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Molecular imaging of prostate cancer with ^{18}F -fluorodeoxyglucose PET

Hossein Jadvar

Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.

Abstract

Prostate cancer poses a major public health problem, particularly in the US and Europe, where it constitutes the most common type of malignancy among men, excluding nonmelanoma skin cancers. The disease is characterized by a wide spectrum of biological and clinical phenotypes, and its evaluation by imaging remains a challenge in view of this heterogeneity. Imaging in prostate cancer can be used in the initial diagnosis of the primary tumor, to determine the occurrence and extent of any extracapsular spread, for guidance in delivery and evaluation of local therapy in organ-confined disease, in locoregional lymph node staging, to detect locally recurrent and metastatic disease in biochemical relapse, to predict and assess tumor response to systemic therapy or salvage therapy, and in disease prognostication (in terms of the length of time taken for castrate-sensitive disease to become refractory to hormones and overall patient survival). Evidence from animal-based translational and human-based clinical studies points to a potential and emerging role for PET, using ^{18}F -fluorodeoxyglucose as a radiotracer, in the imaging evaluation of prostate cancer.

Introduction

Prostate cancer is a major public health problem; the disease is the most common cancer and the second leading cause of cancer-specific mortality affecting men in the US.¹ Biologically and clinically, prostate cancer is a heterogeneous disease that is characterized by states ranging from indolent to aggressive.^{2–4} PSA has been useful in monitoring the disease despite its limited sensitivity (PSA levels might be undetectable or low in some cases of disseminated disease) and specificity (high levels are sometimes associated with benign disease). Furthermore, the measurement of PSA and other associated parameters (for example, density, velocity, half-life, nadir, doubling time, time to elevation, age-specific reference ranges, and the ratio of free to total levels) cannot localize the disease (if present), and might be affected by factors other than therapy.^{5–10} These measurements are the cause of great anxiety and overstated diagnostic expectations by the patient, and there is continued controversy in relation to their exact impact on survival and risk–benefit ratio.¹¹

In the post-PSA era, about 92% of patients are diagnosed with locoregional disease, while metastatic disease is the initial presentation in about 5% of patients; the remaining 3% are classified as unknown.¹ Despite highly successful treatments for localized prostate cancer, around 40% of men experience a detectable rise in the serum PSA level within approximately

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Correspondence: 2250 Alcazar Street, CSC 102, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA jadvar@usc.edu.

Competing interests

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10 years of primary treatment (biochemical failure), suggesting that prostate cancer can metastasize relatively early in the course of the disease.¹²

The use of imaging to assess prostate cancer remains a challenge, owing to the inherent heterogeneity of disease.^{13,14} The value of PET using ¹⁸F-labeled 2-fluoro-2-deoxy-D-glucose (FDG) for the imaging evaluation of patients with cancer is irrefutable, and the clinical use of PET and PET-CT using FDG as a tracer in prostate cancer is being explored. This article provides a brief overview of the imaging techniques that are currently used to evaluate various aspects of prostate cancer. The relatively limited available data on the molecular basis of FDG accumulation in prostate tumors is summarized before providing a brief review of current clinical experience using PET with FDG in the imaging evaluation of prostate cancer.

Current modes of imaging evaluation

Initial differential diagnosis can be undertaken when prostate cancer is suspected with ultrasonography and/or MRI using contrast agents, endorectal probes and image-guided biopsies. Results from imaging studies also provide important information on the extent of the disease and any potential regional and distant metastases in high-risk patients. The optimal method for imaging evaluation of men with PSA relapse (biochemical failure) is unresolved, but the goal of imaging is to determine if recurrence has occurred in the previously treated prostate bed or whether distant disease is present. The result will influence therapeutic management, including consideration of the use of salvage therapy for local recurrence and systemic treatment for metastatic disease.

Bone scintigraphy can be useful in detecting bone metastases, but the rate of false positives is relatively high;¹⁵ this technique cannot be used to detect the involvement of soft tissue or lymph nodes—sites to which prostate cancer cells commonly metastasize.

