Current status of choline–PET and prostate cancer

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The authors outline the role of the functional imaging technique choline– positron emission tomography in the diagnosis, staging and treatment response assessment of patients with prostate cancer.

Functional imaging techniques are those that image intrinsic physiological and metabolic characteristics of cells and their micro-environment. Such imaging allows quantification of metabolic processes, rather than simply relying on size and morphological criteria. This may provide predictive and prognostic benefits over conventional imaging.

Functional imaging techniques include nuclear medicine imaging methods, with both gamma cameras (including standard bone scans and single photon emission computed tomography [SPECT] scans) and, increasingly, positron emission tomography (PET) scans. Using these technologies it is becoming increasingly feasible to image and measure many aspects of cellular physiology and function, including cellular proliferation, hypoxia, glycolysis, amino-acid transport, expression of membrane antigens and hormone receptors, cell membrane synthesis, bone mineralisation and angiogenesis. PET/CT has become established in cancer decision-making, including diagnosis, disease staging, response assessment and prognostication.

PET/CT

PET imaging uses radioisotopes that emit positrons (antimatter equivalent of electrons with a positive charge) during radioactive decay. Two photons are emitted at 180° to each other in an annihilation reaction when a positron interacts with an electron in the body tissues. These pairs of photons can be detected, and the point of origin can be determined within three-dimensional space; more annihilations will occur in areas within the subject where more radioisotope has accumulated. The underlying biological process being investigated will depend on the compound or ligand that the radioisotope is attached to. Combining PET with CT provides detailed anatomical location to pinpoint areas of radioisotope uptake (Figure 1).

The most widely used clinical PET tracer is 18F-fluorodeoxyglucose (FDG). Although

Figure 1. 11C-Choline–PET scan showing widespread bony metastatic disease (known metastatic prostate cancer) with physiological liver, renal, salivary gland, parotid gland and bowel uptake

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readily taken up into cells in the same way as standard glucose, FDG remains trapped in the cell following phosphorylation. Cells that have a high glucose uptake and phosphorylation will consequently accumulate more FDG than other cells, and in this way many tumour deposits (as well as the brain, kidneys and active muscles) can be identified.

\(^{18}\text{F}\)-FDG imaging of prostate cancer has, however, a limited sensitivity (57 per cent for accurate staging at diagnosis, and 26 per cent for detecting recurrent disease). This is probably because many prostate cancers have low metabolic activity, and most have a low rate of growth. In addition, \(^{18}\text{F}\)-FDG has significant urinary excretion, and this can mask pathological uptake in the pelvis. However, many other tracers have shown imaging benefits in prostate cancer, including fluoride and acetate, although choline-based tracers are currently attracting most interest.

**CHOLINE-PET/CT**

Choline is an essential component of cell-membrane phospholipid synthesis, a process enhanced in malignant tissue. In prostate cancer cells, upregulation of specific cellular transporters and choline kinase results in increased intracellular transport of choline and incorporation into tumour cell membranes (see Figure 1).

Several radiolabelled choline tracers have been developed, including \(^{11}\text{C}\)-choline and \(^{18}\text{F}\)-choline. \(^{18}\text{F}\)-choline has a much longer half-life than \(^{11}\text{C}\) (110 versus 20 min), but \(^{18}\text{F}\)-choline has a greater renal clearance. The shorter half-life of \(^{11}\text{C}\) requires an onsite cyclotron, unlike the \(^{18}\text{F}\)-labelled tracers, which may offer many departments logistical advantages. Much of the preclinical and clinical data have used the \(^{11}\text{C}\)-labelled tracer, but comparable results between the two tracers have been confirmed.

**ROLE OF CHOLINE-PET/CT IN PROSTATE CANCER**

**Diagnosis**

The current literature is conflicting as to the role of choline-PET for localised prostate cancer staging. A sensitivity/specificity of 90/86 per cent has been reported for the detection of localised prosthetic malignancy, but this is dependent on the size of the lesion. Others have reported that choline uptake corresponded to histological localisation of the tumour in fewer than 50 per cent of cases, with a great deal of interpatient variability. Some have not even been able to demonstrate significant difference in \(^{18}\text{F}\)-choline uptake between benign and malignant prostate lesions.

Currently there is not enough evidence to recommend the use of choline-PET/CT as a first-line screening procedure. There may be a role for choline-PET-guided biopsy in high-risk patients with persistently elevated PSA and repeatedly negative random prostate biopsies.

**T-staging**

There is currently no evidence to recommend the use of choline-PET for assessing or predicting the T-stage of prosthetic malignancy. The poor spatial resolution of PET is likely to limit useful visualisation of extracapsular extension. PET-MRI may lead to the use of choline-PET imaging in this area.

**N-staging**

Published data suggest that positive nodal choline uptake is specific (80–98 per cent), but the reported sensitivity is variable (10–80 per cent). A choline-PET scan showing nodal uptake is of clinical value, but a negative scan does not rule out occult nodal involvement, particularly for small deposits (<5mm).

Contractor et al. have shown a significantly better sensitivity of \(^{11}\text{C}\)-choline-PET/CT compared to MRI for nodal staging (p=0.0007), with a higher detection rate including for sub-centimetre nodes (51.9 versus 18.5 per cent).

