A Short Review of Prostate Cancer Molecular Imaging

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Background:

Prostate cancer (PC) is the most common non-cutaneous malignancy in adult males in the United States and the second most common cause of cancer death in this population. In 2018, it is projected there will be 164,690 new cases of PC and about 29,430 deaths attributable to this disease [1]. Due to aggressive screening with serum total prostate specific antigen (PSA) and routine digital rectal examination, the diagnosis is usually made at an early stage of the disease while still localized to the prostate gland. When localized, it is characterized by a good prognosis, displaying an indolent course. However, PC can be a progressive disease for patients who are categorized as high risk [2] and many times is diagnosed after it has already spread locoregionally or to distant sites. Approximately 6% of new PC cases present with metastatic disease with a 5-yr survival rate of only 29% [3]. For all stages combined, overall survival is 99% [1]. For patients who decide to undergo curative treatment, radical prostatectomy (RP) or radiation therapy (RT), PSA is used as a marker for disease recurrence. According to international consensus, after radical prostatectomy, biochemical recurrence (BCR) of PC may be defined by two consecutive PSA values of >0.2 ng/ml and if rising [4-6]. Following primary radiotherapy, the RTOG-ASTRO Phoenix Consensus Conference definition of PSA failure is any PSA increase >2 ng/ml higher than the PSA nadir value, regardless of the serum concentration of the nadir. Despite all the advances that have been made in primary treatment options and the improvement in the overall survival of prostate cancer, 20-40% of patients experience disease relapse in the form of BCR [7, 8], and it is well
known that a rising PSA level can precede metastatic spread [6]. Some of the clinical parameters that determine the likelihood of recurrence or metastasis are PSA doubling time, PSA velocity, Gleason’s score, and pathological stage. Currently, the imaging workup for patients with high-risk primary prostate cancer, BCR, or metastatic disease includes conventional imaging modalities $^{99m}$Tc-methylenediphosphonate bone scan, CT, and sometimes MRI. However, CIM have a notoriously low sensitivity in detecting lesions when the patient has a low disease volume or low serum total PSA level [9]. Early detection of recurrence or small volume metastatic disease in specific patients, along with new treatment options, can potentially increase the overall survival for these patients [10]. Molecular imaging offers us the ability to identify previously undetectable metastases, which can directly affect the clinical staging and treatment outcomes [11].

Positron emission tomography (PET) imaging is a functional molecular imaging technique and is considered the standard of care for the initial staging and for post-treatment follow-up to assess treatment response and/or disease progression for many different malignancies. $^{18}$F-fluorodeoxyglucose ($^{18}$F–FDG) is the most common radiopharmaceutical used for oncologic PET imaging, although it has a limited role in PC, because PC cells (especially hormone-naïve) have low glycemic activity, which limits the $^{18}$F–FDG uptake. Traditionally, $^{18}$F–FDG-PET imaging has been utilized to detect metabolic activity, blood flow, and apoptosis. However, newer PET radiopharmaceuticals have the ability to identify upregulated molecular targets/receptors or novel biological pathways [12].
$^{18}$F NaF (sodium fluoride) is a radiotracer that has a favorable biodistribution as it diffuses into the active bone remodeling sites (both lytic and blastic lesions) by exchanging fluoride ions with hydroxide ions of the hydroxyapatite crystals, forming fluorapatite [13]. Despite its superior diagnostic performance in the detection of bone metastases (compared to $^{99}$Tc bone scan) [14] as well its ability to visualize smaller lesions better, with higher resolution and high target/background ratio, $^{18}$F-NAF-PET/CT is no longer reimbursed by the Centers for Medicare and Medicaid Services (CMS).

$^{18}$F Fluciclovine PET/CT ($^{18}$F FACBC, Axumin®)

Anti-1-amino-3-F-18-fluorocyclobutane-1-carboxylic acid ($^{18}$F-FACBC or fluciclovine) is a synthetic L–leucine analog that has high tumor-specific accumulation through amino acid transporters-alanine-serine-cysteine transporter 2 (ASCT2) and large neutral amino acid transporter 1 (LAT1), which are known to be upregulated in PC [15,16]. The FDA approved this radiopharmaceutical in May 2016 for patients with suspected recurrence based on elevated PSA following prior treatment. Biodistribution of fluciclovine is similar to other amino acid–based PET radiopharmaceuticals, and the primary sites of uptake include pancreas, liver, bone marrow, salivary glands, lymphoid tissue, and the pituitary gland. There is minimal uptake by the brain and little urinary excretion (in the first 24 hours), which can be advantageous to image cerebrum, retroperitoneal space, and the pelvis [17]. Dosimetry is similar to $^{18}$F FDG [18].

Most experience with fluciclovine has been gained in the recurrent PC disease subset. In one study, investigators reported higher sensitivity and specificity for detecting local and
extra-prostatic disease in comparison to $^{11}$C-choline [19], in patients radically treated for PC who had developed BCR. A meta-analysis of different PET tracers demonstrated that $^{18}$F-fluciclovine had greater ability to detect locally recurrent disease versus $^{18}$F-choline, although the difference was not statistically significant [20]. Additionally, fluciclovine is easy to produce, has a longer half-life, and has better tumor-to-background activity. CIM for BCR has limited accuracy, especially when the PSA level is low [21]. Multiple trials have now shown that fluciclovine can detect low-volume disease (small lymph nodes, small soft tissue, and bone lesions) otherwise not visualized on CIM but confirmed by histological findings [22].

