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ARTICLE

Positron emission tomography in uro-oncology

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Abstract

Positron emission tomography (PET) in uro-oncology has been one of the slowest areas to develop. There are problems because of the excretion of tracer through the renal tract. Its use in prostate cancer has generally being disappointing, with PET being unable to differentiate malignancy from benign prostatic hypertrophy. In more advanced disease and in the search for the site of recurrence, PET can be of more use. Also, new tracers may prove to be more effective. PET has been shown to be of value in testicular cancer, particularly in defining recurrent disease in residual masses and in patients with raised markers. There is a clear place for PET in some of these cases. Early studies at staging are promising but more work is required to define its exact place. In renal and bladder cancer, PET may be a useful adjunct to conventional imaging in difficult cases and may assist in local staging. In all tumours it is valuable to differentiate fibrosis from recurrent disease in the treatment bed, an area of difficulty for CT/MR.

Keywords: *FDG-PET; uro-oncology; prostate; testicular cancer.*

Introduction

Positron emission tomography (PET), particularly with [^{18}F]fluorodeoxyglucose (FDG) has undergone rapid expansion and is becoming widely used in clinical oncology. In many cancers including lung and lymphoma it has been useful for diagnosis, staging, assessment of recurrence and for prognostic information[1,2]. The use of FDG-PET in uro-oncology has been slower to develop partly due to the excretion of tracer through the renal tract, potentially making structures and tumours difficult to see against this high background. PET therefore is of limited use to define the primary urological tumour. However, there is good evidence that FDG-PET may be useful in these tumours particularly for local staging and recurrence. It does also have good uptake in metastatic disease. Furthermore, for local staging one of the problems is the identification of involved lymph nodes. On CT these are generally regarded as malignant if >1 cm and benign if <1 cm. There are of course very small lymph nodes that contain disease and very large ones that are merely reactive. PET has the potential to assist in differentiating the composition of these nodes as it relies on metabolism of tumour cells. Thus, particularly in renal and bladder cancer, it can be a useful addition for local staging. In urological tumours, PET is helpful in differentiating fibrosis from recurrent tumour in previously treated sites, again overcoming one of the limitations of conventional anatomical imaging.

Prostate cancer

Prostate cancer is one the most important cancers in society. Due to limitations with other imaging and the fact that more accurate staging would improve disease treatment and survival, PET has been evaluated for diagnosis and staging. The results are generally poor with PET unable to distinguish benign prostatic hypertrophy (BPH) from cancer in a number of cases[3,4].

Initial studies were even more confusing in that they suggested that there was no correlation between FDG

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uptake and grade of tumour which is in stark contrast to FDG uptake in other cancers such as lung and head and neck[1,5] although one study[6] did show that this was also the case for prostate.

The identification of regional lymph nodes is potentially more important at initial diagnosis as the primary is identified by other means and accurate staging may improve management and outcome. Increased FDG uptake has been found in some regional lymph nodes even where the primary was PET negative[3,6] but this was of insufficient sensitivity to warrant the routine use of PET in pre-surgical staging. The reason for uptake in a regional node but not in the primary is also not clear and it was suggested that this might be due to increased proliferative activity in the metastases[3]. The true reasons for the unusual and conflicting results with FDG-PET and prostate cancer are far from clear as the postulated reasons for low sensitivity including low tumour volume and camera spatial resolution are not a problem in other tumours.

PET may be of value in local recurrence following therapy. In many tumours PET has been found to distinguish scar tissue from active tumour following surgery, chemotherapy and/or radiotherapy[7,8]. One study by Hofer *et al.*[9] found that this was true in a group of patients with prostate cancer being investigated for local recurrence following radical prostatectomy.

Widespread metastatic disease remains a problem in prostate cancer. In particular, bony metastases are a common site for spread. The best examination for detection remains radionuclide bone scanning. FDG-PET can certainly detect bone disease[3,10] with positive predictive values up to 98% in a study of 202 patients[11]. It can also discriminate active bone lesions from radioistopically quiescent lesions[12] but it has poorer sensitivity, and does miss some metastases seen on bone scintigraphy[11,13,14]. As bone scintigraphy is widely available and cheap this should remain the mainstay of evaluation of bone metastases.

