The role of PET in prostate cancer management

RAD Magazine, 38, 451, 19-21

by Dr Benjamin Taylor
Clinical oncology research fellow
e-mail: benjamin.p.taylor@kcl.ac.uk

Professor Gary Cook
Professor of clinical PET
e-mail: gary.cook@kcl.ac.uk

Kings College London Division of Imaging Sciences and Biomedical Engineering;
Guy’s and St Thomas’ NHS Foundation Trust,
London

Overview
The integration of position emission tomography (PET) and combined computed tomography (CT) imaging modalities into prostate cancer management strategies continues apace, with possible roles including:

- identifying and diagnosing prostatic malignancy;
- tumour, nodal and metastatic staging of the disease;
- re-staging disease at the time of biochemical or disease relapse/identifying sites of recurrence;
- prognostication;
- radiotherapy planning.

Diagnosing prostate cancer
The diagnosis of prostate cancer is currently based on the prostate specific antigen (PSA) measurement, digital rectal examination (DRE), and trans-rectal ultrasound scan (TRUS), with guided biopsy for histological confirmation. However, pre-surgical biopsy and the Gleason score of the surgical specimen only correlate in 69% of patients. MRI is used for localised tumour (T) staging, but differentiating benign from malignant disease is fallible, with false positives resulting from inflammation and haemorrhage after biopsy.

Staging prostate cancer at diagnosis and relapse
It is essential to correctly identify, stage (TNM), and perform risk-stratification of prostate cancer, prior to deciding the therapeutic strategy. MRI T-staging is now standard practice, with better soft tissue resolution compared to CT enabling assessment of capsular invasion, peri-prostatic extension of tumour, and seminal vesicle involvement. Curative therapy might be appropriate if imaging excludes metastatic disease. Unfortunately, biochemical relapses after initial radical therapy occur without radiological evidence of disease. Transrectal ultrasound-guided biopsy only detects recurrence in 25-54% of such cases, and is especially poor when PSA values are low. CT has low diagnostic accuracy for localisation of recurrent disease. Imaging developments are therefore needed to assess for local tumour recurrence, nodal relapse and distant metastatic deposits.

PET imaging tracers
The combination of PET images registered with the anatomical detail from a CT scan produces an imaging modality (PETCT) with great sensitivity (from the PET) and specificity (from the CT). "F-FDG PET imaging is well established in current oncological practice, but it has a limited role in prostate cancer. Other radio-tracers target specific cellular metabolic pathways, or cellular receptors, and have the potential benefit of providing functional information about the tumour molecular phenotype. There are many tracers under development, but the PET tracers of cellular metabolic function that have the most robust clinical evidence in prostate cancer include 11C or 18F labelled choline and acetate. 18F-fluoride is a marker of osteoblastic activity, and can provide indirect evidence of bony metastatic disease.

"F-FDG
"F-FDG accumulates in cells with a high glycotic rate, enabling localisation of active tumour cell masses, but also highlights areas of inflammation. Stimulation of the glycotic pathway in hypoxic tumour tissue further increases "F-FDG accumulation. The sensitivity, and usefulness, of "F-FDG PET is limited in prostate cancer due to the low glycotic rate and low tracer uptake of prostate tumours, but also by the urinary excretion and high background uptake within loops of bowel in the pelvis, limiting assessment of the prostate. "F-FDG has been shown to have a similar accumulation in normal prostatic tissue, benign prostatic hyperplasia and carcinoma. If "F-FDG uptake is present at diagnosis, it predicts prognosis. 5,6,12 "F-FDG uptake has been noted to be less than "C-acetate uptake in local prostate disease, but can be greater at distant metastatic sites. 3 "F-FDG PET is less sensitive than bone scintigraphy for identifying bone metastases, and is usually inadequate for assessment of metastatic prostate cancer.

Choline (11C- or 18F-)
Choline is an essential compound for cell-membrane phospholipid synthesis, a process enhanced in malignant tissue. Prostate cancer particularly is associated with increased intracellular transport of choline, and up-regulation and increased activity of choline kinase, resulting in phosphorylation of choline and incorporation into the cell membrane; the higher level of choline in prostate cancer cells has been confirmed by MRI-spectroscopy. The role of choline tracers in T-staging of prostate cancer is not established; PET imaging lacks the necessary image resolution, and the differential uptake between benign and malignant prostatic tissue has yet to be fully characterised. However, a sensitivity of 90.5% and a specificity of 85.7% for the detection of localised prostate malignancy have been reported for "CH-choline PETCT after comparison with the surgical histology; others suggest a lower sensitivity for smaller tumours. The results for nodal staging appear more hopeful. In newly diagnosed patients, a sensitivity and specificity of 60-80% and 96-97.6% respectively have been reported. Nodal analysis (rather than patient-based) shows a lower sensitivity (41-45%), although this is increased to 66% when only nodes ≥4cm are analysed. These studies included a heterogeneous patient group with wide PSA ranges; a low PSA reduces nodal staging sensitivity to 20%. Choline-tracers may prove a useful tool for categorising...
lymphadenopathy rather than a staging tool for subclinical disease. The PET images do, however, provide a systemic review, and incidental bony metastatic disease has been identified in these trials, including early bone marrow involvement not visible of CT imaging.\textsuperscript{20} \textsuperscript{18}F-Fluoride PET achieves bone staging with greater sensitivity.\textsuperscript{24}