Key points

- Generally, high uptake of ¹⁸F-fluorodeoxyglucose (FDG) is expected in prostate tumors that are poorly differentiated, hypoxic and have a high Gleason score
- Glucose metabolism in prostate tumors is modulated by androgen; FDG-PET can, therefore, be useful in monitoring response to androgen deprivation therapy
- FDG-PET has limited use in diagnosis and staging of clinically organ-confined disease and can be falsely negative or falsely positive
- FDG-PET might be useful for diagnosing and staging primary tumors, detecting locally recurrent and/or metastatic disease, assessing the extent of metabolically active castrate-resistant disease, monitoring treatment responses and in prognostication
- Results from the NOPR show that FDG-PET influenced clinical management in 35.1% of prostate cancer cases
- Different PET radiotracers are likely to be suited to various clinical states of prostate cancer, taking advantage of the most relevant biological markers of disease

Newer imaging methods, such as ¹¹¹In-capromab pendetide scintigraphy (a technique using a radiolabeled antibody that targets prostate-specific membrane antigen [PSMA], the levels of which are upregulated in hormone-resistant states and in metastatic disease) can be used to help with management decisions in a select group of men at high risk for recurrent and metastatic spread. Despite this utility, the technique also has drawbacks: it has a limited predictive value when used to image the prostate fossa, particularly following radiation therapy; it shows low sensitivity for detecting osseous metastases; furthermore, the technique

is demanding and the results require interpretation by skilled and experienced staff.^{16,17} High-resolution MRI using lymphotropic superparamagnetic nanoparticles might also allow the detection of small, and otherwise undetectable, lymph node metastases in patients with prostate cancer.¹⁸ However, the exact clinical use of this diagnostic imaging approach in a diverse group of patients still needs to be determined.

The role of PET using FDG as a tracer is undoubtedly important in the assessment of cancer patients. The development of hybrid PET–CT imaging systems (which can precisely localize metabolic abnormalities and characterize the metabolic activity of normal and abnormal structures, thereby increasing diagnostic confidence and reducing equivocal image interpretations), the presence of regional distribution centers for FDG, expanding clinical experience, and improved reimbursement have all facilitated the use of FDG-PET and PET–CT in cancer imaging. FDG-PET is widely used for diagnosis, initial staging, restaging, prediction and monitoring of treatment response, surveillance and prognostication in a variety of cancers, and this use has led to improved clinical decision-making and cost-effective management changes in substantial numbers of patients.^{19–21} Investigations into the potential use of PET and PET–CT to assess various clinical aspects of prostate cancer are being undertaken. Interestingly, in summaries of the findings of the National Oncologic PET Registry (NOPR),²² the enrollment rates for patients with prostate cancer were among the highest of all cancers studied.^{23,24}

Molecular basis of FDG accumulation

Hallmarks of cancer include self-sufficiency with respect to growth signals, insensitivity to growth-inhibitory signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion and meta-static potentiation, evasion of tumors from the immune system and increased glucose metabolism.^{25,26}

Tumor growth and glucose metabolism

The relationship between tumor growth and energy production by glucose metabolism is multifactorial and complex, and might be influenced by tumor-related components (such as factors relating to the type of cancer and differentiation grade), biochemical and molecular alterations (for example, hypoxia, inhibition of tumor suppressor genes), and non-tumor-related elements (for example, inflammatory cells).^{27–30} It has been postulated that increased levels of glucose transporters and their translocation to the cell membrane, together with increased enzymatic activity of hexokinase, might be the consequences of adaptation by the tumor to hypoxia, despite the inefficiency of energy production by subsequent glycolysis (compared with oxidative metabolism) and the creation of a toxic, acidic microenvironment.^{31,32} The latter phenomenon might provide the tumor cell with a survival advantage over normal cells through maintenance of normal intra-cellular pH and mobilization of the molecular machinery in evading apoptosis.³³ Despite this interesting hypothesis, however, further research is needed to improve our understanding of the exact molecular mechanisms underlying the enhanced glycolysis by tumor cells.

