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Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography Is Useless for the Detection of Local Recurrence after Radical Prostatectomy

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Key Words
Prostate cancer · Fluorine-18-fluorodeoxyglucose · Positron emission tomography

Abstract
Objective: After radical retropubic prostatectomy a rise of the prostate-specific antigen (PSA) indicates a local recurrent or metastatic disease. If the bone scan shows no apparent bone metastasis, morphological imaging methods like x-ray computed tomography, magnetic resonance imaging or transrectal ultrasound often cannot distinguish between postoperative scar and local recurrence. Therefore we investigated the feasibility of fluorine-18-fluorodeoxyglucose positron emission tomography (F-18 FDG PET) for metabolic characterization of prostatic cancer, especially for differentiation of scar or recurrent prostate cancer after radical prostatectomy. ***Methods:*** Dynamic PET with 370 MBq F-18 deoxyglucose (F-18 FDG) up to 60 min p.i. was performed in 2 patients with biopsy-proven benign prostatic hyperplasia, in 11 patients with a histologically proven prostate cancer prior to radical retropubic prostatectomy (RRP) and 7 patients with suspected local recurrence (with negative bone scan) after RRP prior to biopsy of anastomosis (3 local recurrence, 4 postoperative scar). ***Results:*** Prostate cancer showed a very low F-18 FDG uptake. The placement of regions of interest was only possible by the use of other imaging methods. There was not difference between the F-18 FDG uptake of benign prostate hyperplasia, prostate carcinoma, postoperative scar or local recurrence after radical prostatectomy. ***Conclusion:*** F-18 FDG seems not to be useful to distinguish between postoperative scar and local recurrence after radical prostatectomy.

Introduction

Prostate cancer is the most frequently diagnosed cancer in men in many countries. For patients with locally confined disease, radical prostatectomy or radiotherapy has high survival rates [1]. Prostate-specific antigen (PSA), an organ-specific marker for prostatic tissue, is a valuable tumor marker. Detectable PSA levels after radical prostatectomy indicate local treatment failure or metastatic disease [2]. This event occurs months to years before clinical recurrence. Several groups of investigators have found that the postoperative doubling time of PSA was able to distinguish between subsequent development of either local or metastatic disease [3, 4]. Therefore slow

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changes suggest that the disease is local-regional, whereas the existence of systemic disease seems to be connected with a rapid doubling time of PSA.

Consideration may be given to postoperative radiotherapy for patients who are suspected to have local recurrence because of a slow rise or no decrease in postoperative PSA levels [5]. On the other hand, distant metastasis should be treated by systemic therapy. It is often difficult to distinguish between local recurrence and systemic disease, because digital rectal examination and conventional morphological-based methods like transrectal ultrasonography and others are not effective in monitoring patients for local recurrence after radical prostatectomy, because they cannot distinguish between recurrence and other nonmalignant findings in the rectal fossa [5].

Positron emission tomography (PET) represents a new imaging approach that permits measurement of physiologic and biochemical processes within various human organs [6]. Because of promising experimental and clinical results, fluorine-18-fluorodeoxyglucose (F-18 FDG) PET represents an important clinical diagnostic modality in oncology. Numerous studies are currently under way to investigate the diagnostic accuracy of F-18 FDG PET imaging for detection and staging of cancer. There also seems to be a benefit in the detection of recurrent tumors by PET. Some investigators showed that a differentiation between necrosis or scar and recurrent tumor after primary therapy of brain and colorectal tumors is possible [7–9].

The purpose of this study was to investigate the feasibility of F-18 FDG PET for metabolic characterization of prostatic cancer, especially for differentiation of scar or recurrent prostate cancer after radical prostatectomy.

Materials and Methods

Patients

2 patients with biopsy-proven benign prostatic hyperplasia (BPH) before transurethral resection of the prostate and 11 patients with biopsy-proven primary prostate cancer with negative bone scan were investigated before retropubic radical prostatectomy (RRP). Systemic transrectal ultrasound-guided biopsies were performed by experienced urologists, obtaining at least six biopsies as described by Niesel et al. [10]. 7 patients with negative bone scan and suspected local recurrence were studied because of elevated PSA (Tandem-E, Hybritech) after RRP. They underwent a transrectal ultrasound (TRUS)-guided biopsy of the urethrovesical anastomosis.