The question of raised prostate-specific antigen (PSA) indicating probable progressive or recurrent disease and negative or equivocal imaging is a place where FDG-PET has some potential value. Chang *et al.*[15] examined the use of PET in patients with raised PSA and who had negative bone scans and equivocal pelvic lymph nodes on CT. They found that the sensitivity and specificity for PET was 75% and 100%, respectively. Previously unsuspected disease in lymph nodes outside the pelvis and in the liver has been detected on PET[10,11]. This is possible because as a single, one-step investigation, PET enables rapid whole body assessment.

In the future it may be possible to use PET as a monitor of disease activity. Oyama *et al.*[16] examined the effect of androgen ablation therapy on FDG uptake in tumours where the primary and all bone metastases were FDG positive. Along with the PSA, the degree of uptake of FDG decreased with initiation of therapy.

Due to the disappointment with the results of FDG in prostate cancer, many authors have examined other tracers and these may be more useful. Choline has upregulated uptake and phosphorylation in tumour cells and this labelled with the positron emitter ^{11}C has been found to be better than FDG for evaluating the primary, local and metastatic disease in prostate cancer[17,18]. It appears to be useful in restaging cases with raised PSA where it is better than FDG and complementary to conventional imaging. [^{11}C]acetate PET imaging has also been assessed. Oyama *et al.*[19] showed that all primary tumours accumulated [^{11}C]acetate in a study of 22 patients, and in detection of recurrent disease at PSA relapse, it also demonstrates marked uptake with a higher sensitivity than FDG[20].

Both ^{11}C tracers require on site cyclotrons due to the short half-life and undoubtedly ^{18}F is a more useful commercial tracer. Choline has been successfully labelled with ^{18}F and an early study shows good uptake in prostate cancer. A great deal of work needs to be done on these if they are to be of general use.

Testicular cancer

Undoubtedly the most useful place for FDG-PET in uro-oncology is in testicular cancers, especially in residual/recurrent disease.

Following treatment of primary disease, up to 30% of patients have residual masses and treatment of these remains difficult. In non-seminomatous germ cell tumour (NSGCT), these may contain tumour, fibrosis/necrosis or mature teratoma (MTD). In the case of fibrosis/necrosis, no further action needs to be taken but those with residual disease need further treatment, usually surgical removal early on. In the case of MTD, the tumour must be removed but this can be delayed if the patient has suffered morbidity due to the chemotherapy.

In seminoma, para-aortic radiotherapy is standard practice and more widespread disease is treated with chemotherapy. Residual masses following treatment are also seen.

CT and the change in size of the mass has been the standard for assessing residual masses. There have now been many studies with FDG-PET in the assessment of residual masses[8,21–23]. PET can readily identify residual tumour with sensitivities and specificities higher than CT. Clinical FDG-PET cannot, however, differentiate MTD from fibrosis although with non-standard dynamic imaging, this is possible[24]. This suggests a more limited role for PET in this case. As with all technologies, there is a limit of detection and PET did miss some very small volume tumour[8,22]. In addition, timing of the PET scan is important as patients scanned within 10–14 days of chemotherapy may have false negative results[8,22]. This should be taken into account in the timing of investigations post-treatment.

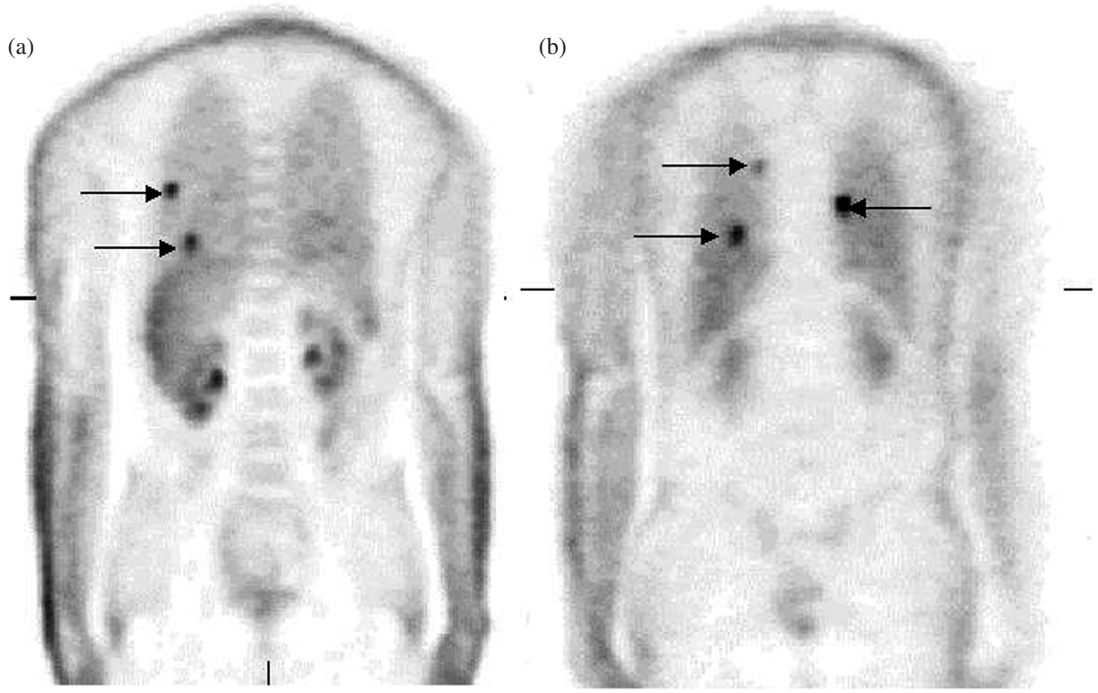

Figure 1 **A patient with known metastatic testicular cancer had a CT showing a single right lung metastases. Surgery was to be performed. FDG-PET was performed to exclude other sites of disease. The coronal ((a) and (b)) FDG-PET scans show uptake in multiple lung lesions. This led to a management change as surgery was cancelled and the patient given more chemotherapy.**

In seminoma, PET may be of more value and more important. These residual masses contain either tumour or fibrosis/necrosis. In addition, treatment has been difficult as radiotherapy following chemotherapy is of little value[25]. Initial studies showed good results for seminoma in small numbers[8,22,26]. A recent study of 56 scans by De Santis *et al.*[27] found that PET had a sensitivity, specificity, positive predictive value and negative predictive value of 100%, 80%, 100%, 96%, respectively, vs. 74%, 70%, 37% and 90% for CT. In addition PET was positive in 100% of cases for masses >3 cm and 95% in those <3 cm. They concluded that FDG-PET is the best predictor of viable residual seminoma in postchemotherapy masses. Further, they stated that it should be used as standard in decision making in this circumstance.

Patients with testicular cancer can also present with recurrence suspected on the basis of raised markers. These patients will have CT performed. The CT may be normal or equivocal or may show persistent previously defined masses and it is unknown which if any contain the recurrent tumour. Establishing the site has direct management implications as to whether the patient has a single mass removed or has chemotherapy. A positive PET is an accurate marker of disease location[8,22]. The problem in the studies reviewing this lie in the small numbers of patients with raised markers and negative PET scans. Interestingly, follow-up studies showed subsequent PET to be the first study to identify the site of disease[8]. This implies a clear role for PET in this circumstance.

With such good results, FDG-PET does affect management of the patient (Fig. 1). Certainly, in complicated multiple relapse patients, the use of FDG-PET has been shown to change the decision on therapy in 57% of cases[8]. In postchemotherapy seminoma, the results also suggest direct management implications based on PET[27].

In other tumours, namely lymphoma and breast[28–30], FDG-PET has been found to be an accurate predictor of response to chemotherapy both immediate and for long-term outcome. One study has compared PET to CT/MR and markers after 2–3 cycles of chemotherapy in testicular cancer[31]. PET identified patients most likely to achieve a favourable response from subsequent high dose chemotherapy. In addition, in patients with a response on CT/MR and with decreasing markers, PET added valuable information to detect patients with an overall poor outcome.

At diagnosis, accurate staging of testicular cancer is important and risk stratification is based on tumour spread and inherent tumour factors such as vascular invasion. This is not perfect and patients are often under- or overstaged. Despite this, cure rates are good[32,33] but a system that more accurately stages disease would save some patients from unnecessary chemotherapy.

In addition, there have been recent further concerns about long-term effects of treatment including second malignancy and cardiovascular complications[34] and to limit this would be beneficial.

CT has been the standard imaging technique for staging. The main limitation is the definition of 1 cm as the differentiating factor between benign and malignant lymph nodes. The main potential for PET would be if it could better define these nodes. There are a number of small studies[35–37] showing good results for PET but not sufficient at this stage to justify any changes in imaging protocols.

PET has detected disease not seen in other imaging in bone and soft tissue[35]. This has not so far made significant management changes particularly as those patients with NSGCT will receive chemotherapy in any case.

In NSGCT the definition of true stage I disease is extremely important as true stage I can undergo surveillance only. In a prospective trial, Lassen *et al.*[38] found that PET has a clear role in these cases as a high number of relapsed patients had positive PET studies in the face of negative conventional imaging. An MRC funded trial in the UK has also commenced to examine this issue (Fig. 2).

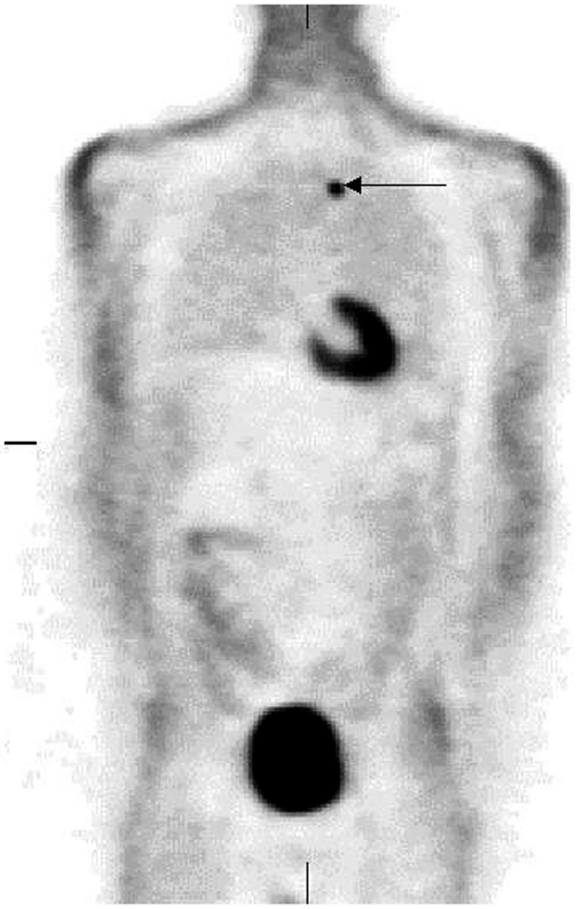

Figure 2 **A patient with Stage I (on conventional imaging) testicular cancer underwent PET scanning. The coronal FDG-PET shows uptake in a mediastinal lymph node. This was shown on biopsy to be metastatic disease.**

Bladder cancer

Few studies have examined PET and bladder cancer. Certainly the excretion of FDG through the renal tract may make visualisation of the bladder difficult particularly in assessing primary disease. It can be useful in specific cases particularly with equivocal conventional imaging. It is of value in local staging with sensitivities of 67% and specificity of 86% both of which are better than CT/MR[39]. It may also differentiate fibrosis from recurrent disease in the treatment bed[40]. Where metastatic disease is an issue away from the renal tract, bladder metastases are FDG avid and in this instance PET would be complementary to other imaging.

Other tracers have been assessed due to the difficulties with urinary FDG excretion. The primary is visualised with [^{11}C]methionine[41] but there is no evidence that this improves local staging and should not be routinely used.

Renal cancer

Primary renal cancer is undoubtedly FDG positive despite excretion of tracer through the kidney[42]. Study results have been conflicting for identification of the primary with some studies indicating high sensitivity and some with high false negative rates[43,44]. Even in the studies with good results, some tumours were missed including a 6 cm tumour[44]. It is not entirely clear why there should be such variable uptake but Miyachui *et al.*[45] found that higher grade tumours were PET positive and low grade tumours negative as well as showing that GLUT-1 transporter protein expression was raised in high grade PET positive tumours.

An important question can be the differentiation of a benign cyst from a tumour. No benign cysts have been found to be FDG positive, which may be helpful in evaluation[43]. However, small areas of malignancy can be falsely negative with one cyst with 4 mm of malignancy being negative in Goldberg's study[43]. Thus, PET does not obviate the need for biopsy despite this papers claim to the contrary.

Ramdave *et al.*[44] found that PET altered management in 35% of cases at diagnosis mainly on the basis of identifying metastatic disease. This was not confirmed in the more recent and largest study in renal cancer so far[46]. This study found a management alteration of only 13.3% suggesting a very limited role for PET in clinical management. The authors did, however, find 100% specificity for PET for the primary, renal bed recurrences, retroperitoneal lymph node metastases, liver metastases (Fig. 3) and bone lesions which may be of use in certain cases.

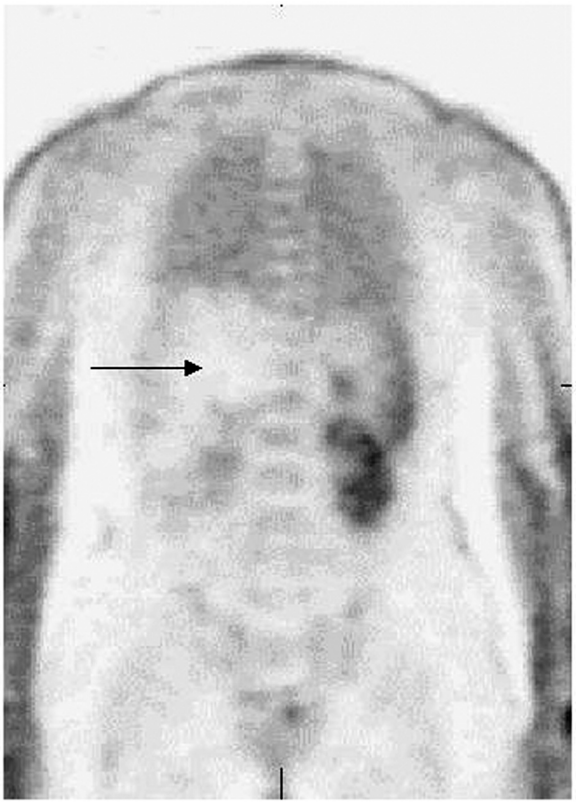

Figure 3 **A patient with known renal cell carcinoma was found to have cystic lesions in the liver CT. A PET was performed to determine if these were metastatic. The PET shows photopaenic regions in the liver consistent with benign cysts which these were shown to be.**

Malignant lymph nodes can be less than 1 cm and will be missed on CT and large lymph nodes may contain only inflammation. In this circumstance PET is an extremely useful adjunct to CT. CT can also lead to questionable results where fibrosis/scarring has occurred due to previous treatment and PET can differentiate these conditions[44,46]. PET has also been able to differentiate clot from tumour in the renal vein[47].

While having no advantage over CT for identification of primary masses, PET is efficient for detection of metastatic disease[48,49]. It is the best test to establish bone metastases[46,50] and appears to overcome some of the problems with bone scanning[46] in particular differentiating degenerative disease. On the basis of this, Aide *et al.*[48] suggested that a selection process could be implemented to determine which patients should undergo PET scanning. This would include those who had solitary metastases identified or doubtful CT images (Fig. 4). They also suggested basing selection on the histology of the resected tumour with poor prognosis patients having a PET scan early after nephrectomy to assist staging and therefore management.

Studies have found PET of use in follow-up and assessment of patients with a history of renal cell cancer who have suspicious lesions of unknown significance

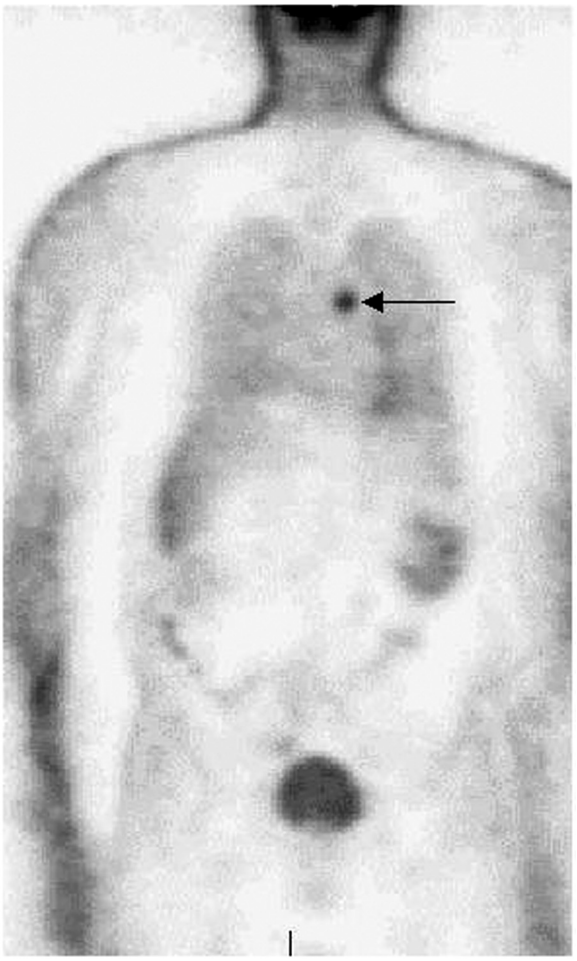

Figure 4 **A patient with known renal cell carcinoma and lung metastases was being treated with interferon. The mediastinal lesions were stable on CT. An FDG-PET was performed to determine if the lesions still contained active disease. The scan shows increased uptake in the mediastinum (arrow) corresponding to one of these lesions seen on CT and indicated active disease.**

identified on conventional imaging. Safaei *et al.*[51] found an accuracy of 89% for identifying such lesions.

Overall it appears that FDG-PET may alter management in some cases of renal cell cancer. It is particularly useful where other imaging particularly CT is equivocal and where CT is limited (e.g. in scar tissue).

Conclusion

For FDG-PET scanning the uro-oncological cancers have been one of the last to be developed and often show poor results. In general, in prostate, bladder and renal cancer, the main place of FDG-PET is as an adjunct to conventional imaging, to be used where conventional imaging is equivocal and more information is needed to make appropriate management decisions. PET appears

to be particularly good at finding more widespread disease, often unsuspected on other imaging. It has a clear advantage over CT/MR in differentiating scar tissue from active disease in treatment fields. The newer tracers particularly [^{11}C]choline and -acetate in prostate cancer hold some promise for the future. Testicular cancer is where PET is of most use in uro-oncology. For the assessment of residual masses and finding disease in the presence of raised markers, it has been found to be very valuable. As with all imaging there is some limit and small disease may be missed. It is also vital in all tumours that the timing of scanning following treatment is understood so that the most accurate result can be obtained.

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