The ability of FDG-PET to detect tumor cells is based on this increase in glucose metabolism (the so-called Warburg effect) through upregulation of facilitative glucose transporter (GLUT) proteins, primarily GLUT1 and/or GLUT3,³⁴ and/or the expression and activity of hexokinases (primarily hexokinase II).^{35–37} GLUT proteins (the currently approved nomenclature for *GLUT* genes is *SLC2A*_x; we shall, however, be using the former *GLUT*_x designation) allow energy-independent glucose transport across the cell membrane down the concentration gradient (the first rate-limiting step in glucose metabolism), whereas hexokinase II efficiently phosphorylates glucose to glucose-6-phosphate. Similarly, FDG is phosphorylated to FDG-6-phosphate but, unlike glucose-6-phosphate, FDG-6-phosphate cannot be further metabolized

and becomes trapped in the cell, owing to its negative charge and the very low levels of glucose-6-phosphatase activity in most tumor cells.³⁸

Few studies have reported specifically on the expression of GLUT proteins in human prostate cancer. One study investigated the expression of GLUT1 messenger RNA in the androgen-independent prostate cancer cell lines DU-145 and PC-3 and the androgen-sensitive LNCaP cell line.³⁹ GLUT1 messenger RNA expression was higher in the poorly differentiated cell lines DU-145 and PC-3 than in the well-differentiated hormone-sensitive LNCaP cell line, indicating a potential increase in GLUT1 expression with increasing malignancy. Another group reported the expression of GLUT12 in human prostate cancer cell lines, and suggested that this protein might contribute to enhanced glucose metabolism in prostate cancer.⁴⁰

Hypoxia, androgens and glucose metabolism

When the expression of a number of hypoxia-associated genes within benign prostatic hyperplasia (BPH) and prostate cancer (Gleason score 5–10) human tissue specimens was evaluated, *GLUT1* levels were significantly higher in prostate cancer than in BPH and correlated directly with Gleason score ($r = 0.274$, $P = 0.026$).⁴¹ Increased FDG uptake occurs during hypoxia in androgen-sensitive and androgen-independent prostate cancer cell lines.⁴² In a related study using PC-3 and DU-145 cells, hypoxia resulted in the upregulation of the hypoxia-inducible factors HIF-1 α and HIF-2 α ; this upregulation could be inhibited by the NSAID ibuprofen, subsequently leading to the downregulation of the HIF-regulated proteins vascular endothelial growth factor and GLUT1.⁴³

Androgen also has an effect on glucose metabolism in tumor cells. The accumulation of higher levels of FDG has been observed in castrate-resistant (androgen-independent) tumors than in castrate-sensitive tumors.⁴⁴ It has also been shown that castration (surgical or medical) decreases glucose metabolism in prostate tumors.^{44–46} This observation could be incorporated into an imaging-based method to monitor androgen deprivation therapy and to potentially predict an impending hormone-refractory state in patients with castrate-responsive disease.⁴⁴ These findings also suggest that GLUT-mediated FDG accumulation in prostate tumor cells is complex and depends on many interrelated factors.

Experience of FDG-PET in the clinic

Clinical experience of the use of FDG-PET in the context of prostate cancer comes from studies that differ with regard to disease states, validation criteria and end points.^{47–49} The inherent biological and clinical heterogeneity of the disease, including the effects of factors such as hypoxia and tumor microenvironment, might also contribute to the observed variability of glucose metabolism in prostate cancer.^{42,50} Furthermore, technical issues and factors involved in image processing might further affect the observed heterogeneity of FDG accumulation in tumors. The accumulation of FDG is measured semi-quantitatively as the amount of tracer localization in a region of interest normalized to the body weight of the patient and dose of injected tracer, and is expressed as the standardized uptake value (SUV). Significantly lower levels of FDG accumulation in tissue have been noted, irrespective of biological heterogeneity, using filtered-back projection in comparison to iterative reconstruction with segmented attenuation.^{51,52} In selected patients, iterative reconstruction can contribute significantly to the detection, by FDG-PET, of prostate cancer.^{52,53}