Positron Emission Tomography

F-18 FDG was produced by a method modified from the synthesis of Hamacher et al. [11]. All patients were studied after at least 6 h fasting. Plasma glucose levels were measured by a standard clinical test (Glucometer II and Glucostix, Bayer Diagnostics). To have a continuous bladder irrigation all patients had a bladder catheter during PET and a continuous infusion of 20 mg furosemide in 500 ml 0.9% NaCl solution beginning 20 min after F-18 FDG injection.

Patients were positioned on a 31-slice whole-body PET scanner (ECAT 951 R, CTI/Siemens), which has 16 detector rings to allow simultaneous acquisition of 31 contiguous transaxial images with a slice separation of 3.375 mm. Before emission scanning, transmission scans were obtained for 20 min over the prostatic bed, which yielded more than 4 million counts per slice. Patients were intravenously injected with 370 MBq F-18 FDG and dynamic emission scans were obtained (6 × 5 min and 3 × 10 min). PET images were generated using filtered backprojection and were corrected for decay and attenuation. The reconstructed in-plane image resolution was 7 mm at full-width half maximum, and the axial resolution was 5 mm full-width half maximum.

Because of low F-18 FDG uptake of prostatic tissue irregular regions of interest (ROI) for semiquantitative evaluation were defined over the lesions using other imaging modalities (TRUS). The correct placement of the ROIs was cross-checked postoperatively with the histology of the biopsies and the RRP. To assess F-18 FDG uptake in normal prostatic tissue, a circular ROI was defined over cross-checked nonmalignant tissue. Regional F-18 FDG uptake was expressed as the standardized uptake value (SUV) based on the maximum pixel value within the ROI on body weight. For assessment of the kinectics of F-18 FDG uptake, SUVs were calculated for each time frame and in a sum image, consisting of frame 8–9 (51–60 min p.i.).

Histopathological Examination

The location of dissected tissue or the site of biopsy was documented by the surgeon to allow correlation between findings and PET results. The specimens, obtained by RRP, were embedded in paraffin and routine staining was performed.

Results

Patients

There were 2 patients with a BPH, 11 patients with histologically proven carcinoma of the prostate, 3 patients with local recurrent tumor after RRP proven by ultrasound-guided biopsy of the urethrovesical anastomosis and 4 patients with elevated PSA after RRP without carcinoma in the urethrovesical biopsy. Age, weight and blood glucose of the patients are given in table 1.

The mean PSA serum was 3 ng/ml (range: 2–4 ng/ml) levels in patients with BPH, 32.5 ng/ml (1.8–100 ng/ml) in patients with carcinoma of the prostate, 4.4 ng/ml (2.9–6.9 ng/ml) in patients with local recurrence and 15.1 ng/ml (0.8–53.9 ng/ml) in patients with postoperative scar (table 1). The patients who underwent RRP after PET examination had no nodal metastasis. Histopathological staging showed one pT2a, four pT2c, three pT3a and three pT4a carcinomas.

F-18 FDG Uptake

Figure 1 shows a typical coronal F-18 FDG PET corresponding to transrectal ultrasound of primary left-sided prostate carcinoma. SUV in tumor tissue, local recurrent cancer, normal prostatic tissue and in scar was calculated for each time frame. The time course of F-18 FDG uptake was similar in the different categories demonstrating identical slopes. The localization of the primary tumors and the three local recurrent carcinomas was very difficult because of the low F-18 FDG uptake. Placement of ROIs was only possible with the use of other imaging modalities and the comparison with the histological specimen. There was no difference between the SUV values in BPH, normal tissue of the RRP specimen, primary prostate cancer, local recurrence and scar after RRP. The mean value of SUV of BPH was 1.7 and ranged from 1.6 to 1.8. Primary prostate cancer and local recurrence after RRP showed a mean value of 1.8 and 1.6 with a range from 1.4 to 2.4 and 1.4 to 1.8, whereas postoperative scar had a mean SUV of 1.5 (1.3–1.7) (table 2).

