ROLE OF POSITRON EMISSION TOMOGRAPHY WITH FLUORODEOXYGLUCOSE IN PROSTATE CANCER

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ABSTRACT

Fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET/CT) has undergone explosive growth in clinical applications and has emerged as one of the most important imaging modalities in staging, restaging, detecting recurrence and/or metastasis, and monitoring therapeutic response, in most kinds of malignant diseases. However, to date, available experience with FDG PET/CT is limited in prostate cancer, mainly because prostate tumour is characterised by a slow glycolysis and low FDG avidity on PET imaging. Limited data suggested that FDG PET/CT might impact the clinical management of some prostate cancer in an adequate clinical setting, although this impact may be lower than that for other cancers. FDG PET/CT is useful for staging advanced prostate cancer with high Gleason score, detecting local recurrent or metastatic disease in some patients with biochemical failure, assessing treatment response, and providing prognostic information. More prospective clinical trials are underway to define the role of FDG PET/CT in prostate cancer, and more efforts will be made to develop novel radiotracers for PET imaging of prostate cancer.

Keywords: Fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET/CT), prostate cancer, glycolysis.

INTRODUCTION

Prostate cancer is the most common non-cutaneous cancer in men, and continuously poses a major public health problem. During the last decade, there has been a significant advancement in the imaging of prostate cancer. Conventional imaging, which includes ultrasound, computed tomography (CT), and magnetic resonance (MR), is still used to detect organ-confined or metastatic disease for staging and determining prognosis, but a variety of emerging imaging techniques and probes have been accomplished. Today, the major goal for prostate cancer imaging is more accurate disease characterisation with anatomic, functional, and molecular imaging modalities. Since prostate cancer is clinically a heterogeneous disease characterised by biological behaviour that ranges between indolent and aggressive states, the selection of an imaging method should be based on the questions that need to be answered for a particular patient.

In recent years, positron emission tomography (PET) has undergone explosive growth in clinical applications and has emerged as one of the most important imaging modalities in staging, restaging, detecting recurrence and/or metastasis, and monitoring therapeutic response in most kinds of malignant diseases.[1,2] In PET, a trace amount of a radioactive compound is administered and the resultant images are obtained from three-dimensional spatial reconstructions. The intensity of the imaging signal is proportional to the amount of tracer, and therefore, is potentially semi-quantitative.[3] The major advantage of PET imaging over conventional imaging techniques is that PET provides information about changes of metabolism and function, which usually precede the anatomic abnormalities seen on conventional imaging. Combining molecular biology and *in vivo* imaging, PET enables the visualisation of cellular functions such as glucose metabolism, cell proliferation, cell membrane metabolism, or

receptor expression. In addition, the integrated PET/CT units allow correct co-registration and fused imaging of anatomical and functional data. CT imaging in an integrated PET/CT scanner significantly decreases false positive results and improves accuracy of the PET study.[4-6]

2-deoxy-2-(^{18}F)-fluoro-D-glucose (^{18}F-FDG) is the most commonly used radiotracer in PET imaging today. FDG is a non-physiological compound with a chemical structure very similar to that of naturally occurring glucose. Like glucose, FDG enters the cells through membrane glucose transporter proteins, which are commonly over-expressed in cancer cells.[7,8] The principle of FDG imaging is based on Warburg's observation, that the increased metabolic demands of rapidly dividing tumour cells require adenosine triphosphate generated by glycolysis. FDG is actively transported into cells through the membrane glucose transporters, and converted into FDG-6-phosphate by hexokinase. Since FDG-6-phosphate is not a substrate for the enzyme responsible for the next step in glycolysis, it is then trapped and accumulates in the cell in proportion to its glucose metabolic activity. Malignant cells exhibit increased FDG accumulation due to increased membrane transporters, increased intracellular hexokinase, and low glucose-6-phosphatase.

Unlike most malignancies, prostate tumour is characterised by a slow glycolysis and low FDG avidity on PET imaging. There is significant overlap between FDG uptake in prostate cancer and benign prostate hyperplasia.[9] An additional confounding problem is that FDG is normally excreted by the kidneys, and intense activity in the distended urinary bladder usually obscures the prostate, interfering with identification of pelvic lymph nodes.[10,11] Therefore, the exact clinical use of PET/CT in prostate cancer is not clear, and it is currently being explored. The following review will briefly discuss and illustrate the role of FDG PET/CT in prostate cancer.