**Acetate (\textsuperscript{11}C- or \textsuperscript{18}F-J)**

Acetate accumulation is linked with cellular lipid metabolism, and the acetyl-CoA metabolic pathway. There is little urinary excretion.\textsuperscript{25} There is little evidence reviewing the initial staging of prostate tumours with acetate-PET tracers. Similarly to choline-tracers, some suggest little difference in uptake between malignant and benign prostatic tissue.\textsuperscript{26} Others have been more positive, with suggestion that \textsuperscript{11}C-acetate PET is more sensitive than \textsuperscript{18}F-FDG PET for this use.\textsuperscript{27}

The superiority of \textsuperscript{11}C-acetate PET over current investigations for the detection of recurrent disease has not been established. Most of the studies are hindered by small samples and patient heterogeneity. Albrecht et al demonstrated that \textsuperscript{11}C-acetate PET could identify local recurrence at early biochemical failure (mean PSA = 6ng/ml), but MRI with an endorectal coil was more successful.\textsuperscript{28} MRI approaches might be a more useful investigation in patients at low risk of distant metastatic disease. Kotzerke et al reported that positive \textsuperscript{11}C-acetate PET images can be obtained with low PSA levels (<2.5ng/ml), but TRUS and biopsy was a superior technique for identifying local relapse, except that the PET images identified distant lymph node involvement and/or bone metastases in some patients.\textsuperscript{29} Oyama et al concluded that \textsuperscript{11}C-acetate PET was more sensitive than \textsuperscript{18}F-FDG PET for detecting recurrent disease at PSA relapse,\textsuperscript{30} but the acetate-PET only identified 30% of lesions demonstrated by other modalities, and \textsuperscript{18}F-FDG PET only revealed 9%.\textsuperscript{26}

**\textsuperscript{18}F-Fluoride PET**

In contrast to the metabolic markers, \textsuperscript{18}F-fluoride is not a marker of metabolic tumour activity, but targets the osteoblastic reaction in bone caused by a metastatic deposit. Uptake into bone is related to blood flow and osteoblastic activity, similarly to \textsuperscript{99m}Tc-phosphonate bone scintigraphy tracers, although \textsuperscript{18}F-fluoride has a higher affinity and, as it is not protein-bound, it shows a rapid uptake into bone with almost 100% first-pass extraction.\textsuperscript{31}

\textsuperscript{18}F-Fluoride PET is more accurate in detecting and localising skeletal metastases than bone scintigraphy,\textsuperscript{32} with a higher sensitivity and specificity,\textsuperscript{33} reported at 81% and 93% respectively.\textsuperscript{34} This is, in part, because the spatial resolution of \textsuperscript{18}F-fluoride PET is superior to bone scintigraphy. This advantage is greatest for spinal and pelvic deposits,\textsuperscript{35} and further enhanced by the combination of PET with CT images.\textsuperscript{36}

**Other tracers**

As the knowledge of cancer biology at the molecular level continues to broaden, and targeted cancer therapies become the focus of cancer research, the possibility of labelling metabolic- and receptor-specific ligands with radionuclides for imaging and therapy continues in parallel. Where these imaging modalities fit into the clinical management paradigm has yet to be determined; their role may lie in targeted systemic therapy development, or for the development of targeted radiouclide therapy, rather than routine clinical use.

Prostate cancer is (initially) an androgen driven tumour; androgen receptor antagonists prevent normal translocation. The androgen receptor and signalling axis are potential targets for nuclear imaging, and tracers including \textsuperscript{18}F-\textsuperscript{5a}-dihydrotestosterone (DHTH) (a structural analog of \textsuperscript{5a}-dihydrotestosterone, the principle intra-prostatic androgen) and zirconium-89 (\textsuperscript{99}Zr) based tracers (targeting the prostate-specific membrane (PSMA) antigen), have been developed.\textsuperscript{37} Prostate-specific membrane antigen is a transmembrane glycoprotein that is expressed by most prostate cancer cells, and has increased expression in high-grade, metastatic and castrate-resistant tumours. It is expressed on tumour neo-vasculature but, unlike PSA, it is not released into the circulation.\textsuperscript{41}

Over-expression and amplification of the HER2 gene have been implemented in a number of tumours, and are linked to tumour development, progression, and prognosis; there is increasing evidence of its role in prostate cancer. A number of PET tracers targeting HER2 are in development.

**Summary**

PET imaging for prostate cancer is a continually developing field. \textsuperscript{18}F-FDG tracers have proved of limited value, but development of new functional imaging tracers, including choline and fluoride PET tracers, has demonstrated the potential value, including the initial staging of disease and identifying disease relapse and monitoring therapy. PET imaging could have further roles in targeting radiotherapy treatment, and in targeted drug development. It is likely that PET imaging will become an integral part of prostate management paradigms in the near future.

**Acknowledgements**

Dr Sue Chua, department of nuclear medicine and PET, Royal Marsden Hospital, Sutton.

**References**

29, Vos H, Buchegger F, Albrecht S et al. 18F-choline and/or 11C-acetate positron emission tomography; detection of residual or progressive subclinical disease at very low prostate-specific antigen values (<1ng/mL) after radical prostatectomy. BJU Int 2007;99:1415-20.

**FIGURE 1**
63-year-old patient with metastatic prostate cancer, treated with hormonal therapy, but PSA rising. 18F-choline PET images showing seminal vesicle involvement (figure 1.1), progression in a presacral node (figure 1.2).

**FIGURE 2**
18F-PET of patient with metastatic prostate cancer, clearly demonstrating multiple bony metastatic deposits.