Advances in the Imaging of the Prostate in the Setting of Elevated PSA Levels

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Abstract

Mirroring exciting advances in the treatment of prostate cancer, advanced imaging techniques are providing improved detection and staging of this disease. Whereas treatment decisions were previously often made on the basis of probability, more sensitive and specific localisation of disease sites will allow choices that are better tailored to an individual patient’s disease. Multi-parametric MRI and PET/CT, particularly using ligands of the prostate specific membrane antigen receptor, provide improved assessment of the prostate and, in the post-treatment setting, prostate bed and of nodal and distant metastatic disease both prior to definitive treatment of high-risk cases and at PSA failure following definitive treatment of the prostate. PET/CT may also help to select patients for targeted therapies based on prostate specific membrane antigen receptor expression, including emerging radionuclide therapy approaches. As well as localising disease sites, molecular imaging also provides opportunities to better characterise and predict biological behaviour and therapeutic response than current imaging techniques. However, despite great enthusiasm and rapid adoption of these techniques in clinical practice, there is a pressing need to better define their role in selecting, planning and monitoring treatment through further, well designed and validated studies.

Background

Management of prostate cancer is being revolutionised by a range of new therapeutic options, as detailed elsewhere in this Forum. Unfortunately, conventional staging is rather insensitive for other than advanced disease, limiting the precise application of these treatments. Conventional imaging with CT and, to some extent, whole-body bone scan also lacks the ability to characterise disease biology, which can have very significant prognostic implications and be vital in determining the need for and timing of active treatment. While the prostate specific antigen (PSA) is a sensitive biomarker of disease, it doesn’t provide information about the location of disease and only limited information about the burden of tumour.

When prostate cancer is suspected, diagnosis has relied on ultrasound-guided biopsy but false-negative results occur.1 Once the diagnosis of prostate cancer has been made, the choice between active surveillance, radical surgery, brachytherapy, external beam radiotherapy and systemic therapies has been fraught with difficulty due to challenges associated with defining the extent of tumour. CT has limited accuracy for T-staging and N-staging due to low soft tissue contrast and the similar radiologic appearances of normal and involved nodes. CT also has significant limitations for M-staging, particularly with respect to the specificity of sclerotic bone lesions. Whole body bone scanning has higher accuracy than CT for bone disease, but provides no information with respect to soft tissue involvement. Tomographic imaging combined with CT has improved the accuracy of diagnosis of bone involvement in prostate cancer, but it still remains suboptimal.2 Despite an increasingly conservative approach to management of primary prostate cancer, more aggressive treatment of high-risk and oligometastatic disease is also being pursued. Thus, when deciding on treatment, there is clearly need for imaging technologies that provide both more accurate non-invasive staging and improved characterisation of disease biology, whether at initial diagnosis or biochemical relapse. In this review, advances in imaging that may address these needs will be discussed.

The role of advanced imaging techniques in primary staging

Compared to ultrasound-guided biopsy, MRI-guided biopsy has been shown to be more accurate.3 This technique can use ‘cognitive guidance,’ ‘software fusion’ with ultrasound or ‘in-bore biopsy,’ with the
The ability to more accurately recognize DWI as the determinant sequence in diagnosis of cancer involving the transition zone. DWI with generation of apparent diffusion coefficient maps is indicative of cellular density of a tumour and correlates with the aggressiveness of prostate cancer and Gleason score. PI-RADS V2 recognises DWI as the determinant MR sequence in peripheral zone cancer. DCE MRI assesses angiogenesis but delivers little cost-benefit. Spectroscopy can also provide complementary information to DWI but it is not routinely performed due to technical challenges. A pooled study of 14 mpMRI studies (1785 patients) showed an overall sensitivity of 0.78 and specificity of 0.79 for prostate cancer detection with more accurate results in studies with correct use of PI-RADS in studies using less strict criteria. The enhanced soft tissue contrast of T2-weighted MRI compared to CT improves detection of regional nodal involvement but is still limited by size criteria that fail to correctly classify normal size nodes involved by tumour or enlarged nodes that are reactive. Apparent diffusion coefficient measurement can help to increase the specificity for nodal involvement but remains inaccurate for small or necrotic nodes. Contrast agents with specific uptake in lymph nodes increase the sensitivity for nodal involvement but are not approved for use in Australia.

Advanced prostate cancer that has spread beyond the prostate is increasingly being considered for multimodal therapy including local surgery, external beam radiotherapy, androgen deprivation and chemotherapy. This approach is however, controversial and not strongly supported by evidence. The ability to more accurately determine the presence, location and burden of metastatic disease at baseline diagnosis would almost certainly aid stratification within randomised control trials to address this controversy. Whole-body DWI may be a useful technique for evaluating subsequent therapeutic response of bone lesions due to a lack of the ‘flare’ response seen on bone scanning. The long acquisition protocols currently required for mpMRI of the pelvis combined with body DWI makes this a costly investigation.

