
Imaging approaches with advanced prostate cancer: techniques and timing

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LEUNG D, KRISHNAMOORTHYS, SCHWARTZ L, DIVGI C. Imaging approaches with advanced prostate cancer: techniques and timing. *Can J Urol* 2014;21(Suppl 1):42-47.

Introduction: In conjunction with biomarkers, imaging is an important component of the diagnostic work up and subsequent management of men with prostate cancer.

Materials and methods: The relevant literature was retrieved from a search of MEDLINE with appropriate key words.

Results: Osseous metastases develop in close to 90% of patients with metastatic prostate cancer, thus making bone scans (single photon, using Tc-99m labeled phosphonates) the mainstay of imaging in advanced prostate cancer. Bone scans are limited by their lack of specificity and an unclear relationship between bone scan changes and disease progression or response to therapy.

In addition to Tc-99m bone scans, other technologies that accurately identify sites of active disease would considerably aid castration resistant prostate cancer (CRPC) management. Accordingly, metabolic imaging, cell surface receptor targeting, and magnetic resonance imaging (MRI) are being studied for their role in evaluating metastatic disease. Due to the increasing availability of advanced imaging modalities, the optimal modality and appropriate clinical time point for its use remains unclear.

Conclusion: A number of imaging modalities are currently or imminently available for use in advanced prostate cancer. Future research will focus on the appropriate incorporation of these modalities in prostate cancer management.

Key Words: castration resistant prostate cancer, CRPC, molecular imaging, FDG, NaF, PET, MRI, androgen receptors

Introduction

The focus of this review is imaging in advanced prostate cancer. Imaging to identify cancer in the intact prostate gland is not currently a part of standard of care, and is achieved usually by magnetic resonance imaging (MRI).

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Rising PSA after definitive primary therapy

Typically, after definitive surgical or radiation therapy for primary prostate cancer, patients are followed with serial prostate-specific antigen (PSA). A rapidly rising PSA has been found to portend a poor prognosis,² and the PSA doubling time has been found to be predictive of positive imaging studies, typically bone scans.³

Bone scans, most frequently carried out using single photon scintigraphic imaging of a bone-seeking radiopharmaceutical –technetium-99m linked to a

TABLE 1. Main differences between two imaging modalities

	Bone scan with Tc-99m phosphonate	Bone PET scan with F-18 sodium fluoride (NaF)
Radionuclide	Tc-99m	Fluorine-18
Half-life	6 hours	2 hours
Radiation dose	5 milli Sievert	2.5 milli Sievert
Time for scan	Typically 30 minutes, starting 2-3 hours after injection	Typically 15 minutes, starting 30 minutes after injection
Cost	Approved imaging study	Carried out under NOPR, for Medicare patients; costs variable, typically more expensive than single photon bone scan
Accuracy	High	More sensitive and specific

suitable phosphonate (MDP most commonly) – remain the mainstay of imaging metastatic prostate cancer. Bone scans are typically carried out to identify metastatic disease. Bone is the site of metastases in 90% of patients with metastatic prostate cancer.⁴ The Bone Scan Index, an estimate of metastatic bone,⁵ is a metric that has shown promise as a pharmacodynamic biomarker⁶ and these measurements have been automated with some success,⁷ though the overall technique remains rather cumbersome to use. Sodium fluoride-18 ([¹⁸F]NaF) PET, Figure 1, is generally considered more sensitive than

bone scintigraphy, though comprehensive prospective comparisons are lacking and are now being addressed in a National Oncologic PET Registry (NOPR) trial.⁸ Several small studies have demonstrated the greater accuracy of NaF PET in the detection of bone metastases.^{9,10} In particular, NaF has a higher specificity than conventional bone scintigraphy, leading to its higher accuracy. Table 1 illustrates the main differences between these two imaging modalities.

Computed tomography (CT) is carried out to assess extra-osseous tumor involvement, though bone lesions may also be identified as blastic or mixed lesions. Soft tissue disease is usually nodal, identified using CT scans, and does not contribute much to disease morbidity.¹¹

Identification of disease outside the prostate bed by one or more of the imaging modalities described above leads to systemic therapy. Such therapy is followed with serial bone scans, though these are useful primarily to identify progression of disease. The frequency with which bone scans are carried out is highly variable, based on reimbursement as well as on patient characteristics – elderly patients with underlying bone and joint disease may have confounding results, limiting the utility of the bone scans; usually, bone scans are carried out only when PSA changes are such that treating physicians need objective evidence of osseous metastases.

Imaging of castration resistant prostate cancer

Metabolic imaging

The mainstay of imaging prostate cancer remains the bone scan, either using scintigraphy or PET/CT. However, several molecular agents are being studied, particularly with PET/CT.

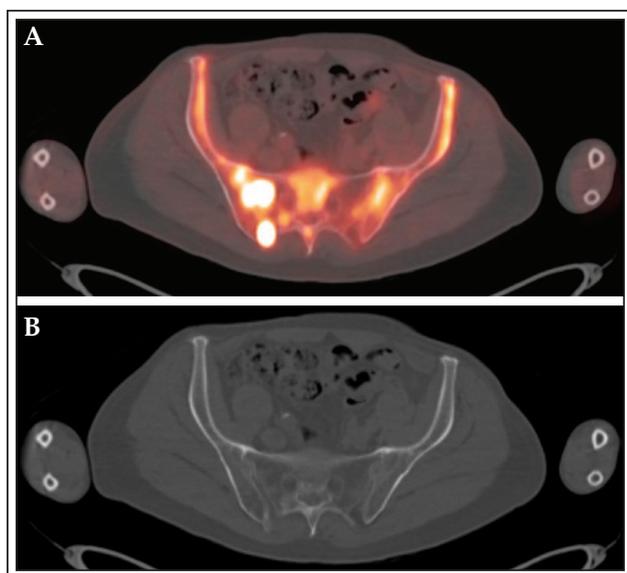


Figure 1. Bone PET with fluorine-18 (F-18) sodium fluoride in a patient with CRPC. The lesions seen on the PET/CT are not always evident on the CT alone. **A.** Fused PET/CT. **B.** CT bone window.

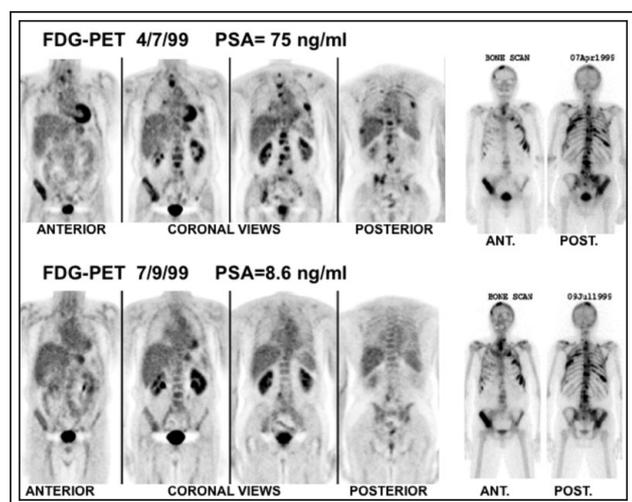


Figure 2. FDG PET and bone scans in a patient with CRPC receiving chemotherapy. Upper panel, baseline images. Lower panel, after 4 cycles of taxane therapy. Note that the lesions seen on FDG PET at baseline have largely disappeared, while conventional bone scintigraphy appears unchanged.

Metabolic imaging with fluorine-18 fludeoxyglucose (FDG) has been studied in prostate cancer, and has been demonstrated to target metastases, particularly in castration resistant prostate cancer (CRPC).¹² Moreover, at least one study has demonstrated that improvement on FDG PET/CT being concordant with PSA decreases.¹³ FDG-avid cancers are probably more likely to be castration resistant, and thus FDG may be useful both for the identification of a castration resistant phenotype as well as a pharmacodynamic biomarker, Figure 2.

