^{68}Gallium–Prostate-Specific Membrane Antigen PET/Computed Tomography for Primary and Secondary Staging in Prostate Cancer

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KEYWORDS

• Prostate cancer staging • PSMA • PET/CT • Biochemical recurrence

KEY POINTS

- Preoperative staging is a generally recommended tool for risk stratification of intermediate- to high-risk prostate cancer.
- So far, staging of patients with prostate cancer relies mostly on morphologic imaging. Prostate-specific membrane antigen (PSMA) PET has shown to be able to contribute molecular information on distribution of the disease.
- Studies have shown that PSMA PET combined with conventional imaging offers similar or higher detection rates in primary staging.
- In patients with biochemical recurrence of prostate cancer, PSMA imaging is able to distinguish between local recurrence or lymph node metastases even at very low prostate-specific antigen levels, thus, guiding treatment decisions.

INTRODUCTION

Preoperative imaging is important to accurately risk classify oncologic patients and to guide treatment decisions. Patients diagnosed with intermediate-risk (predominant Gleason pattern 4) or high-risk prostate cancer (PCa) should undergo clinical staging before curative therapy.[1]

Several imaging techniques are used to evaluate local extension, nodal involvement, or bone metastasis. Common methods, such as computed tomography (CT) or MRI, rely on morphologic patterns, such as size, shape, or increased contrast enhancement of tumor lesions. During the past 2 decades, the combination of CT or

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MRI with PET improved our knowledge about the extent of the disease. In contrast to CT or MRI, PET scans visualize biochemical and molecular characteristics of suspect lesions. So far, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the most commonly used radiotracer in oncology. However, its ability to detect PCa in primary and secondary staging is limited to patients with poorly differentiated cancer,[2] most likely because of a low level of metabolic activity in differentiated PCa cells.[3,4] Choline-based tracers, which are more frequently used in patients with PCa, are also of limited sensitivity.[5] However, new radiotracers targeting the prostate-specific membrane antigen (PSMA) have shown promising results in the evaluation of primary and recurrent disease and in monitoring treatment response.

PROSTATE-SPECIFIC MEMBRANE ANTIGEN

PSMA is a 750-amino-acid type II transmembrane protein located within the apical epithelium of the secretory ducts of noncancerous prostate tissue. Several functions have been described for this protein, including enzyme activity in nutrient uptake, cell migration, signal transduction, and receptor activity for yet mostly unidentified physiologic ligands.[6] After binding to PSMA, the physiologic or artificial ligand is taken up into endosomal compartments or the cytoplasm of the cell via an internalization motif. During neoplastic transformation, PSMA transforms from the apical membrane to the luminal surface of the ducts.[7] PSMA expression is elevated in malignant prostate tissue, in contrast to benign prostatic hyperplasia specimens, in which no elevated expression was observed.[8] Studies have shown that PSMA expression positively correlates with Gleason score and prostate-specific antigen (PSA) level and is largely expressed in hormone-refractory PCa.[9] These features make PSMA an ideal target for diagnosis and treatment of PCa. Antibodies as well as synthetic small molecules are currently being used to target PSMA. However, antibodies lack diagnostic efficacy because of poor tumor penetrability, long circulating half-life, and high unspecific background activity.[10] The small molecule PSMA-inhibitor[11] radiolabeled with ^{68}gallium (^{68}Ga) is the most common agent for PET imaging to date. After ligation, the inhibitor is internalized into the malignant cell and cleared rapidly from nontarget tissue, resulting in a beneficial target to background ratio. Still, PSMA is not entirely prostate specific; there is physiologic uptake in the kidneys, parotid and submandibular glands, small intestines, spleen, and liver.[12,13] It is also expressed in tumor-associated neoangiogenesis and has, therefore, been described in other tumor entities, such as gastric, colorectal, breast cancer, and renal cell carcinoma.[14–17]

PRIMARY PROSTATE CANCER STAGING

For local staging, MRI of the prostate has a high diagnostic value for the detection of suspicious lesions within the prostate and for the evaluation of capsule penetration and invasion of adjacent structures due to excellent soft tissue resolution and comprehensive multi-parametric assessment.[18,19] It can also facilitate diagnostic yield after negative standardized biopsy and persistent clinical suspicion of PCa by the use of MRI–transrectal ultrasound fused biopsy or cognitive targeting.[20] However, accuracy of MRI of the prostate may be hindered by diagnostic challenges, such as benign changes mimicking malignancy, or technical issues considering acquisition. Differences in imaging interpretation due to interobserver variability may also lead to decreased sensitivity in tumor detection.[21] PET scans have been evaluated to address some of these limitations but performed generally poorly. PET alone cannot offer the necessary spatial resolution to detect small tumors within the organ. In combination with conventional imaging, PET/MRI is considered to be superior to PET/CT for the evaluation of local infiltration. Several studies have shown positive correlation between morphologic lesion plus increased uptake of choline-based tracers and postoperative pathologic finding, thus, offering beneficial diagnostic value compared with MRI alone.[22] PSMA ligands outperformed other radiotracers in detection rates. Tumor lesions were detected in PET/MRI with a specificity of 97% compared with 78% when using different radiotracers. However, sensitivity was similar with both techniques (76% vs 79%).[23]

In intermediate- to high-risk PCa, the current standard of care for preoperative evaluation of lymphatic spread and visceral or bone metastases includes MRI/CT and bone scintigraphy. Thus, for detection of suspect lymph nodes, the current standard of care relies solely on morphologic factors, whereas lymph nodes are considered likely to be tumor infiltrated if larger than 8 mm in diameter. However, many lymph node metastases are too small to be classified as positive by either CT or MRI. Both methods do not differ in accuracy to identify lymphatic spread with a sensitivity of 42% and 39% and a specificity of 82% and 82% for CT and MRI, respectively.[24] By providing additional molecular information, combination of conventional imaging