Discussion

A PSA rise after RRP indicates recurrent prostate cancer. It is often difficult to distinguish between a local recurrent tumor and disseminated disease in patients, who have a negative bone scan but increasing PSA. Definitive radiotherapy can be given to patients who fail only locally following prostatectomy [12].

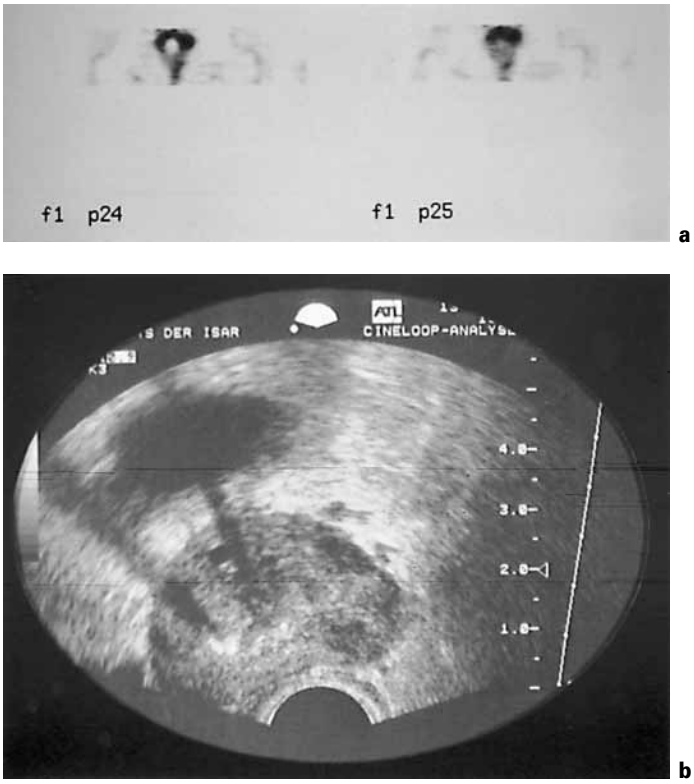

Fig. 1. Typical example of a left-sided primary prostatic cancer (SUV 2.2). Static attenuation-corrected PET image in coronal orientation demonstrating no exactly detectable lesion (**a**). The corresponding TRUS in transversal orientation (**b**) shows the corresponding hypoechoic inhomogeneous zone representing the carcinoma.

Table 1. Descriptive characteristics of age, body weight, blood glucose and PSA levels in patients with BPH (n = 2), prostate carcinoma (PC; n = 11), local recurrence (LR; n = 3) and scar (n = 4) after radical prostatectomy

	Age years	Weight kg	Glucose mg/dl	PSA ng/ml
BPH	67.5 (65–70)	78.5 (75–82)	95 (90–100)	3 (2–4)
PC	66.8 (73–81)	79.7 (57–98)	90 (60–128)	32.5 (1.8–100)
LR	74.9 (70–79)	76.7 (74–78)	60 (53–69)	4.4 (2.9–6.9)
Scar	71.9 (64–74)	82.3 (69–100)	73 (60–86)	15.1 (0.8–53.9)

Mean values with the range in parentheses are shown.

Table 2. SUV in patients with BPH (n = 2), prostate carcinoma (PC; n = 11), local recurrence (LR; n = 3) and scar (n = 4) after radical prostatectomy

	SUV	
	mean	range
BPH	1.7	1.6–1.8
PC	1.8	1.4–2.4
LR	1.6	1.4–1.8
Scar	1.5	1.3–1.7

Conventional imaging techniques like CT scan and TRUS are of limited use in detecting the source of PSA production. PET represents a new imaging approach that permits measurement of physiologic and biochemical processes within various human organs [6]. F-18 FDG is the most commonly used metabolic tracer for PET imaging [13]. F-18 fluorine-18-labeled deoxyglucose is transported into tissue and phosphorylated in a manner identical to glucose. However, deoxyglucose-6-phosphate is trapped in the cells and accumulates in proportion to exogenous glucose utilization. The labeling of deoxyglucose with F-18 provides a positron-emitting form of this sugar for the application in human subjects.

