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Investigations with FDG-PET Scanning in Prostate Cancer Show Limited Value for Clinical Practice

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The aim of this study was to investigate FDG-PET (fluorodeoxyglucose positron emission tomography) imaging in the management of prostate cancer. Twenty-two patients were studied during different disease phases of prostate cancer, for staging or restaging to clarify specific clinical questions. FDG-PET was performed encompassing the thorax, abdomen and pelvis using the Penn PET 300H scanner. Scanning was begun 60 min after ^{18}F fluorodeoxyglucose marker. Patients were catheterized and administered diuretics to minimize urinary activity. Information obtained with FDG-PET was concordant with findings from other investigations in 7/22 (32%) patients, discordant in 15/22 (68%) patients and equivalent in one patient (4%). PET indicated progressive disease in five patients with prostate-specific antigen (PSA) <4 ng/L. The impact on management of the patients was high in 46% of cases, low in 41% and for 14% there was no impact on management. The accuracy of FDG-PET was 72% (95% CI 50–89) as confirmed by invasive diagnostics/follow-up. FDG-PET can provide useful information and improve the clinician's decision on further management procedures in selected patients with low PSA and bone or lymph node changes. A negative PET scan in prostate cancer should be interpreted with caution.

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Prostate cancer is the most common cancer among men in the Western world and the USA and it is the second cause of cancer death among men (1). In the majority of cases, the disease is indolent and can be managed conservatively. The incidence of aggressive prostate cancer, however, has been reported to be more frequent in the younger age group (<60 years) (2). Eighty percent of cases that recur after primary treatment with radical surgery or radiotherapy are sensitive to hormone manipulation, which can effectively control the disease for years. Therefore, with the definition of true tumour extent/residual tumour, e.g. after radical surgery, the clinician can decide whether further treatment should be given with radiation or hormones. The rationale behind the use of fluorodeoxyglucose positron emission tomography (FDG-PET) scans in prostate cancer is that with recurrent disease and at low levels of prostate-specific antigen (PSA), bone scanning and CT scans may fail to give an accurate diagnosis. As such, it is difficult to determine whether we are dealing with extra pelvic disease that would require hormone therapy, or local disease that would require postoperative radiotherapy.

The sensitivity of diagnostic imaging of pelvic lymph nodes with conventional methods, such as CT and MRI is limited (3). Technetium bone scanning is a reliable technique in diagnosing metastatic disease with PSA >15 (4) and therefore it has been suggested by Rudoni and coworkers (5) that a PSA value of less than 10 ng/mL effectively excludes bone metastases. Owing to the high prevalence of degenerative disease in elderly patients with prostate cancer, abnormalities found by bone scanning are common even where there is no metastatic disease. This can mask true metastatic disease, especially in the absence of markedly elevated PSA.

PET as a method of metabolic imaging has proved valuable in staging, restaging and assessment of clinical outcome in several cancer types (6). PET scanning is sensitive for the detection of increased cellular retention of the glucose analogue, fluorine-18 fluorodeoxyglucose (F-18 FDG), which is present in many types of cancer. Preliminary experience using FDG-PET in prostate cancer has suggested relatively poor sensitivity because of the generally low FDG avidity of prostate cancer metastases and therefore the use of this technique has not been widely adopted in clinical practice (7, 8). However, some studies and reviews have advocated FDG-PET as a useful and valuable tool in the management of urological diseases, including prostate cancer (9, 10). Therefore, we have retrospectively evaluated the clinical impact of FDG-PET imaging in prostate cancer patients to clarify the clinical

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situations where FDG-PET imaging may be beneficial in the management of prostate cancer.

MATERIAL AND METHODS

Twenty-two prostate cancer patients were studied with FDG-PET at the Peter MacCallum Institute PET Centre, from May 1998 to March 2000. PET scanning was performed on a dedicated 3-D scanner (PENN-PET 300H, UGM Medical Systems, Philadelphia, PA), which has a spatial resolution of approximately 6 mm. The department's standard protocol for abdominal and pelvic PET scans was followed for preparation and scanning. The administered activity of FDG was 55 to 111 MBq. Fluorine-18 production and FDG synthesis were performed on site. Patients were instructed to fast for a minimum of 6 h prior to the investigation but were encouraged to drink water only. They were catheterized prior to administration of FDG and infused with 500 ml I.V. normal saline during the uptake phase. Patients were administered diuretics 15 min prior to scanning to minimize the concentration and pooling of activity in the urinary tract. The scanning commenced at least one hour after radiotracer administrations. FDG-PET was performed to encompass the thorax, abdomen and pelvis. Five minutes prior to imaging the pelvis, the catheter drainage tube was clamped to allow partial filling of the bladder, which, owing to induced diuresis, contained low amounts of activity. This preliminary step allowed better visualization of the bladder margins, which was helpful in delineating surrounding pelvic structures.

For tomographic reconstruction, the ordered subset expectation maximization (OSEM) method was utilized and the resulting images were processed with and without attenuation correction. Standardized uptake values were not routinely calculated.

Assessment of PET scans was performed by an experienced nuclear medicine physician (RH). Analysis of images was done from the screen, with an interactive display program allowing multiple orthogonal images to be displayed simultaneously. Rotating count rendered images were found to be helpful in many patients. Reports routinely involved a review of all available clinical information including other imaging results. Sites of increased radiotracer uptake on bone scan and PET were coded as uninvolved when uptake was specifically reported as being due to intercurrent pathology, reaction to treatment or physiological uptake. Each patient was classified as positive, equivocal or negative for disease, according to the most positive site on each of the assessments including CT, bone scans and PET.

The impact of the PET results on the management of prostate cancer was evaluated using the following score: *high*—the treatment modality was changed based on PET; *moderate*—the treatment modality remained the same but the delivery was modified based on PET; *low*—there was no change in the treatment modality or delivery as a result of PET scans; *none*—the PET result was ignored when further treatment was planned. The information obtained was scored as true if confirmed by invasive investigations or clinical outcome and false if proven not true.

RESULTS

The indications leading to an investigation were staging (prior to any treatment) for 7 patients (32%) and restaging (after primary treatment) for 15 patients (68%). At the time of PET scanning, 3 patients had PSA levels of over 20 ng/L, 8 patients had PSA levels between 4 and 10.5 ng/L and 10 had a PSA level of less than 4 ng/L. The PSA level was not available for one patient. The indications for requesting FDG-PET investigation are summarized in Table 1.

The evaluation of the results of FDG-PET scanning included a review of all available clinical and imaging results, as indicated in Table 2. Information obtained with FDG-PET was concordant with findings from other imaging, clinical status and follow-up PSA investigations in 7/22 (32%) of patients and discordant in 15/22 (68%) of patients. PET excluded metastases in a patient with Paget's disease and showed bone metastases confirmed later by biopsy in another patient with schwannoma. FDG-PET was false positive in a patient with reactive lymph nodes showing fatty degeneration. PET correctly interpreted enlarged lymph nodes as benign in a patient with 2-cm lymph nodes detected by CT, proven to be benign at operation.

PET indicated progressive disease in 5 patients with PSA < 4 ng/L. These patients with slightly elevated PSA, having increased from nadir to 0.6–1.6 ng/L, were treated with local radiotherapy to the prostate area after excluding metastatic disease outside the pelvis by FDG-PET. The PSA levels of these patients decreased following treatment and all of them have remained free of disease during follow-up.

Table 1

Reasons of referral to PET investigation

Reason of referral	No. of patients (%)
Rising PSA	9 (41)
Abnormal bone scan finding + rising PSA	3 (14)
Suspected lymph node metastases in CT + rising PSA	1 (5)
Symptoms/findings unclarified by other investigations	5 (22)
Pretreatment staging of high-risk patients with suspected metastases	4 (18)
Total	22 (100)

Abbreviations: PET = Positron emission tomography; PSA = prostate-specific antigen.

Table 2

Indications to PET, PSA values and results of CT and PET evaluation in prostate cancer patients

Patient	Clinical question/study indication[1]	PSA ng/L	CT	CT evaluation	PET	PET evaluation
	Primary staging					
I[1]	Elevated PSA, repeatedly benign prostate biopsies	72–118	Negative	FN	Increased tracer uptake in prostate	TP
II[1]	Preoperative staging	7.2	Negative	TN	No evidence of metastases cardiac insufficiency	TN
III[1]	Preoperative staging	6.9	2 cm lnn in common iliac region	FP	Lnn area clear, heavy uptake in prostate	TN (lnn)
IV[1]	Preoperative staging	NA	Invasion to seminal vesicles	FP (not confirmed at OP)	Uptake in pelvic lymph nodes, suggesting small volume iliac lnn metastases	FP (reactive changes in lymph nodes)
V[1]	Abnormal CT, primary staging	0.7	1.2 × 0.8 cm lnn R. ext. iliac	TP	No increased activity/uptake	FN (PSA decreased after radiation)
VI[1]	Paget's disease complicating primary staging	27	Paget's disease	TN	No metastases, prostate shows abnormal uptake	TP
VII[1]	Lung tumour, 2 cm, primary staging	5.1	2-cm lung nodule	TP	No abnormal uptake	TN (carsinoid tumour)
Restaging after primary treatment						
1	Postoperative rising PSA	0.7	Negative	FN	Suspected early lnn metastases/prostatic bed recurrence	TP
2	Abnormal MRI-swannoma?	5.4	Swannoma + bone invasion	FN	High uptake suggesting metastases	TP
3	Postoperative rising PSA. Abnormal bone scan	0.8	NA	NA	Mildly increased uptake in L1 metastases?	TP
4	Pain after radiotherapy, rising PSA	10	Suspected lymph node metastases	FP	No definitive metastases	TN
5	Abnormal bone scan Rising post-treatment PSA	2.3	Negative	FN	Intense uptake in L ileum, metastases suspected	TP
6	Postoperative rising PSA	1.4	Undefined changes	NA	Focal increased uptake in prostate area	TP
7	Postoperative rising PSA	10	NA	NA	Suspected pelvic metastases, different area to bone scan	TP
8	Postoperative rising PSA	0.3–0.6	Negative	FN	Negative	FN (biopsy: local recurrence)
9	Postoperative rising PSA	0.3–0.9	Negative	FN	Pelvic metastases suspected, increased uptake	TP
10	Postoperative rising PSA	20	Negative	NA	Metastases suspected in bone	TP
11	Postoperative rising PSA	3.5	NA	NA	High uptake in pelvic lymph nodes, metastases?	TP
12	Post-treatment abnormal bone scan, rising PSA	6.9	Negative	TN	No abnormal skeletal uptake	TN
13	Postoperative rising PSA	0.9	No evidence of malignancy	FN	Negative	FN (biopsy: local recurrence)
14	Post-treatment rising PSA Abnormal CT	6.3	Metastases in pelvic lnn	TP	High uptake in left pelvic lnn, suggesting metastases	TP
15	Postoperative rising PSA	0.3–1.6	Negative	FN	Negative	FN (PSA decreased after radiation)

Abbreviations: Lnn = lymph nodes; NED = no evidence of disease; NA = not available; TP = true positive; FP = false positive; TN = true negative; FN = false negative; PET = positron emission tomography; PSA = prostate-specific antigen.

[1] Initial pretreatment staging.

Two cases with anastomosis recurrence and a PSA level < 1 were false negative in CT and FDG-PET investigations. These recurrences were confirmed by biopsy of the prostate bed.

The impact on management of the patients was high in 46% of cases, low in 41% and with no impact in the management of 14%. The accuracy of FDG-PET was 72% (95% CI 50–89) as confirmed by invasive diagnostics/follow-up.

DISCUSSION

The applicability of FDG-PET in imaging of prostate cancer has not been convincingly demonstrated because of the low metabolic activity of this type of cancer (11). Effert et al. (12) failed to differentiate between benign prostate hyperplasia and carcinoma in several patients using this technique. Bares and collaborators observed that FDG-PET allowed differentiation between hypermetabolic and normometabolic prostate cancer, the latter showing uptake equivalent to benign hyperplasia (13). In their series, no correlation was observed between FDG uptake, tumour stage, histopathological grade or DNA ploidy. In contrast, Liu and collaborators did not find FDG-PET useful in the evaluation of clinically organ-confined prostate cancer (10). The experience in the current study suggests that PET scanning in prostate cancer demonstrates variable metabolic activity with the majority of prostate cancer metastases having relatively low uptake of FDG. We recognize some limitations in our study, owing to a small and heterogeneous patient population. All but two of the patients with PSA values below 10 were investigated; patients with higher PSA levels would have a higher prevalence of both bone and lymph node metastases. Although the study group was small, it was representative of the difficulties in clinical decision-making in the management of mainly advanced or recurrent prostate cancer. Our experience and current strategy are summarized in Table 3.

In a comparative study with histopathological verification of the lesions, FDG-PET had a better specificity but a lower sensitivity for detecting malignant bone metastases when compared with bone scans (14). Also in our series, PET defined metastatic lesions on two occasions where bone scans and MRI failed to do so. FDG-PET can be used for therapeutic monitoring of response to hormone deprivation therapy when bone scans remain abnormal (15). Biologically aggressive malignancies tend to have fairly intensive metabolic activity in PET scans, as seen in the case of patients with low PSA but high FDG uptake activity in biopsy-proven metastases. This could be an advantage when compared to bone scanning, which has limited specificity in patients without significantly elevated PSA (4). This finding is in concordance with the results of Oyama et al. (16), which showed a tendency for FDG uptake to be higher with higher histological Gleason grades and in tumours with extensive aggressive disease. In their series, the sensitivity of FDG-PET was 64%, similar to that observed in the present data.

PSA is the standard guide in the follow-up of prostate cancer patients, but information may be difficult to interpret in early recurrences or rare cases with aggressive PSA-negative tumours. In the present series, some of the patients with slightly elevated PSA were successfully treated with curative postoperative radiotherapy after restaging with PET. Using FDG-PET imaging, some cases without marked PSA elevation were shown to have metastatic disease. For patients with aggressive prostate cancer without PSA elevation, FDG-PET may provide a method of defining disease extent, while it has been shown, that FDG uptake is higher in tumours with higher biological aggressivity and more advanced stage (15). Differential diagnoses in cases such as the patient with degenerative or benign bone changes and pulmonary nodules can be clarified with FDG-PET. Standard uptake value changes have been shown to correspond with declining PSA in patients responding to treatment (17). Evaluation of spread in prostate cancer with FDG-PET is confounded with the excretion of FDG in the urine, which we aimed to overcome by using forced diuresis and continuous drainage, However, local recurrence at the site of anastomosis could only be diagnosed by biopsy.

In restaging of patients after radical surgery or radiotherapy having only slightly elevated PSA with discrepant or equivocal findings that confuse clinical decision-making, FDG-PET should be considered (18). We agree with Engelbrecht and collaborators (19) on the importance of cost effectiveness in the future and its influence on the use of accurate imaging. Preventing unnecessary radical treatment in the case of advanced disease and the use of appropriate palliation with correct diagnostic findings of metastatic disease should be weighted against the cost of imaging. Furthermore, other tracers, such as ^{11}C-choline (8, 20) may have higher sensitivity (82%) and specificity (94%), as reported recently (21).

In conclusion, CT and MRI remain the essential investigations for anatomical structures in treatment planning and follow-up of prostate cancer. As a functional imagin-

Table 3

Role of FDG-PET in management of prostate cancer

1. Not suitable for primary tumour delineation with current tracers, unable to differentiate between benign hyperplasia and cancer in prostate
2. Able to indicate bony metastases with lower PSA levels than bone scan
3. Superior to CT in evaluation pelvic lymph nodes for metastases
4. In PSA negative cases, may improve the detection of metastatic disease

Abbreviation: PSA = prostate-specific antigen.

ing modality, FDG-PET provides potentially valuable information on the biological activity of the findings, with limitations on small and diffuse lesions. Although not feasible for routine use in the staging of prostate cancer because of relatively low sensitivity and specificity, FDG-PET can provide useful incremental information in characterizing nodal spread or organ lesions in appropriately selected patients with low PSA.

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