Normal prostate tissue

The glucose metabolism and CT density of the normal prostate gland in relation to age and prostate size has been assessed using FDG-PET–CT in 145 men who had indications unrelated to prostate pathology.⁵⁴ The average prostate size was 4.3 ± 0.5 cm (mean $\pm$ SD), with a range

of 2.9–5.5 cm. Mean and maximum CT densities were 36.0 ± 5.1 Hounsfield units (HU) (range 23–57 HU) and 91.7 ± 20.1 HU (range 62–211 HU), respectively, whereas mean and maximum SUVs were 1.3 ± 0.4 (range 0.1–2.7) and 1.6 ± 0.4 (range 1.1–3.7), respectively. The mean SUV tended to decrease as the prostate size increased ($r = -0.16$, $P = 0.058$), whereas the prostate size tended to increase with increasing age ($r = 0.32$, $P < 0.001$).

Primary prostate cancer and staging

The extent of FDG accumulation can be similar in normal prostate, BPH and prostate cancer tissues.^{48,49,55–58} FDG-PET might not be useful in the diagnosis or staging of clinically organ-confined disease or in the detection of locally recurrent disease owing to uptake of FDG by scar tissue as well as tumor cells and because the radiotracer can be excreted into the urinary bladder and thereby mask any lesions in the vicinity.^{56,59} Cases of prostatitis might also yield false-positive results.⁶⁰

Despite the aforementioned drawbacks and the overall heterogeneity of published studies with relatively small numbers of subjects, several animal-based translational and human-based clinical studies have demonstrated that FDG-PET can be useful in certain clinical circumstances in prostate cancer.

FDG uptake is reportedly higher in primary tumors of a higher Gleason score, a more advanced clinical stage and with higher serum PSA levels than those with a lower Gleason score, more localized clinical stage and lower serum PSA values.^{61,62} In a study of 34 patients with biopsy-proven prostate cancer and confirmed or suspected metastatic disease, SUVs ranged from 2.1 to 5.7 for the metastatic lesions (with higher SUVs being suggestive of malignancy);⁶³ PET was less sensitive than bone scintigraphy at identifying bone metastases, and detection of pelvic lymph node metastases was limited owing to bladder urine activity.⁶⁴ In patients with known osseous metastatic disease, however, FDG-PET might distinguish the metabolically active lesions from the metabolically dormant lesions.^{65–67} Furthermore, data from our laboratory suggest that the rate of concordance of FDG-PET analysis with other imaging studies seems to be higher in castrate-resistant disease in comparison to castrate-sensitive disease, and also higher for lymph nodes and visceral lesions than for osseous lesions.⁶⁸

Biochemical failure (PSA relapse)

Investigations have shown that FDG-PET might be useful in detecting disease in a fraction of the large proportion of men who present with PSA relapse, in whom, by definition, there is no standard imaging evidence of disease. In this group of men, detection of disease by ‘non standard’ imaging can direct appropriate treatment, such as salvage radiation therapy for local recurrence in the prostate bed, or systemic therapy for metastatic disease (Figure 1).

In one study of 24 patients who had rising serum PSA levels after treatment for localized prostate tumors, FDG-PET was performed before pelvic lymph nodes were dissected.⁶⁹ In none of the patients did whole-body bone scan or pelvic CT yield positive findings. Histology of the pelvic lymph nodes obtained from surgery confirmed the presence of metastases in 67% of patients. Increased FDG uptake was shown at the sites of histopathologically proven metastases in 75% of these patients. The sensitivity, specificity and accuracy values, as well as the positive predictive and negative predictive values of FDG-PET in detecting metastatic pelvic lymph nodes, were 75.0%, 100%, 83.3%, 100% and 67.7%, respectively.