One of the limitations to optimal use of fluciclovine is increased uptake in non-malignant conditions such as benign prostatic hyperplasia and prostatitis, which may coexist with localized PC disease, thus limiting the interpretation of the images.

Representative cases of metastatic PC imaged with fluciclovine radiopharmaceutical:
Figure 1. Patient diagnosed with PC. Physiological uptake in the liver is seen and nonspecific uptake in the bone marrow. The fluciclovin-avid left posterior mediastinal lymph node along with a focus of intense uptake in the L1 vertebra are highly suspicious for malignant disease.
Figure 2: PC patient imaged with fluciclovine. Physiological uptake is seen in the liver. Moderate-to-intense increased uptake in the bilateral paraaortic retroperitoneal lymph nodes thoracic vertebral body is suspicious for metastatic disease. Mild uptake in the left renal cortex is likely physiological.
Gallium-68 (\(^{68}\text{Ga}\))–PSMA PET/CT

Prostate-specific membrane antigen (PSMA) is a type II membrane metalloenzyme. The healthy prostate gland expresses comparatively little PSMA, which is confined within the apical membrane of secretory duct. Unlike PSA, which can be elevated in many benign conditions (like benign prostate hyperplasia, prostatitis, instrumentation), PSMA is upregulated in PC cells (100–1000 times more in PC than in benign prostate cells and other tissues), preferentially localizes to the luminal surface of the ducts during the transition to androgen independence, and is most often associated with high-grade disease [23]. PSMA expression increases with increasing tumor stage and grade and in castration-resistant PC. The newer generation \(^{68}\text{Ga}\)-PSMA ligands target the extracellular domain of PSMA, with strong binding affinity, and are internalized into the endosomal recycling system with rapid blood clearance and low background activity. These characteristics lead to high-quality images with high tumor-to-background ratios [24].

\(^{68}\text{Ga}\)-labeled PSMA-HBED-CC is the most common radiopharmaceutical used for PSMA PET/CT imaging. It consists of a urea-based small molecule ligand that is structured to attach to the extracellular domain, significantly increasing sensitivity. Biodistribution of \(^{68}\text{Ga}\)-PSMA-HBED-CC includes uptake in the salivary and lacrimal glands, liver, spleen, kidneys, and intestine [25]. High physiologic liver uptake can be confounding to evaluate for any occult liver metastases. Also, uptake is seen in ganglia as well as minimal uptake in bone marrow (less than \(^{11}\text{C}\)-choline). \(^{68}\text{Ga}\)-labeled PSMA–HBED–CC is primarily excreted in the urine.
In a systemic review and meta-analysis of 16 articles with a total 1,309 patients, for those with BCR, the detection rate by PSMA-based PET/CT imaging increased with an increase in serum PSA levels (42% at PSA <0.2 ng/mL to 95% at PSA >2 ng/mL). Shorter PSA doubling time also increased $^{68}$Ga–PSMA-PET positivity. Overall sensitivity and specificity were 86% each on per-patient analysis, and the overall sensitivity and specificity were 80% and 97%, respectively, on per-lesion analysis [26]. $^{68}$Ga-PSMA-PET/CT can be an important diagnostic tool in the setting of initial staging. In a study with 130 patients with intermediate and high-risk patients, $^{68}$Ga–PSMA PET/CT outperformed conventional imaging modalities (CT or MRI) in assessing nodal disease assessment [27].

Hepatic uptake (limiting liver metastases evaluation), the investigational nature of $^{68}$Ga-PSMA-HBED-CC, and the requirement for a $^{68}$Ga generator limits its current availability in the US. Other PSMA ligands such as $^{18}$F-DFPyL show promising results. In a small prospective comparative study with $^{68}$Ga-PSMA-HBED-CC in 14 PC patients with BCR, $^{18}$F-DCFPyL detected all the suspicious lesions detected by $^{68}$Ga-PSMA-HBED-CC and additional suspicious lesions in 3 patients, indicating a higher sensitivity for 18F-DCFPyL [28].

Representative cases of metastatic PC imaged with $^{68}$Ga-PSMA-HBED-CC PET/CT
Figure 3: 67 year-old male diagnosed with high risk PC. Physiological urine excretion is seen in the urinary bladder. PSMA-avid left internal iliac node (SUVmax 26.8, measuring 1.3 x 0.9 cm) is seen.
Figure 4 – 76-year-old gentleman diagnosed with PC in 2013. Status-post hormonal therapy (2013 to 2017) and Enzalutamide (February 2016 to August 2018). Two sets of images from the same patient (March 2018 and August 2018) are displayed for comparison. There is overall interval progression of disease on the later images. New PSMA uptake is seen in several nodes and in the bones. New PSMA-avid para-aortic (SUVmax 19.8, 0.4 cm), left external iliac, perirectal, and presacral nodes are seen. New PSMA uptake is seen in the bilateral humeri and clavicles, manubrium, sternum, bilateral ribs, bilateral scapulae, a few vertebrae, right iliac bone (SUVmax 79.5), left iliac bone, the sacrum, bilateral acetabulae, and bilateral femurs. Interval increased PSMA uptake is seen in L3. Mild grossly stable nonspecific focal PSMA uptake is seen in the lateral aspect of the left 5th rib. Interval more extensive PSMA uptake is seen in the prostate (SUVmax 75.1, previous SUVmax 59.2) and the right seminal vesicle.

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References:


