2-\[^{18}\text{F}]\text{Fluoro-2-Deoxyglucose Positron Emission Tomography for the Detection of Disease in Patients with Prostate-Specific Antigen Relapse after Radical Prostatectomy

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Abstract

Experimental Design: Retrospective cohort study in 91 patients with prostate-specific antigen (PSA) relapse following prostatectomy, imaged with 2-\[^{18}\text{F}]\text{fluoro-2-deoxyglucose positron emission tomography (FDG-PET) in a tertiary care cancer center between February 1997 and March 2003. Comparison was made with magnetic resonance imaging (n = 64), bone scan (n = 56), and computed tomography (n = 37). The standard of reference included biopsy or clinical and imaging follow-up. We calculated sensitivity and specificity of PET and correlated PET findings with PSA values, other clinical parameters, and conventional imaging, when available.

Results: PET was true positive in 28 of 91 (31%) patients, showing isolated disease in the prostate bed (n = 3) or metastatic disease with (n = 2) or without (n = 23) simultaneous disease in the prostate bed. In detail, PET identified lesions in the prostate bed (n = 5, all true positives), bones (n = 22; 20 true positives, 2 false positives), lymph nodes (n = 7; 6 true positives, 1 likely false positive), and one liver metastasis. Mean PSA was higher in PET-positive than in PET-negative patients (9.5 ± 2.2 versus 2.1 ± 3.3 ng/mL). PSA of 2.4 ng/mL and PSA velocity of 1.3 ng/mL/y provided the best tradeoff between sensitivity (80%; 71%) and specificity (73%; 77%) of PET in a receiver operating curve analysis. Combination with other clinical parameters in a multivariate analysis did not improve disease prediction. There were only two patients in whom other imaging studies showed isolated local recurrence or metastatic disease. Conclusions: FDG-PET detected local or systemic disease in 31% of patients with PSA relapse referred for this test. There is a link to tumor burden and tumor biology in that the probability for disease detection increased with PSA levels.

Prostate cancer is the most common cancer among men in the United States, with ~230,000 new cases diagnosed in 2004 (1). Treatment with curative intent can be provided by radical prostatectomy or radiation therapy. Regardless of the treatment modality, an estimated one third of patients will develop biochemical recurrence as defined by increases in prostate-specific antigen (PSA) levels after definitive therapy (2); among patients with prostatectomy, such PSA relapse is seen in 20% to 40% of individuals at 10 years (3–7). Biochemical recurrence is usually the first evidence of disease recurrence and very frequently occurs without any objective findings by clinical exam or imaging studies (8, 9). The prognosis of these patients is highly variable. Some have persistent local disease that may still be curable by additional local therapy, whereas others have a systemic recurrence that is effectively incurable with currently available therapies. For this latter group, the likelihood of developing metastases and of a prostate cancer–specific death is inversely related to the rate of increase in PSA, measured as PSA doubling time (10). A critical issue in management is to determine whether the increasing PSA indicates a failure of primary treatment, represents local disease, systemic disease, or both. Currently, Prostascint imaging is the only Food and Drug Administration–approved test to detect disease in this patient group, although this test suffers from a number of limitations (11–13). 2-\[^{18}\text{F}]\text{Fluoro-2-deoxyglucose positron emission tomography (FDG-PET) imaging is now widely available and has shown utility in a number of solid tumors (14). Previous reports with this modality in prostate cancer imaging have been decidedly mixed, as some have concluded that FDG-PET was of limited value (15), whereas others reported that it is useful in imaging local recurrence (16), osseous metastases (17, 18), or nodal and soft tissue lesions (11, 17). Some of these controversies may be due to patient selection as it has now become clear that imaging modalities need to be evaluated in carefully defined subgroups of patients with prostate cancer (18). Another major problem for FDG imaging in prostate cancer has been the fact that this tracer undergoes renal excretion with subsequent accumulation in the urinary bladder.
High radioactivity in the urinary bladder can cause image artifacts ("streaks") in the lower pelvis; hence, the close proximity of excreted FDG in the bladder to the sites of expected local recurrence (i.e., the prostate bed and adjacent lymph nodes) has made it difficult to interpret FDG-PET images of the pelvis. Essentially all of the early PET studies suffered from this artifact. This problem has been significantly reduced by the clinical introduction of newer iterative image reconstruction (16). The present retrospective analysis was done to assess the potential clinical role of FDG-PET using optimal image reconstruction in a large group of patients with PSA relapse.

**Materials and Methods**

From our PET database, we retrospectively identified all studies done in patients with prostate cancer between February 1997 and March 2003, using the radiotracer FDG. During this time frame, 734 PET scans had been done in 425 patients for various indications, including primary staging of patients with locally advanced disease, localization of recurrent disease in patients with PSA relapse, and monitoring the response to androgen ablation, chemotherapy, or experimental therapy. All patients were referred for a PET scan based on the discretion of the treating physician. We limited our analysis to individuals without clinical or imaging evidence of recurrence (except elevated PSA) >3 weeks before the time of PET; the time interval of 3 weeks was chosen because imaging studies are frequently ordered at the same time, but due to scheduling issues are done a few days or weeks apart. In addition, the following inclusion criteria were applied: (a) initial treatment of prostate cancer with radical retropubic prostatectomy; (b) PSA relapse, defined as PSA >0.1 ng/mL in three consecutive measurements at least 2 weeks apart; and (c) no systemic therapy (hormonal or chemotherapy) between prostatectomy and PET. Patients who had received radiation therapy to the prostate bed for presumed local recurrence were eligible, provided they met the PSA relapse criteria defined in (b).

Ninety-one patients met these inclusion criteria. PET scans were ordered to detect disease, either in the primary site or elsewhere. The official clinical PET reports were retrieved, and findings were catalogued. When available, concurrent bone scan, computed tomography (CT), or magnetic resonance imaging (MRI) reports were also retrieved and findings from the official report catalogued. All imaging findings were compared with a standard of reference (see below). Data collection and analysis were approved by the Institutional Review Board. Patient consent was not required for this retrospective analysis.

**Imaging protocols: Positron emission tomography.** All patients were imaged using a standard clinical PET protocol: 555 MBq (15 mCi) of FDG were injected i.v. and images were acquired from the skull base to the upper thighs ~45 to 60 minutes afterward. Between 1997 and November 2001, all studies were done using an Advance PET tomograph (GE Medical Systems, Waukesha, WI). Emission and transmission images were both acquired for 4 minutes per bed position. Transmission data were used for attenuation correction in all cases. Beginning in November 2001, studies were also acquired on combined PET/CT tomographs, either Biograph (Siemens/CTI, Knoxville, TN) or Discovery LS (GE Medical Systems). Both machines combine a multislice CT with a state-of-the-art PET tomograph. The CT data were used for attenuation correction.

**Other imaging studies.** Bone scans were done ~2 hours after the i.v. injection of 925 MBq (25 mCi) 99mTc methylene-diphosphonate. Whole-body images were acquired in anterior and posterior projections on a dual-head γ camera (ADAC Laboratories, Milpitas, CA). CT images were acquired on multislice helical scanners (GE Medical Systems) following i.v. injection of contrast material and with a slice thickness of 7.5 mm. In some patients, concurrent CT of chest, abdomen, and pelvis were available; in other cases, only a CT of the pelvis was available.

MRI studies of the pelvis were acquired on a 1.5 T whole-body magnetic resonance scanner (Signa, GE Medical Systems), using axial spin-echo T1-weighted and fast spin-echo T2-weighted sequences (with fat suppression). Sagittal single-shot fast spin-echo images were also obtained. Additional coronal and sagittal sequences were acquired as needed. In a subset of patients (n = 30), dedicated MRI of the prostate bed was done using pelvic phased array and endorectal coils; small field-of-view fast spin-echo T2-weighted images in axial, coronal, and sometimes sagittal planes were acquired.

**Image interpretation: Positron emission tomography.** Clinical PET reports were generated by board-certified nuclear medicine physicians. In all cases, attenuation-corrected images were reviewed on a workstation, displaying three orthogonal planes (transaxial, coronal, sagittal) and a maximum intensity projection image. FDG accumulation was considered abnormal when it was thought to be located outside of normal anatomic structures (such as the bladder or ureters) and of an intensity greater than that in adjacent normal tissue (for instance for lesions in the liver) or greater than background blood pool activity. In addition to this visual analysis, standardized uptake values were also measured for findings considered abnormal. For this purpose, circular regions of interest were drawn around such findings, and the maximum radioactivity concentration in the regions of interest, normalized to body weight and injected activity, was calculated. PET studies for which equivocal reports had been generated by the original attending nuclear medicine physician (n = 10) were re-reviewed by one of the investigators (H. Schöder) who had 9 years of experience in PET imaging. Using the above criteria, these studies were then classified as either abnormal or normal.

**Other imaging studies.** The official clinical reports from CT, MRI, and bone scan studies, generated by staff radiologists at this institution, were used. Only imaging studies obtained between 3 weeks before PET and 3 months after PET were considered. CT and MRI studies with equivocal reports (n = 12) were re-reviewed by a genitourinary radiologist (S. Eberhard) and classified as normal or abnormal. There were no equivocal bone scan reports. At the time of image analysis, the radiologists who reinterpreted PET, CT, or MRI studies with previously equivocal reports were aware of the general clinical history (PSA relapse), but were unaware of the specific PSA values in a given patient and unaware of findings in other concurrent imaging studies or follow-up data.

**Data analysis.** Images were interpreted in a binary fashion as either normal/probably normal or abnormal/probably abnormal. The following standard of reference was used for verification (19): Imaging findings were considered true positive for local or metastatic disease if they were confirmed by any one of the following: (a) a positive biopsy (biopsies were done at the discretion of the treating physician), (b) a decrease in PSA after irradiation to the primary site, (c) the development of a detectable lesion in the primary site on a follow-up conventional imaging studies, (d) an increase in lesions size on follow-up imaging, or (e) concurrent other imaging studies within 90 days of PET.

Imaging findings were classified as false positive if apparent abnormalities did not meet any of the above criteria. Apparent PET abnormalities that seemed unchanged in intensity and size despite further increase in PSA upon follow-up were also classified as false positive.

All imaging studies without clear abnormality were classified as false negative. Receiver operating characteristic (ROC) analysis was done to determine optimal cutoff values, and compute sensitivity and specificity of PSA, PSA doubling time, and PSA velocity in predicting PET positivity.

**Statistical analysis.** The purpose of this study was 2-fold: (a) to assess the sensitivity of FDG-PET in detecting disease in patients with PSA relapse after retropubic radical prostatectomy (RRP) and (b) to
investigate the potential relationship between PET findings and tumor
biology.

Analysis of sensitivity. By definition, all patients have recurrent local
disease, systemic disease, or both. Therefore, we could only compute
true positive (proven disease), false positive (PET-suggested disease
that could not be confirmed), and false negative (all other patients)
rates.

Correlation with tumor biology. We investigated the potential
relationship between PET findings and clinical, histopathologic, and
biochemical parameters (primary tumor stage, Gleason score; PSA, PSA
doubling time, and PSA velocity at time of PET). Using a ROC curve
analysis, we investigated whether these clinical parameters are associated
with positive or negative PET findings. The area under the curve was
computed using the trapezoidal estimate and used as an overall measure
of predictive accuracy. In addition, for each ROC curve, an optimal
cutoff point is found by minimizing the distance between the points on
the curve and the ideal operating point (100% sensitivity and
specificity). We also considered clinical variables (Gleason score and
primary tumor stage, including surgical margin status, presence of
extracapsular extension or seminal vesicle invasion, and lymph node
involvement) in combination with the PSA parameters. These combi-
nations were explored using multivariable logistic regression and their
accuracy was quantified through ROC curves (20). Diagnostic likelihood
ratios (DLR) were calculated using standard definitions: DLR+ is the
ratio of the true-positive fraction to the false-positive fraction, whereas
DLR− is the ratio of the false-negative fraction to the true-negative fraction (20).

### Results

#### Patient population

Ninety-one patients with a mean age of 65 ± 7 years (range, 45-77 years) met the inclusion criteria. Of these, 69 had only been treated with radical prostatectomy and presented with PSA relapse as their first sign of recurrence. Their average time interval between retropubic radical prostatectomy and PET scan was 36 ± 31 months (range, 4 months-10.4 years). The remaining 22 patients had been treated with external beam irradiation after prostatectomy. In 7 of these 22 individuals, the time interval between prostatectomy and radiation therapy was <8 months, and the indications included positive surgical margins, extraprostatic extension of tumor, vascular or perineural invasion, or an early increase in postsurgical PSA. The other 15 patients underwent radiation therapy between 14 months and 9 years after retropubic radical prostatectomy because of PSA relapse. In patients treated with irradiation for a first recurrence, the time interval between

#### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>All patients (N = 91)</th>
<th>PET-positive studies (n = 31)</th>
<th>PET-negative studies (n = 60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65 ± 7</td>
<td>65.6 ± 7.4</td>
<td>64.3 ± 7.2</td>
</tr>
<tr>
<td>PSA at time of RRP (ng/mL)</td>
<td>11.1 ± 10.3</td>
<td>10.0 ± 6.9</td>
<td>11.3 ± 11.4</td>
</tr>
<tr>
<td>Highest Gleason score</td>
<td>5 ± 4</td>
<td>5 ± 4</td>
<td>5 ± 4</td>
</tr>
<tr>
<td>Lowest PSA after RRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonmeasurable or &lt;0.05 ng/mL (n)</td>
<td>46/91</td>
<td>16/31</td>
<td>30/60</td>
</tr>
<tr>
<td>PSA nadir when measurable (ng/mL), mean ± SD</td>
<td>0.34 ± 0.45</td>
<td>0.31 ± 0.33</td>
<td>0.28 ± 0.32</td>
</tr>
<tr>
<td>Range</td>
<td>0.07-1.44</td>
<td>0.07-0.98</td>
<td>0.07-1.44</td>
</tr>
<tr>
<td>Time between RRP and PSA relapse (mo)</td>
<td>27 ± 23</td>
<td>26 ± 27</td>
<td>23 ± 20</td>
</tr>
<tr>
<td>Time between RRP and PET (mo)</td>
<td>43.2 ± 34.9</td>
<td>54.3 ± 36.2</td>
<td>37.4 ± 32.7</td>
</tr>
<tr>
<td>PSA at time of PET (ng/mL), mean ± SD</td>
<td>4.6 ± 8.3</td>
<td>9.5 ± 12.2</td>
<td>2.1 ± 3.3</td>
</tr>
<tr>
<td>Range</td>
<td>0.12-49.3</td>
<td>0.27-49.3</td>
<td>0.12-20.3</td>
</tr>
<tr>
<td>PSA doubling time at time of PET (mo)</td>
<td>10.0 ± 14.7</td>
<td>6.8 ± 11.2</td>
<td>11.7 ± 16.0</td>
</tr>
<tr>
<td>PSA velocity at time of PET (ng/mL/y)</td>
<td>3.6 ± 5.8</td>
<td>8.5 ± 8.0</td>
<td>1.2 ± 1.8</td>
</tr>
<tr>
<td>Patients with disease on bone scan or MRI Bone scan positive</td>
<td>16/56 (28%)</td>
<td>15/23 (65%)</td>
<td>1/33 (3%)</td>
</tr>
<tr>
<td>MRI endorectal coil true positive</td>
<td>6/31 (19%)</td>
<td>5/8 (62%)</td>
<td>1/23 (4%)</td>
</tr>
<tr>
<td>MRI body coil or MRI spine true positive</td>
<td>12/33 (36%)</td>
<td>11/14 (78%)</td>
<td>1/19 (5%)</td>
</tr>
</tbody>
</table>

**Note:** Data are mean ± 1 SD, except when stated otherwise.

Abbreviations: RRP, retropubic radical prostatectomy; NS, not significant.
irradiation and PET ranged from 6 months to 10.1 years, with a mean of 3.6 years. Further patient characteristics, including PSA parameters, are shown in Table 1.

Positron emission tomography imaging findings. Overall, PET showed abnormalities in 31 patients (Table 1); in 28 of these 31 patients (31% of the entire study population), the PET was true positive (Fig. 1). Isolated local disease was detected in three patients. Metastatic disease with \( n = 2 \) or without \( n = 23 \) simultaneous local disease was shown in 25 patients. There were three false-positive studies where PET suspected metastases in bone \( n = 2 \) or lymph nodes \( n = 1 \); see below. Image examples are shown in Figs. 2 and 3.

Based on our standard of reference in the study design, 19 patients had evidence of isolated local recurrence (in 4 of 19, the recurrence was biopsy proven; in 15 of 19, the PSA declined after local radiation treatment). PET imaging identified isolated local recurrence in 3 of 19 patients (all true positives), whereas the remaining 16 studies were false negative. Simultaneous local and metastatic disease was detected in two patients (both true positives). Metastatic disease without involvement of the prostate bed was suspected by PET in 26 patients and confirmed in 23 of them (three false positives). Further details are shown in Table 2. Of note, an unsuspected liver metastasis was identified in one patient.

Standardized uptake value, measured at sites of suspected disease by visual analysis, was \( 3.2 \pm 0.6 \) (range, 2.6-3.9) for local disease, \( 3.8 \pm 1.2 \) (range, 2.1-6.0) for bone metastases, and \( 5.2 \pm 1.8 \) (range, 3.9-7.4) on lymph node and soft tissue metastases.

The proportion of PET-positive studies was significantly higher in patients with higher PSA values (Table 1). The lowest PSA in a PET-positive patient was 0.27 ng/mL; he had local recurrence in the prostate bed and a left obturator lymph node metastasis (biopsy-proven and also noted on MRI).

Considering that all patients had PSA relapse, 66% of PET studies (60 of 91) were classified as false negatives (Table 1). As compared with other imaging studies, confirmed disease was missed in one patient with local recurrence (MRI positive) and one patient with osseous metastases (MRI and bone scan positive). In the remaining patients, all other concurrent imaging studies were also negative.

Univariate ROC analysis (areas under the curve in parentheses) revealed that PSA (76%), PSA doubling time (70%), and PSA velocity (81%) were reasonable predictors of a positive PET. A PSA of 2.4 ng/mL, a PSA doubling time of 6 months, and a PSA velocity of 1.3 ng/mL/y were identified as best cutoff for the detection of local recurrence or metastatic disease by PET (see Fig. 4; Tables 3 and 4). For comparison, other points on the ROC for PSA would have provided the following sensitivity/specificities (0.75 ng/mL: 52%/74%; 1.50 ng/mL: 65%/70%; 4.20 ng/mL: 85%/55%). Similarly, a PSA velocity of 0.43, 0.69, and 3.30 ng/mL/y would have provided sensitivity/specificity pairs of 43%/85%, 62%/80%, and 84%/64%.

Fig. 2. Coronal, sagittal, and transaxial FDG-PET images (A-C) for a 79-year-old man with increasing serum PSA of 6.24 ng/mL 9 years after radical prostatectomy. There is focal FDG accumulation in the prostate bed (arrow). Concurrent transaxial MRI (D; T2-weighted image) showed a mass in the same location. The patient subsequently underwent radiation therapy to the prostate bed; afterward, his PSA decreased to 0.09 ng/mL.
We tested various combinations of the PSA-related variables, as well as presence or absence of prior radiation therapy, Gleason score and clinical stage using a multivariable logistic regression. We were unable to improve the accuracy significantly through these combinations. Therefore, PSA velocity was the best parameter to predict the diagnostic yield of FDG-PET in patients with PSA relapse. However, if PSA velocity cannot be calculated, a simple PSA measurement could serve to identify patients likely to benefit from this imaging study.

Comparison with other imaging studies by imaging modality and anatomic site. Sixty-four of the 91 patients underwent MRI, 37 patients had a CT scan, and 56 had a bone scan (Tables 1 and 2). PET and MRI were concordantly positive in 16 patients and concordantly negative in 35 individuals. In the discrepant 13 cases, the PET abnormality was outside the MRI field of view ($n = 6$; five true positives, one false positive), or abnormalities were only noted on MRI ($n = 7$; two true positives, two false positives, three without confirmation).

CT and PET findings were concordantly positive in seven cases and concordantly negative in 14 cases. Regarding the 16 cases with discrepant findings, the CT failed to detect 13 proven sites of disease (in nine cases, the CT was false negative; in another four cases, the site of disease was outside the CT field of view), two false-positive PET findings in the lumbar spine were true negative on CT, and in one other patient the CT suspected metastasis but this could not be validated independently.

A bone scan was done in 56 patients. In 37 instances, both the PET and the bone scan were concordantly negative; in 15 patients, both studies were concordantly positive and discrepant findings were noted in four cases (two false-positive PET studies, 1 true-positive lesion each only noted on PET or bone scan, respectively). A summary of this analysis is shown in Table 4.

Disease in the prostate bed. Twenty-one patients had disease in the prostate bed (19 isolated local recurrence, 2 disease in prostate bed and at distant sites). PET correctly detected disease in the prostate bed in only 5 of 21 patients, compared with MRI in 7 of 21 patients. In addition, the MRI suspected local disease in three more cases; one was false positive (negative biopsy) and the other two remained without verification. There was no patient in whom PET detected true local recurrence that would have been missed by MRI. There was no case in which CT detected disease in the prostate bed.

Lymph node metastases. Ten patients were suspected of having nodal metastases by at least one imaging study. PET showed abnormal FDG uptake in lymph nodes in seven individuals; in six the finding was proven to be true positive, whereas one was false positive. Concurrent MRI or CT that included the suspected site of disease were available in two and three patients, respectively, and showed these lymph node lesions in two of two cases (one true positive, one false-positive) and two of three cases (two true positives, one false negative paraaortic nodal metastasis). The patient with concordantly false-positive PET and MRI had a PSA of 1.2 ng/mL and enlarged inguinal nodes with abnormal FDG uptake; there was no change in imaging findings or PSA for 18 months, while the patient remained under observation and off therapy. In another case, a para-aortic metastasis was outside the field of view of the pelvic MRI. Two enlarged pelvic lymph nodes were only noted by MRI; one was true positive, one false positive (1.7 cm obturator node without change over 2 years whereas his PSA increased from 2.3 to 15.3 ng/mL). One enlarged left internal iliac lymph node was only noted on CT but it remained unclear if this was due to metastatic disease from prostate carcinoma.
**Bone metastases.** Twenty-three patients were suspected of having osseous metastases on imaging (21 with bone disease only, 2 with disease in bones and at other sites). PET showed osseous lesions in 22 cases (20 true positives, 2 false positives). In two cases, these (true positive) lesions were only visualized by PET (one case without comparison studies; one case with false-negative bone scan). The two false-positive PET findings, in retrospect, seemed rather characteristic for degenerative changes in the lower lumbar spine. PET did not detect one true-positive bone lesion that was detected only by MRI. All osseous metastases noted on CT were also visualized by PET.

Whereas PET and bone scan were concordantly positive for osseous metastases in 15 individuals, in only eight of these cases the extent of metastatic bone disease was similar in both studies. In the other seven studies, the number and the extent of the disease between the two studies was discrepant. The mean PSA in patients with positive bone scan was 10.5 ± 11.4 ng/mL (range, 0.80-49.3), compared with 3.4 ± 6.8 ng/mL (range, 0.12-45.6) in those with normal bone scan ($P = 0.04$). PSA velocity was also higher in patients with a positive compared with those with a negative bone scan (10.1.1 ± 7.7 versus 2.3 ± 4.5 ng/mL/y; $P = 0.01$).

**Patients with negative imaging studies.** Fifty-two of the 60 patients with negative PET underwent at least one other concurrent imaging study. In 45 of these 52 cases (86%), all imaging studies failed to show any disease, including 34 MRI, 9 CT scans of the abdomen and pelvis, and 29 bone scans. The mean PSA was 2.2 ± 3.6 ng/mL in this subgroup. During the subsequent 6 months, imaging studies showed local recurrence ($n = 1$) or metastatic disease ($n = 2$) in three patients, accompanied by a further increase in PSA by 0.5 to 16 ng/mL, and treatment with hormonal or radiation therapy was initiated. In 15 patients, radiation therapy was done for suspected local recurrence, and in three additional patients hormonal or experimental vaccine therapy was initiated despite a lack of abnormalities on imaging studies. The other 24 patients remained untreated and showed a further increase in PSA by 2.6 ± 3.7 ng/mL (range, 0.15-14.1), without any evidence for disease on imaging studies.

Further follow-up (mean, 888 ± 360 days, range, 13 months-4.2 years) was available for 22 of these 24 patients. In 17 individuals, treatment was eventually initiated; in 10 of them, this was associated with positive imaging findings. The remaining five patients, with PSA ranging from 0.4 to 24.4 ng/mL, had various negative studies and were not treated for their PSA relapse; their follow-up time ranged from 1.1 to 2.3 years. However, two of these individuals developed a second malignancy (one hepatocellular carcinoma, one cholangiocarcinoma) during that time.

**Discussion**

PSA relapse after radical prostatectomy is a clinical dilemma. Among patients who fail primary therapy of prostate cancer, PSA relapse occurs in 45% during the first 2 years and in 77% during the first 5 years after surgery (8). Frequently, the PSA begins to increase long before recurrent disease can be localized clinically or by imaging (8). There is, therefore, continuing controversy regarding when treatment should be initiated and which treatment modality is most appropriate (21). Attempts have been made to predict the probability for PSA relapse, to determine the likelihood for local recurrence versus systemic relapse (e.g., in lymph nodes or bones; refs. 22–25), and to predict the likely progression of recurrent local or metastatic disease (8, 26). For instance, metastatic disease is more likely in patients with PSA relapse <2 years after retropubic radical prostatectomy (27) and PSA doubling time <6 months (28–30). Nevertheless, in most cases, rational treatment decisions require knowledge about the location and extent of the disease, and this knowledge cannot be derived reliably from biochemical data or nomograms alone. Therefore, imaging studies are used frequently in patients with PSA relapse with the main goal to differentiate between local recurrence and distant metastatic disease (11, 28, 31–33).

In the current study, local or systemic disease was detected in 31% of cases. Although this percentage is slightly higher than in previous studies, ranging from 0% to 27% (11, 15, 34, 35), the large number of negative studies reflects the underlying biology of recurrent prostate cancer (9). The average time between initial PSA relapse and clinical presentation of metastases is 8 years (8). Therefore, oftentimes, all imaging studies are negative during this clinical state.

### Table 2. Summary of imaging findings

<table>
<thead>
<tr>
<th></th>
<th>PET ($n = 91$)</th>
<th>MRI ($n = 64$)</th>
<th>Bone scan ($n = 56$)</th>
<th>CT ($n = 37$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TP</td>
<td>FP</td>
<td>Missed*</td>
<td>TP</td>
</tr>
<tr>
<td>Prostate bed only</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>28</td>
<td>25</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Lymph nodes only</td>
<td>4</td>
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<td>Bone metastases only</td>
<td>20</td>
<td>18</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Combination of sites</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total no. TP studies</td>
<td>28</td>
<td>(31%)</td>
<td>18</td>
<td>(28%)</td>
</tr>
</tbody>
</table>

NOTE: Table only contains imaging findings for which verification was available according to standard of reference defined in Materials and Methods. Note that the MRI field of view frequently only included the pelvis or the spine; therefore, the number of bone metastases detectable by MRI is likely underestimated.

Abbreviations: TP, true positive; FP, false positive; BS, bone scan.

* Sites of proven disease detected by other, concurrent imaging studies, provided the lesion was included in the field of view (for details, see Results).
The probability for disease detection increased in parallel with raises in PSA values (see Fig. 3; Table 2). Thus, whereas a low PSA does not necessarily preclude PET positivity, the diagnostic yield of routine PET imaging in patients with early PSA relapse would be very low. A similar trend to greater lesion detection with higher PSA values is also known for the use of bone scans or MRI (32, 36) and has been suggested for other PET tracers (34). In contrast to these prior studies (11, 32, 34, 36), we used ROC analysis as a more thorough statistical approach. Other previous PET studies included smaller patient samples, were restricted to the analysis of lymph node metastases (11), or did not analyze the relationship between imaging findings and PSA kinetics (35).

In the past, FDG-PET imaging of prostate cancer has led to varying results (15–17, 34, 37) with oftentimes low sensitivity for disease detection and false-positive findings related to urinary excretion of this agent. As a result, other PET tracers, such as $^{[11]}$Cacetate, $^{[11]}$Ccholine, or $^{[18]}$Fcholine, have been proposed for the imaging of prostate cancer. Initial encouraging data have been published (34, 35, 37–40), but few of these studies used a rigorous standard of reference or a comparison with FDG. The largest study to date (35) compared FDG and $^{[11]}$Ccholine in patients with increasing PSA after prostatectomy or radiation therapy. $^{[11]}$Ccholine proved to be superior in detecting local recurrence, osseus, and nodal metastases. However, with the evolving nosological concept of prostate cancer (9), it has become increasingly clear that proper patient selection is a prerequisite for the meaningful application of any imaging test in this disease. For instance, FDG may be superior for the detection of distant metastases, whereas $^{11}$C acetate may be superior in identifying local recurrence and nodal metastases (37). There is also evidence that PET imaging with FDG provides prognostic information in patients with prostate cancer and that it can be used for treatment monitoring (17, 18, 41–43). Thus, rather than replacing one PET tracer with another, a multi-tracer imaging approach may be needed in prostate cancer, depending on the specific clinical question. The present study

Fig. 4. A. ROC curves for PSA, PSA doubling time, and PSA velocity. The areas under the curve were 76%, 70%, and 81%, demonstrating that PSA velocity was the most accurate parameter for predicting a positive (abnormal) PET scan in patients with PSA relapse. — PSA; — PSA doubling time; — PSA velocity. B and C, ROC curves for PSA and PSA velocity showing varying sensitivity and specificity of FDG-PET for different cutoff points along the respective ROC curves.