In a similar retrospective study of 91 patients with PSA relapse following prostatectomy and validation of tumor presence by biopsy or clinical and imaging follow-up, mean serum PSA levels were higher in FDG-PET-positive patients than in FDG-PET-negative patients (9.5 ± 2.2 ng/ml versus 2.1 ± 3.3 ng/ml).⁷⁰ A PSA level of 2.4 ng/ml and PSA velocity of 1.3 ng/ml

per year provided the best compromise between sensitivity (80% for FDG-PET-positive and 71% for FDG-PET-negative patients) and specificity (73% for FDG-PET-positive and 77% for FDG-PET-negative patients) in a receiver operating characteristic curve analysis. Overall, FDG-PET detected local or systemic disease in 31% of patients with PSA relapse. However, confidence in the accuracy and relevance of this figure is limited in view of the heterogeneity and limitation of the validation criteria, which is an issue with other similar studies.⁷¹ Other investigators have suggested that FDG-PET might be particularly useful in staging of advanced prostate cancer in patients who have a rising PSA level despite treatment.⁷² Moreover, in this clinical setting, FDG-PET has also been found to be more useful than ¹¹¹In-capromab pendetide scintigraphy in the detection of metastatic disease in patients with high PSA levels or high PSA velocity.⁷³

Evaluation of treatment response

FDG-PET has been investigated for its use in the assessment of response to treatment of prostate cancer. In one report, FDG accumulation in the primary prostate cancer and metastatic sites decreased over a period of 1–5 months after initiation of androgen deprivation therapy, which was consistent with results from animal xenograft studies.^{44,74,75} However, an earlier study of prostate cancer in rats showed that the global FDG SUV was unchanged after treatment with gemcitabine.⁷⁶ Preliminary results show that tumor FDG uptake decreases with successful treatment (using androgen deprivation or various chemotherapy regimens), in concordance with other measures of response, such as a decline in serum PSA level (Figure 2).⁶⁸

Prognostication

It has also been shown that the level and extent of FDG accumulation in metastatic lesions might provide information on prognosis. An increase of over 33% in the average maximum SUV measurement from up to 5 lesions, or the appearance of new lesions, was reported to be able to categorize castrate-sensitive metastatic prostate cancer patients treated with antimicrotubule chemotherapy into progressors or nonprogressors.⁷⁷ Similarly, another group reported that patients with primary prostate tumors with high SUVs had a poorer prognosis in comparison to those with low SUVs.⁷⁸ Furthermore, as FDG uptake in prostate tumors seems to depend on the presence and activity of androgen, FDG-PET might also be useful in predicting the length of time to reach the androgen-refractory state (for example, by an early increase in castrate tumor FDG uptake), which might facilitate earlier therapeutic modification to avert or delay this clinical state in order to improve overall outcome (Figure 3).⁴⁴

National Oncologic PET Registry

The NOPR was established in the US in May 2006 to collect and analyze data on the clinical utility of FDG-PET and to provide evidence for reimbursement coverage by the Centers for Medicare and Medicaid Services.²³ The first 2 years of data from 40,863 FDG-PET scans for staging, restaging, or detection of suspected recurrence in patients with pathologically proven cancers have been reported.²⁴ The largest proportion of FDG-PET scans (5,309 scans, equivalent to 13% of all scans) was performed in patients with prostate cancer. Findings from these scans changed the clinical management in 35.1% of prostate cancer cases (95% CI 33.8–36.4%), although the odds ratio for change in management compared with that for other cancers in the NOPR trial was 0.86 (95% CI 0.81–0.92); this figure implies that the chance of changing management was lower for prostate cancer cases than for any other cancer type. The changes in management involved switching from nontreatment to treatment in 25.3% and from treatment to nontreatment in 9.7% of cases; a major change in the type of treatment relative to the plan before the FDG-PET scan occurred in 8.5% of cases. The FDG-PET-directed change in management was nearly equal for all aspects of testing, with 32.0% (30.0–34.1%) for initial

staging ($n = 2,042$ cases), 34.0% (95% CI 31.6–36.4%) for re staging ($n = 1,477$ cases), and 39.4% (95% CI 37.2–41.7%) for detection of suspected recurrence ($n = 1,790$ cases).