PRIMARY DIAGNOSIS AND STAGING

The use of FDG PET in prostate cancer was first investigated in the mid-1990s focusing on the visualisation of primary tumours. It was shown that, unlike many other cancers, the FDG uptake in prostate cancer was similar to that of normal prostate tissue.[12,13] Although the overall clinical experience with FDG PET/CT in prostate cancer suffered from heterogeneity in published studies, with regard to the clinical phases of disease, there were relatively small numbers of patients, and variability and limitations in the validation criteria.[14] In general, FDG PET/CT might not be useful in the diagnosis or staging of clinically organ-confined disease due to low glycolysis of the tumour, or in the detection of locally recurrent disease because of the relatively similar FDG uptake by post-therapeutic changes or inflammation.[15,16] Since initial diagnosis of prostate cancer is relatively easy with serum prostate specific antigen (PSA) screening and transrectal biopsy, with or without ultrasound-guiding, FDG PET/CT is rarely used for the detection of primary prostate lesions.

However, some clinical studies also demonstrated that FDG PET/CT might be useful in certain clinical circumstances in prostate cancer. Sporadic cases showed increased FDG uptake in aggressive local prostate cancer. FDG uptake is higher in poorly differentiated primary tumour and higher PSA values than in tumours with more localised stage, and lower serum PSA values.[17] A recent investigation showed that FDG PET/CT has a sensitivity of 80% and a positive predictive value of 87% for detection of prostate cancer with Gleason score of 7 and greater in men who present with more than an intermediate-risk of prostate cancer based on elevated serum PSA level.[18] A case example in Figure 1 shows increased FDG uptake in a newly diagnosed primary prostate cancer lesion. The patient's serum PSA was 18.8 ng/ml and Gleason score was 7.

Information on lymph node status is of key importance when planning appropriate treatment for patients with newly diagnosed prostate cancer. Although conventional imaging modalities such as CT and MRI are often used to detect nodal disease, some observations suggested that FDG PET/CT is more sensitive than anatomic imaging in detection of nodal metastasis. Heicappel et al.[19] investigated the use of FDG PET in determining pelvic lymph node metastases and found that FDG PET was positive in four of six patients with histologically-confirmed lymph node spread, which was superior to the CT imaging.

The most common organ for distant metastasis in prostate cancer is bone. FDG PET/CT is variable in the detection of bone metastasis and it was reported to be less sensitive than conventional bone scintigraphy.[20,21] But one of the

significant advantages of FDG PET/CT over bone scintigraphy, is that FDG PET can discriminate active osseous disease from quiescent lesions on scintigraphy. In other words, FDG PET is more specific than bone scintigraphy to detect active disease.[20] FDG predominately detects those lesions with increased osteoclastic activity, which is likely to be more aggressive, indicating a poorer prognosis. Oyama et al.[22] reported a decrease in FDG uptake in prostate cancer and metastatic lesions after endocrine therapy, suggesting that glucose use by tumours was suppressed by androgen ablation.

BIOCHEMICAL FAILURE AND RESTAGING

Post-therapeutic biochemical failure in prostate cancer represents a diagnostic dilemma, and poses a great challenge to urologists and oncologists. By definition, biochemical failure indicates PSA relapse, but without evidence of disease with standard imaging. FDG PET/CT has shown a promising role in detection of local recurrence or metastatic disease. In a study of 24 patients with rising PSA after treatment of localised prostate cancer, both CT and FDG PET/CT were obtained prior to pelvic lymph node dissection.[23] The CT was negative in all cases, but

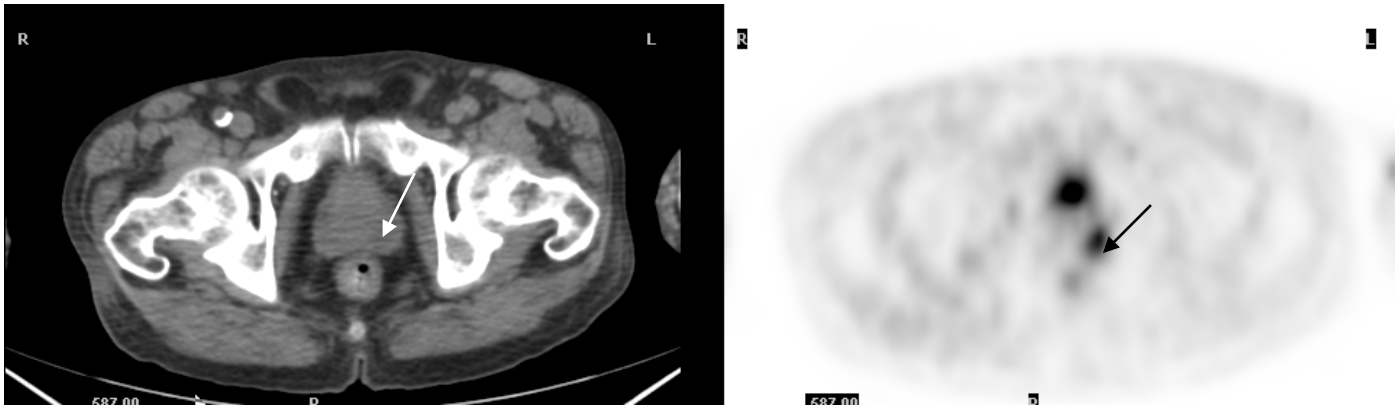

Figure 1. A 63-year-old patient had newly diagnosed prostate cancer with serum PSA 18.8 ng/ml and Gleason score 7.
FDG PET/CT images show a FDG avid low density lesion in the left sided periphery of the prostate (arrows).

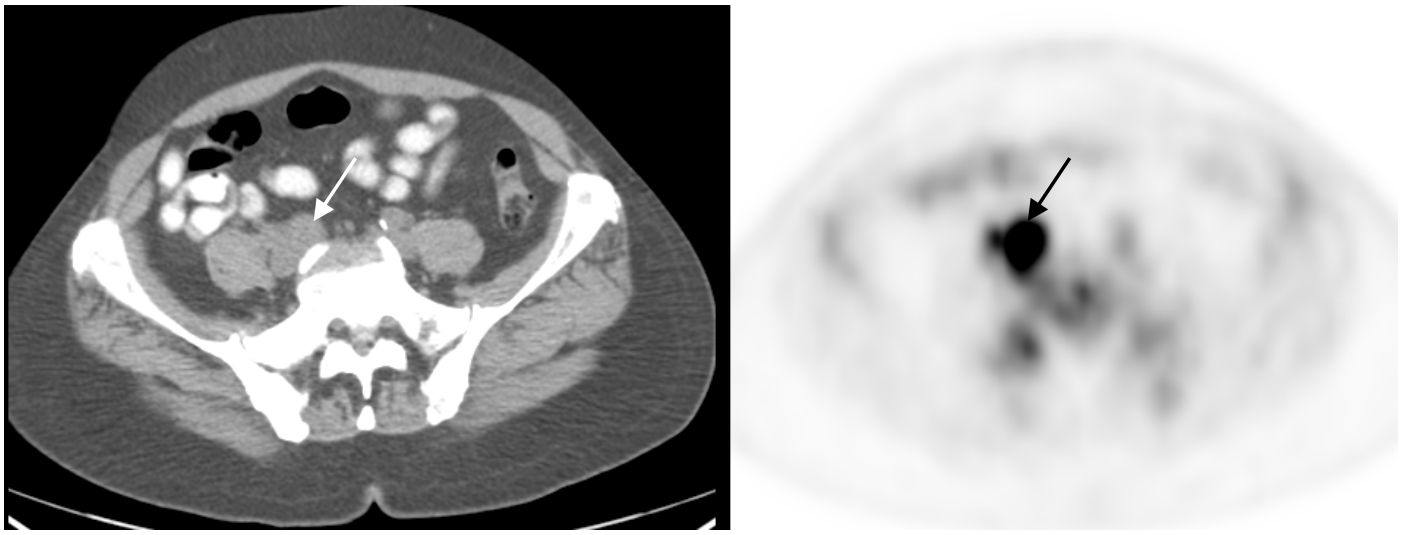

Figure 2. A 62-year-old patient with rising PSA level 2 years after radiation and hormonal therapy.
A whole-body FDG PET/CT showed a highly FDG avid right iliac node, seen on the axial images of the CT (the left) and PET (the right, arrows). Surgical pathology from lymphadenectomy confirmed metastasis from prostate cancer.

FDG PET/CT detected 75% histopathologically-proven metastases. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of FDG PET/CT in detecting metastatic pelvic lymph nodes were 75%, 100%, 83%, 100%, and 68%, respectively. In another retrospective study of 91 patients with PSA, relapse after prostatectomy and validation of tumour presence by biopsy or clinical and imaging follow-up, FDG PET/CT detected local or systemic disease in 31% of patients.[24] The study also demonstrated that mean PSA level was higher in patients with positive PET findings than in those with negative PET. FDG PET may be particularly useful in the restaging of advanced prostate cancer in patients who have a rising PSA level despite treatment.[25] FDG PET is also advantageous over 111In-capromab pendetide scintigraphy in the detection of metastatic disease in patients with high PSA levels or high PSA velocity.[26]

Three case examples are shown in the Figures 2-4, demonstrating FDG-avid metastatic lesions in the lymph node, adrenal gland, and bone.

TREATMENT RESPONSE ASSESSMENT AND PROGNOSTICATION

FDG PET/CT was also incorporated into the evaluation of treatment response. Oyama et al.[22] investigated 10 patients with histologically-proven prostate cancer before and after endocrine treatment. It was shown that FDG accumulation within both prostate and metastatic lesions was reduced in all patients within 1-5 months after commencing therapy. Series FDG PET has also been studied to predict outcome of chemotherapy in castrate-resistant metastatic disease, which demonstrated that FDG PET correctly identified the clinical status in 91% of patients at 4 weeks and 94% of patients at 12

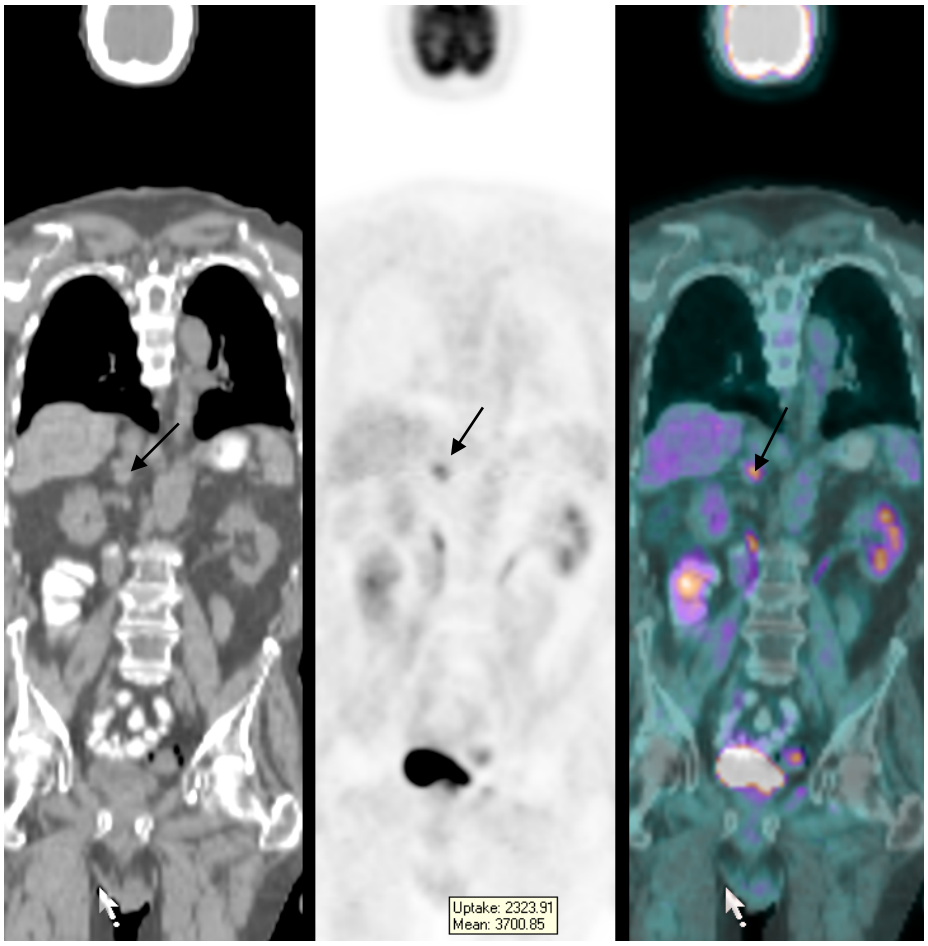

Figure 3. An 83-year-old patient with rising PSA level 3 years post-hormonal therapy for prostate cancer. A whole-body FDG PET/CT showed a right adrenal nodule with intense uptake, as arrows indicated on the coronal imaging of the CT (the left), PET (the middle) and fused imaging (the right). The follow-up CT suggested right adrenal metastasis.