PET has also been evaluated as a modality for primary staging of prostate cancer because of its relatively rapid whole-body screening capability. F-18 fluoro-deoxyglucose (FDG) PET yielded discouragingly low sensitivity for disease detection in patients with known metastatic disease on conventional imaging. This encouraged development of PET radiotracers with higher affinity for prostate cancer. C-11 choline was one of the earliest. Preliminary studies with stand-alone PET confirmed its utility for N-staging. Subsequently, hybrid PET/CT provided greater opportunity for localising the primary tumour with superior yield demonstrated compared to trans-rectal biopsy. High-grade prostate intraepithelial neoplasia was the most common cause of false-positive uptake. Studies comparing C-11 choline and multi-parametric MRI have yielded conflicting information with respect to relative accuracy, and therefore a combination of these technologies has been recommended. Unfortunately, despite being licenced for use in several countries in Europe, C-11 choline is an impractical radioisotope for routine clinical use due to rapid radioactive decay and is not approved or funded in Australia. The logistic limitations of C-11 stimulated development of fluorinated choline analogues. Our own preliminary study demonstrated that both F-18 fluoromethylcholine (FCH) PET/CT and FDG-PET/CT were more sensitive than conventional staging, but FCH PET/CT provided the highest lesion sensitivity.

Other fluorinated tracers are also continuing clinical trial evaluation. Tracers directed against prostate specific membrane antigen (PSMA) represent an exciting development with significantly higher sensitivity than FCH PET/CT and a high diagnostic yield, even in the setting of low level PSA relapse. A recent Australian publication comparing PSMA and FCH PET/CT in 38 patients supports this finding. Our own experience in over 500 patients suggests that this is a highly sensitive and specific imaging agent, even in patients with low PSA levels. Despite the advantages of generator production of Ga-68 rather than requirement for a cyclotron, the rapid decay of this radionuclide also poses significant logistical challenges. PSMA-binding agents using F-18, Y-86 and Zr-89 (in the form of an immunoconjugate) also look promising.

Whilst FDG PET/CT is insensitive in patients with indolent prostate cancers, there is evidence that it can provide powerful prognostic information by reflecting tumour grade. Through identifying patients with more aggressive disease, it might enable selection of patients most likely to respond to and benefit from chemotherapy.
Evaluation of PSA or clinical relapse after radical treatment

PSA measurement enables early detection of treatment failure following radical treatment of primary prostate cancer. However, it is recommended that contrast-enhanced CT and whole-body bone scanning should only be performed in high-risk prostate cancer in order to optimise the yield with respect to positive studies while ensuring that few men with bone metastases are denied appropriate staging. When patients are found to have persistent or rising PSA levels after definitive treatment, these imaging modalities are often performed without availability of prior baseline studies. If negative, as will be the case in the majority of such patients, local salvage treatment is often contemplated whereas, if localised regional nodal enlargement or a limited number of metastatic sites are identified, more aggressive local salvage therapies, including nodal dissection, wide-field external beam radiotherapy and stereotactic ablative body radiotherapy, are more often being considered. Although supported by only low-level evidence, in selected patients, these salvage treatments directed to nodal recurrence can achieve acceptable oncologic outcomes and may delay the time to systemic treatment with an acceptable safety profile. While the patterns of failure have prognostic implications, the evidence base supporting these treatments is compromised by the inability of current imaging techniques to define the true extent of disease.

Assessment of potential residual or recurrent local disease is compromised by post-surgical changes on MRI and by urinary excretion of many of the tracers used for PET/CT. Nevertheless, most of the existing data supporting the use of advanced prostate imaging techniques have been generated in such patients. C-11 choline PET/CT has particular advantages for detecting local recurrence in the setting of prior prostatectomy due to low urinary clearance, but is also more sensitive for nodal and distant metastatic than CT. Early dynamic imaging of the pelvis using F-18 FCH, prior to appearance of activity in the bladder, can improve detection of local tumour recurrence. Delayed whole-body imaging also has good sensitivity for nodal and distant disease.

PET/CT using PSMA ligands might also be helpful for planning salvage nodal dissection. A recent report has confirmed a high yield of Ga-68 PSMA-binding ligands in the restaging setting. The specificity and sensitivity of PSMA PET, combined with the anatomical detail provided by MRI may be an ideal application for hybrid PET-MRI systems.

Conclusion

Those treating prostate cancer clearly need better imaging tests to select, guide and monitor the effectiveness of therapy. In the restaging setting, imaging is an important complementary tool to assess elevated PSA levels. CT and bone scanning have insufficient sensitivity or specificity for disease detection, encouraging widespread adoption of advanced imaging techniques. This is even in the absence of a robust evidence base to support their use and despite lack of reimbursement. MRI is now used for biopsy guidance and even more widely for primary staging or for the evaluation of PSA relapse. Where available, FDG PET/CT has found a limited role in assessing high-grade disease. However, the most promising developments have been in molecular imaging techniques that offer both high sensitivity and specificity. In particular, PSMA PET/CT is being rapidly adopted. Our early experience suggests this is a major advance, but further research is required to define how to use this information to guide and monitor management. Further, PSMA ligands provide options for therapy based on the distribution of disease identified by PET/CT as an example of theranostics.

We live in exciting times with respect to both the diagnosis and treatment of prostate cancer.

References