The sensitivity of choline-PET imaging is related to the absolute PSA level and the PSA kinetics. For low PSA levels, nodal clearance is not necessarily included in standard surgical treatment, denying a gold standard for choline-PET analysis. It is likely that the PSA will be higher at disease presentation compared to biochemical relapse, and therefore we recommend choline-PET only if the PSA at presentation is >5ng/ml, or proceed with an awareness that below this level there will be a low prevalence of nodal disease and an impaired sensitivity of choline-PET imaging.

**M-staging**

When compared with standard bone scintigraphy for detecting skeletal metastases, the specificity of choline-PET/CT is greater (98 versus 75 per cent), but the sensitivity is lower (89 versus 100 per cent). The specificity benefit results from the absence of tracer uptake in chronic degenerative lesions that may be falsely positive on bone scans. It has been suggested that PET/CT imaging can identify bone metastases at an earlier marrow-only stage of involvement, before such disease can be identified on CT imaging.

No evidence has yet shown the superiority of choline-PET over standard systemic staging imaging techniques in establishing the presence of metastatic disease at diagnosis.

**Recurrence**

At disease relapse it is vital to determine if the disease is local (and might be amenable to radical salvage therapy), nodal or distant. Transrectal ultrasound-guided biopsy detects only local recurrence in these situations in 25–54 per cent of patients with biochemical relapse, and is especially poor when PSA values are low. CT has a low diagnostic accuracy for localisation of recurrent disease.

The studies to date evaluating choline-PET/CT have been heterogeneous. Evangelista et al. have published a meta-analysis of 19 studies (1555 patients) examining choline-PET and PET/CT imaging at the time of disease recurrence. They concluded a pooled diagnostic sensitivity of 85.6 per cent (95% CI = 60.6–100 per cent) and specificity of 92.6 per cent (86.4–100 per cent), comprising a nodal sensitivity of 100 per cent (90.5–100 per cent) and specificity of 81.8 per cent (48.2–97.7 per cent), and a prostatic fossa sensitivity of 75.4 per cent (68.9–82.6 per cent) and specificity of 82 per cent (68.6–91.4 per cent).
The benefit of choline-PET imaging is dependent on the PSA, the PSA kinetics, and the initial Gleason stage of the disease.10,13,20–28 Husarik et al.13 reported the sensitivity of choline-PET/CT was 70 per cent with a PSA ≤2ng/ml at the time of the scan, compared with 86 per cent when PSA >2ng/ml. Another group showed a sensitivity of 20 per cent with PSA ≤1ng/ml, 44 per cent for PSA 1–5ng/ml and 82 per cent for PSA >5ng/ml.27 This is likely to be more clinically relevant as the PSA levels at biochemical failure are likely to be lower than for initial disease presentation.

Biochemical recurrence poses a diagnostic dilemma, with the inaccuracy of current imaging modalities. The role of choline-PET/CT in this setting is still being evaluated, and the sensitivity of the investigation depends on many factors, not least the PSA level and the volume of cancer. A positive PET scan result is likely to have more clinical utility than a negative scan for these reasons, and might be of clinical use when clinical uncertainty exists after conventional imaging techniques have been explored.

Treatment response
No evidence yet demonstrates superiority of using choline-PET/CT over standard clinical measures of response to treatment, although it has been shown in small studies that a negative 11C-choline-PET/CT at relapse correlates with a higher disease-specific survival and lower treatment rate,29 and a positive 11C-choline-PET/CT at relapse had a worse freedom-from-recurrence survival.21

Radiotherapy planning
There is increasing interest in using functional imaging to define radiotherapy target volumes; for prostate cancer this lies in with the uncertainty of how best to approach patients with pelvic lymph node involvement. Pinkawa et al.22 have demonstrated the feasibility of using 18F-choline-PET/CT to allow dose escalation using a simultaneous integrated boost during radical radiotherapy, although the long-term survival data from such an approach is unknown. Vees et al.33 combined 99mTc-Nanocoll prostate sentinel lymph node detection using SPECT/CT with 18F-choline-PET/CT in 20 men with high-risk prostate cancer; 40 per cent of patients had nodal involvement outside the standard pelvic radiotherapy target volume, highlighting that this approach may allow for tailoring of the radiotherapy treatment volume.

CONCLUSION
No significant evidence is available yet to support using choline-PET/CT outside clinical trials for differentiating benign from malignant intraprostatic pathology or for assessing the T-stage of primary disease. There is an increasing body of evidence supporting choline-PET for the nodal staging of disease prior to primary treatment, with a good specificity having been identified. The low sensitivity and resulting false-negative rate is likely PSA/PSA-kinetics dependent. Clinically, choline-PET/CT might be of value to patients with equivocal nodes on other imaging modalities or in patients who are considered at particularly high risk; a positive scan is likely to have more clinical bearing than a negative scan.

At the point of biochemical recurrence, choline-PET/CT has shown promise in restaging the patient and identifying localised disease (or excluding distant spread) and is now accepted practice in the UK. There is a good reported specificity but sensitivity is dependent on the PSA/PSA doubling time, and possibly affected by concurrent therapy. Some authors have demonstrated positive choline-PET scans with a PSA <2ng/ml, but the sensitivity is likely lower at these levels. Careful patient selection is necessary, and correlation of findings with other imaging modalities would be currently recommended.

There is no evidence yet to support choline-PET/CT in treatment response assessment, although this is an area currently under investigation. Likewise, evidence of how choline-PET-based radiotherapy planning might benefit patient survival and/or treatment toxicity is currently lacking but an area of active research.

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