**Table 3. Summary of ROC analysis (see also Fig. 4)**

<table>
<thead>
<tr>
<th></th>
<th>AUC (95% confidence interval)</th>
<th>Cutoff</th>
<th>Sensitivity/ specificity</th>
<th>DLR+/DLR−</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA (ng/mL)</td>
<td>75.9% (63.5, 87.7)</td>
<td>2.38</td>
<td>80%/71%</td>
<td>2.76/0.69</td>
</tr>
<tr>
<td>PSA doubling time (mo)</td>
<td>69.7% (58.9, 80.6)</td>
<td>5.6</td>
<td>57%/71%</td>
<td>2.76/0.51</td>
</tr>
<tr>
<td>PSA velocity (ng/mL/y)</td>
<td>81.0% (60.3, 92.1)</td>
<td>1.31</td>
<td>73%/77%</td>
<td>3.17/0.35</td>
</tr>
</tbody>
</table>

Abbreviation: AUC, area under the curve.
shows that even with a standardized clinical PET protocol, FDG can provide meaningful information in appropriately selected patients with PSA relapse.

**Study limitations.** This is a retrospective study with certain method-inherent limitations. Although our standard of reference used strict criteria, a retrospective study may have a selection bias. The mean PSA at the time of PET was 4.6 ng/mL; thus, our study may have included a large group of patients at relatively low risk. Our findings suggest that the number of abnormal PET studies would increase among patients with higher PSA levels.

We did not attempt to define a specific standardized uptake value level to detect disease. We believe the value of standardized uptake values is the greatest in measuring the response to therapy in individuals with metastatic disease rather than in initial disease detection.

Because of potential referral bias and the retrospective nature of this study, the incremental value of FDG-PET (e.g., in addition to MRI or bone scan) and specific effects on patient management cannot be assessed from these data.

Scher et al. (44) have defined clinical states of prostate cancer. These categories are particularly helpful for identifying homogeneous cohorts of patients for therapeutic intervention. The retrospective nature of this imaging study, which depended on clinical referral patterns, did not lend itself to this type of strict classification. Instead, the patients included in this study could have been considered to be in the state of “noncastrate” (44). This distinction may be an important clinical question as local therapy with irradiation or salvage prostatectomy is not appropriate once systemic disease has been proven. In clinical practice, the bone scan and CT or MRI (in some institutions also a Prostascint scan) are ordered to address this issue. Although it is conceivable that PET could detect systemic disease in patients with negative bone scan and negative CT or body MRI, the fraction of such patients among the entire population with increasing PSA is likely very low. Defining the role of PET in these highly preselected patients would require a large patient sample and a prospective study. Rather, the true value of PET might be found in the fact that it can effectively replace a battery of other tests, including bone scan, CT scan, and body MRI, for the detection of systemic disease in patients with PSA relapse. CT in particular is a suboptimal technique for detecting local recurrence in patients with PSA relapse (45), and its sensitivity is not better than that of FDG-PET for the detection of nodal metastases (11). In our study, virtually all disease shown on bone scan and CT was also revealed in a single whole-body PET scan. At the very least, our data suggest that a combination of endorectal or pelvic MRI (for detection of local recurrence) and FDG-PET (for detection of systemic disease) would provide a valuable imaging algorithm in these patients. With this approach, no site of proven disease in this study would have been missed. However, because of limitations inherent to any retrospective analysis, the validity of this suggested approach would have to be confirmed in a prospective study.

We found that a PET scan with FDG would be most useful if the PSA is >2.4 ng/mL or PSA velocity is >1.3 ng/mL/y. These values should not be used in isolation. Clinical findings or abnormalities noted on other imaging studies may sometimes require further evaluation with PET even in patients with relatively low PSA levels. Therefore, the ROC curves (Fig. 4) also show sensitivity and specificity for other PSA cutoff levels.

### Conclusion

In conclusion, FDG-PET identified local or metastatic disease in 31% of patients with PSA relapse after retropubic radical prostatectomy. The likelihood for disease detection improved with increases in PSA levels. In the vast majority of patients with negative PET, other concurrent imaging studies also failed to show sites of recurrent disease. Our study confirms that FDG-PET should not be used to randomly screen patients with PSA relapse; rather, this test should be restricted to a selected subset of patients: FDG-PET seems most useful in patients with PSA >2.4 ng/mL or PSA doubling time >1.3 ng/mL/y. These findings will need confirmation in a prospective study.

### References

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2-[\textsuperscript{18}F]Fluoro-2-Deoxyglucose Positron Emission Tomography for the Detection of Disease in Patients with Prostate-Specific Antigen Relapse after Radical Prostatectomy

Heiko Schöder, Ken Herrmann, Mithat Gönen, et al.


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