificity (79%).[70] Similar to choline PET/CT, acetate PET/CT may be of limited use for the detection of early recurrence of prostate cancer.

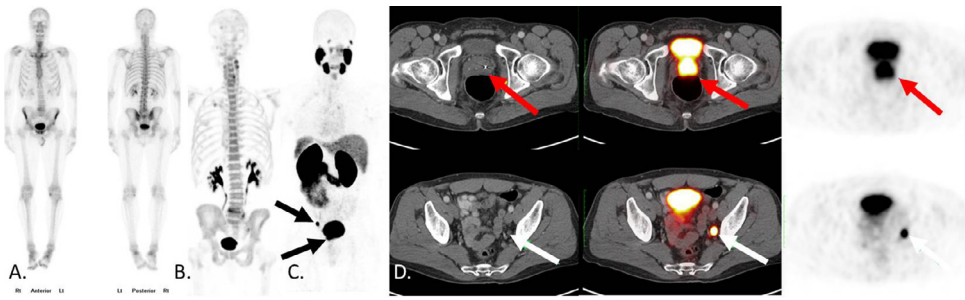

Figure 6 A 55-year-old male with prostate cancer (GS 9) presenting for initial staging. Tc-99 m MDP whole body bone scan (A) and F-18 sodium fluoride PET/CT bone imaging (B) were negative. PSMA/CT MIP (C) with increased tracer the prostate and left internal iliac lymph node (black arrows). PSMA PET/CT axial images with prostate gland with high PSMA expression (red arrows) and pelvic lymph nodes with high PSMA expression (white arrows) consistent with metastatic disease (D).

Another PET tracer, 18F-fluoro-5-alpha-dihydrotestosterone (18F-FDHT), displays where androgen receptors are over expressed.[71] A recent study found that the number and intensity of bone lesions on CT, FDG-PET, and FDHT-PET are associated with overall survival.[72] Very limited data is available for this tracer, but it may be useful to assess systemic androgen receptor blockade.[73,74]

Outlook

The advent of many new PET probes comes with considerable improvement in diagnostic performance at initial staging of prostate cancer. In the future we expect more studies to investigate PSMA based agents with 18F due to their favorable characteristics such as longer half-life, higher production yields and nonrenal excretion compared to 68Ga-PSMA. For primary staging, the combination of PET with multiplanar MRI appears very promising due to the superiority of MRI for T-staging and PET tracers for N- and M-staging. Lastly, with the improvements of artificial intelligence the complex information provided by clinical parameters, dynamic digital PET, and mpMRI has the potential to reduce the number of biopsies as well have to improve treatment stratification.

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