Increased glycolysis is considered to form the most important and specific metabolic characteristics of cancer cells [14]. Therefore, noninvasive determination of glucose metabolism by F-18 FDG PET in tumor tissue has been proposed for detection, staging, therapy monitoring of cancer and detection of recurrent tumors. Strauss et al. [9] reported a high diagnostic accuracy in assessing recurrent colorectal cancer. Therefore, PET seemed to be a promising method to distinguish between postoperative scar and local recurrence in patients with prostate cancer who had undergone RRP and had rising PSA levels.

Only few data of PET for prostate cancer are available. Effert and coworkers [15, 16] evaluated F-18 FDG PET for metabolic grading of untreated primary prostate cancer and differentiation of benign and malignant prostatic disease. Low F-18 FDG uptake was noted in the majority of primary tumors. Accumulation did not correlate with increasing tumor grade or stage. There was a significant overlap in uptake values in BPH and malignant prostatic disease. Increased F-18 FDG accumulation occurred in some primary prostate tumors and in metastatic deposits of prostate cancer.

Hara and coworkers [17] compared ^{11}C-choline PET examinations with F-18 FDG images in 10 patients with prostate cancer. Imaging of prostate cancer and local metastasis was difficult when F-18 FDG was used because of low standardized uptake values and the overwhelming abundant radioactivity in urine (in ureters and bladder). By contrast, it was easy when ^{11}C-choline was used because the urinary activity was negligible and tumor uptake was higher.

Two other studies were carried out in patients known to have bony metastases from carcinoma of the prostate. Of 13 patients with bony metastases 12 were considered hormonally resistant after various types of therapy. All patients had extensive bony metastases shown on the conventional bone scan. Only 18% of bony lesions showed a corresponding increase of FDG uptake. The positive FDG uptake was not related to the duration of illness, level of PSA and previous therapy [18].

F-18 FDG uptake seems to be different in untreated osseous metastases of prostate cancer. Shreve et al. [19] examined 22 untreated patients with osseous metastases. The sensitivity of FDG PET was 65% with a positive predictive value of 98%. PET was less sensitive than bone scan in the identification of osseous metastases. Soft-tissue metastases to the lymph nodes or liver were identified, but evaluation of pelvic lymph node metastases was severely limited because of bladder tracer activity. The detection of occult recurrent prostate cancer by PET was investigated by Haseman et al. [20]. Of 6 patients with biopsy-proven recurrent prostate cancer 5 were negative in PET. On the other hand, 2 of 4 patients with negative biopsy were positive.

There are several reasons why PET is not useful for differentiation and detection of primary prostate cancer, metastatic disease or recurrent prostate cancer. First our results demonstrate that in contrast to other primary carcinomas and their metastases, for example the testicular germ cell tumors (own unpubl. data), prostate carcinoma has a low F-18 FDG uptake. The SUV of primary prostate cancer are similar to the F-18 FDG uptake of other surrounding tissues. Therefore a differentiation between prostate cancer and nonmalignant tissue is not possible. Not even the identification of large carcinomas was possible. A possible explanation may be the fact that prostate carcinoma is a slowly proliferating tumor in contrast to other tumors with a high glucose turnover. Additionally, the renal and following bladder excretion of F-18 FDG deteriorates image quality, even when bladder irrigation, forced diuresis or iterative reconstruction algorithm are used.

Conclusion

Our results confirm that F-18 deoxyglucose PET does not make the differentiation between local recurrent cancer and postoperative scar after RRP possible. Furthermore, there was no difference between F-18 FDG uptake of BPH and carcinoma of the prostate. The clinical value of PET in the detection of lymphatic metastases in prostate cancer awaits further study. Whether radioactive-labeled androgens, which are now tested in animals, will be able to help in therapy planning and monitoring remains to be seen.

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