The use of other PET radiotracers

Different PET radiotracers probably offer different advantages during various clinical states of prostate cancer, depending on the most relevant biological markers of disease at each state.^{45,79} To this end, many other PET radiotracers are currently being explored, including ^{11}C -labelled or ^{18}F -labeled acetate or choline, ^{11}C -labeled methionine, androgen-receptor-avid agents such as ^{18}F -FDHT (16β - ^{18}F -fluoro-5 α -dihydrotestosterone), anti-FACBC (1-amino-3- ^{18}F -fluorocyclobutane-1-carboxylic acid) a synthetic L-leucine analog, a radiolabeled PSMA inhibitor, such as ^{18}F -DCFBC (N-[N-{S-1,3-dicarboxypropyl} carbamoyl]-4- ^{18}F -fluorobenzyl-L-cysteine), and ^{18}F -fluoride (for bone metastases).^{80–86} Prospective clinical imaging trials using various PET tracers in different clinical-state-specific patient cohorts with well-defined end points will be needed to decipher the optimal use of PET in prostate cancer. Moreover, access to and regulatory approval of other PET tracers is another important issue that will need to be addressed.

Conclusions

The use of FDG-PET in prostate cancer should be considered in the context of the limitations and challenges associated with other imaging modalities in prostate cancer. The first NOPR data clearly indicate that FDG-PET can influence the clinical management of men with prostate cancer, albeit a potentially lower influence than that for other cancers.

Current evidence indicates that FDG-PET might be useful in the diagnosis and staging of primary tumors that are known or suspected to have a high Gleason score; in the detection of locally recurrent and/or metastatic disease in a portion of patients with ‘biochemical failure only’ with scan sensitivity that increases with increasing PSA level; in the assessment of the extent of metabolically active castrate-resistant disease; in monitoring the response to androgen deprivation and other therapies; and in prognostication.

FDG-PET has limited use in the diagnosis and staging of clinically organ-confined disease, and can give false-negative results owing to the uptake of FDG by normal tissue, BPH and scar tissue; false-positive results often occur following inflammation and infection. It is clear that more extensive experience is needed to determine the exact clinical use of FDG-PET in the various clinical phases during the course of prostate cancer.

Review criteria

Information for this article was obtained by searching the PubMed database for English and non-English articles (provided that an English abstract was available) published between June 1996 and February 2009. Searched terms included “prostate cancer” in combinations with “FDG”, “PET”, and “PET-CT”. Both animal-based and human-based studies were included.

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Figure 1. FDG-PET and CT scans of locally recurrent and metastatic prostate cancer. **a** | CT scan at bone window level shows sclerotic osseous lesions involving both the pubis and the right ischium. **b** | PET scan shows high accumulation of FDG only in the metabolically active pubis lesions and in the locally recurrent lesion in the left prostate bed. Abbreviations: A, anterior; FDG, fluorodeoxyglucose; P, posterior.

Figure 2.

Fused FDG-PET-CT scans in a patient with castrate-sensitive disease **a** | before and **b** | after androgen deprivation therapy. Note the decline in the hypermetabolic activity of the right pelvic metastatic lymph node in response to therapy. The maximum standardized uptake value of the lesion declined from 3.4 to 2.2, which corresponded to a decline in the levels of serum PSA from 70 ng/ml to 50 ng/ml. Abbreviation: FDG, fluorodeoxyglucose.

Figure 3.

Fused FDG-PET-CT scans in a patient with metastatic prostate cancer. **a** | A low accumulation of FDG can be seen in the mid-thoracic spine sclerotic lesion during castrate-sensitive disease in response to androgen deprivation therapy (maximum SUV = 2.7 at nadir PSA level). **b** | FDG accumulation in the same lesion increased upon development of castrate-resistant disease (maximum SUV = 5.5, rising PSA levels). Abbreviations: FDG, fluorodeoxyglucose; SUV, standardized uptake value.