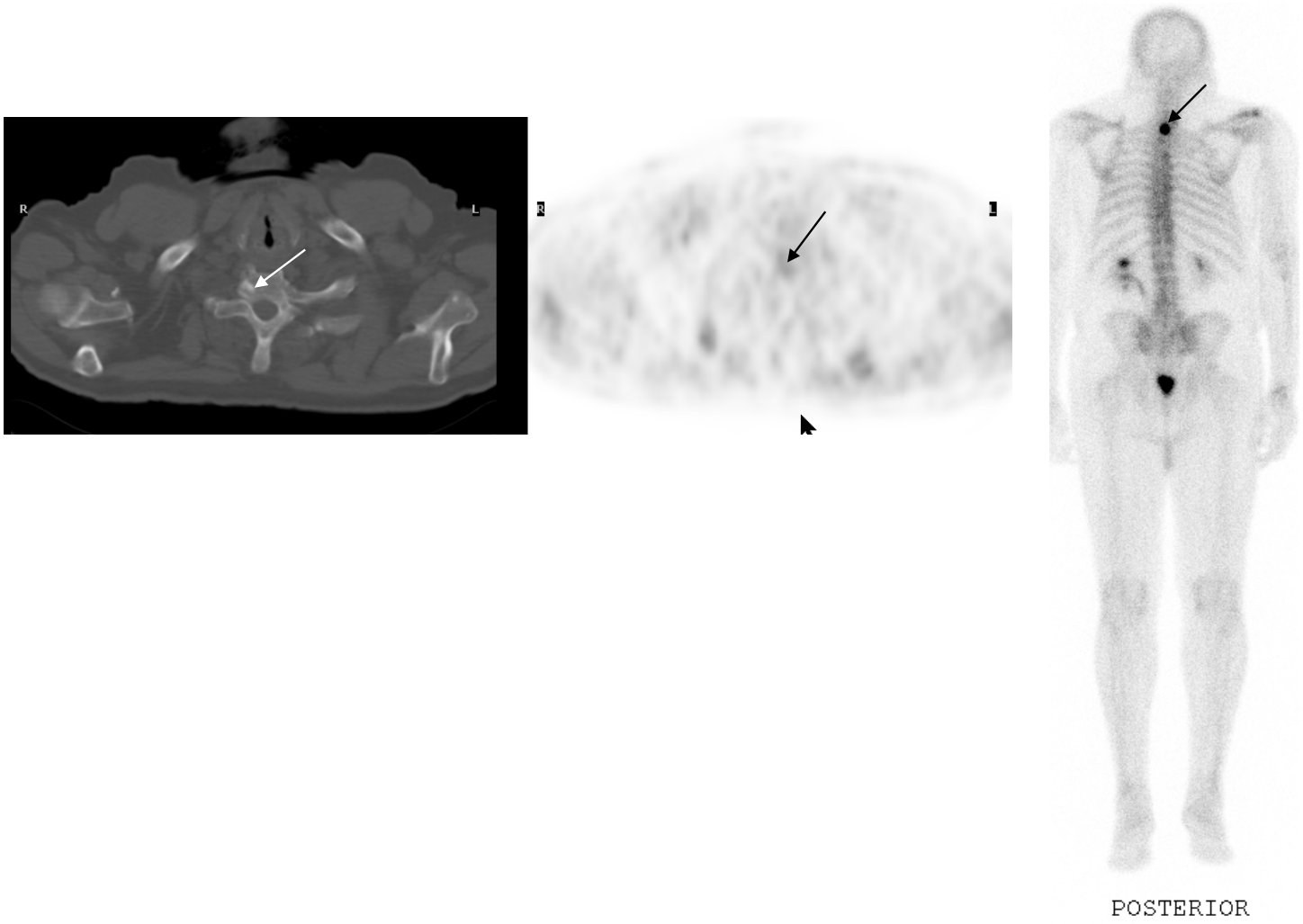

Figure 4. A 70-year-old patient with rising PSA level 5 years after prostatectomy.
A whole-body FDG PET/CT showed a small sclerotic lesion with mild FDG uptake in the right-sided T1 vertebral body (arrows). Bone scintigraphy 2 months later demonstrated intense focal uptake in the same region, consistent with metastasis.

weeks, including combination of PSA, bone scintigraphy and anatomic imaging.[27] FDG PET might have the potential as a surrogate marker of response to chemotherapy in castrate-resistant disease.

The level and extent of FDG accumulation in primary prostate and metastatic lesions may provide information on prognosis. Oyama et al.[28] reported that patients with high FDG avid primary prostate tumours had a poorer prognosis compared to those with low uptake of the tumours. An increase of over 33% in the average maximum FDG uptake was reported to be able to categorise castrate-sensitive metastatic prostate cancer patients treated with antimicrotubule chemotherapy into progressors or nonprogressors.[27] Recently, Jadvar et al.[29] reported prognostic role of FDG PET/CT parameters in castrate-resistant prostate cancer. 87 men with castrate-resistant metastatic prostate cancer underwent FDG PET/CT and were followed prospectively for overall survival. PET parameters included the maximum standardised uptake value (SUVmax) of all metabolically active lesions, after subtraction of patient-specific background-liver average SUV. The result showed that the sum of SUV_{max} derived from FDG PET/CT contributes independent prognostic information on overall survival in men with castrate-resistant metastatic prostate cancer. However, larger prospective studies are further required to substantiate these preliminary findings.

NOVEL PET TRACERS FOR PROSTATE CANCER

In recent years, much effort has been made to develop novel radiotracers for PET imaging of prostate cancer, such as tracers that can identify cell membrane turnover, protein synthesis, DNA synthesis, and testosterone metabolism within the prostate.[30-33] Among them, C11/F18-choline has been studied most extensively. Choline is a substrate for phospholipid synthesis in cell membranes, transmembrane signaling, lipid and cholesterol transport, and metabolism. There is a growing body of literature supporting the utility of choline in early-stage prostate cancer.[34] Acetate is a molecule absorbed by cells and converted into acetyl-CoA. C11-acetate has been investigated for intra-prostatic primary tumour detection and staging as well as restaging.[35] F18-fluoro-5α-dihydrotestosterone (F18-FDHT) targets the androgen receptor and may be particularly useful in the assessment of the pharmacodynamics of the androgen signaling pathway.[36] F18-sodium fluoride (NaF) PET/CT is more valuable to detect osseous metastasis, superior to FDG PET/CT.[37]

CONCLUSION

FDG PET/CT might impact the clinical management of some prostate cancer in adequate clinical settings, although this impact may be lower than that for other cancers. FDG PET/CT is useful for staging advanced prostate cancer with high Gleason score, detecting local recurrent or metastatic disease in some patients with biochemical failure, assessing treatment response, and providing prognostic information. However, to date, available experience with FDG PET/CT is limited, and more prospective clinical trials are underway to define the role of FDG PET/CT in prostate cancer. In addition, much effort was made to develop novel radiotracers for PET imaging of prostate cancer in recent years, such as tracers that can identify cell membrane turnover, protein synthesis, DNA synthesis, and testosterone metabolism within the prostate.

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