PET/CT with radiolabeled choline has been found to be extremely useful in the identification of prostate cancer,¹⁴⁻¹⁶ in the treatment-naïve as well as the castration resistant patient, with no evidence currently of differential phenotype-specific metabolism. Choline is essential to the production of phosphatidyl choline necessary for cell membrane integrity; cancer cell membranes have elevated phosphatidyl choline levels, resulting in increased amounts of exogenous (and perhaps endogenous, detected by MRI) amounts of trapped choline in tumor cell membranes.¹⁴ Initial studies were carried out with carbon-11 labeled choline. An Italian study¹⁵ found that while radiolabeled choline was useful in identification of bone metastases, conventional bone scintigraphy had higher overall accuracy; positron-labeled choline PET/CT therefore is no substitute for bone scintigraphy at this time. The U.S. Food and Drug Administration

(FDA) recently approved a New Drug Application filed by the Mayo Clinic for the production and use of 11 C-choline for PET imaging.¹⁶ It is expected that the agent will have high accuracy in identification of recurrent disease after primary definitive therapy.

The 20-minute half-life of carbon-11 precludes centralized production and distribution of the radiopharmaceutical. Fluorine-18 is a positron-emitting nuclide used for PET, primarily because of its favorable imaging characteristics and its nearly 2-hour half-life. Fluorocholeline has therefore been studied by numerous groups and has been shown to have utility in the detection of recurrent/metastatic prostate cancer.¹⁷ Fluorocholeline has been shown to have better accuracy than NaF bone PET in identification of bone metastases in CRPC.¹⁸

Another metabolic agent that has been studied in prostate cancer has been radiolabeled acetate, a fatty acid. Most studies have reported the use of carbon-11 labeled acetate,^{19,20} and also shown that [11C]-acetate may have better accuracy both in detection as well as in response determination of prostate cancer metastases.²¹⁻²³

A recent review²⁴ provides a comprehensive overview of the utilization of these tracers in prostate cancer, and highlights their characteristics.

Imaging of cell surface receptors

Most prostate cancers are abundant in androgen receptors (AR) at the outset. These receptors may therefore be imaged using a positron-labeled androgen.²⁵ These promising early results by Katzenellenbogen et al led to the clinical exploration of [18F]-labeled dihydroxytestosterone, or FDHT, in the assessment of AR expression in CRPC.^{26,27} These studies have not been developed systematically to assess the utility of this novel hormone receptor imaging agent in CRPC, they have served to illustrate the continuum between AR expression and loss, and its relationship to the "castration resistant" state, in the progression of this disease.

Another receptor that is being increasingly studied in prostate cancer is the prostate specific membrane antigen (PSMA). This transmembrane receptor was first imaged with a single photon emitter, indium-111 linked via a chelate (pendetide) to a murine monoclonal antibody, capromab. Indium-111 labeled capromab pendetide was approved by the FDA for the identification of recurrent prostate cancer after primary definitive therapy.²⁸ However, its relatively low accuracy has restricted its use to those instances where MR is equivocal for prostate bed recurrence, and imaging with this agent is fraught with technical challenges; it is consequently not utilized in most centers.²⁹ It is generally believed that its low accuracy is due partly to the antibody targeting an intracellular domain of the PSMA molecule.³⁰

Bander et al developed an antibody, J591, that targets the extracellular domain, and this antibody, while developed initially as a therapeutic, has shown promise as an imaging agent.³¹ PSMA has several advantages as a target, since its over-expression is directly proportional to the de-differentiation of the prostate cell – it is thus expressed in greater quantities on the castration resistant than in the -sensitive cancer cell.³² While initial imaging studies were carried out with indium-111, with the inherent limitations of single photon scintigraphy, recent reports have suggested that accuracy of detection may improve with PET using zirconium-89 labeled anti-PSMA antibody.³³

Small molecules that target PSMA are also being evaluated. They have shown utility in detection, and an advantage compared to the macromolecular antibody is that clearance is rapid and thus imaging can be carried out the same day with more widely available positron emitters.^{34,35}

Magnetic resonance imaging (MRI)

The lack of widespread utilization of whole body MRI has limited the number of studies that have evaluated the role of this imaging modality in CRPC, Figure 3. More frequent has been assessment of individual lesions, using functional parameters obtained by advanced MRI techniques including dynamic contrast enhanced or DCE MRI, and diffusion-weighted or DW-MRI. Both may have a role as pharmacodynamic biomarkers.

Bone metastases have been evaluated using both these methods.³⁶ DCE MRI has been used to identify marrow

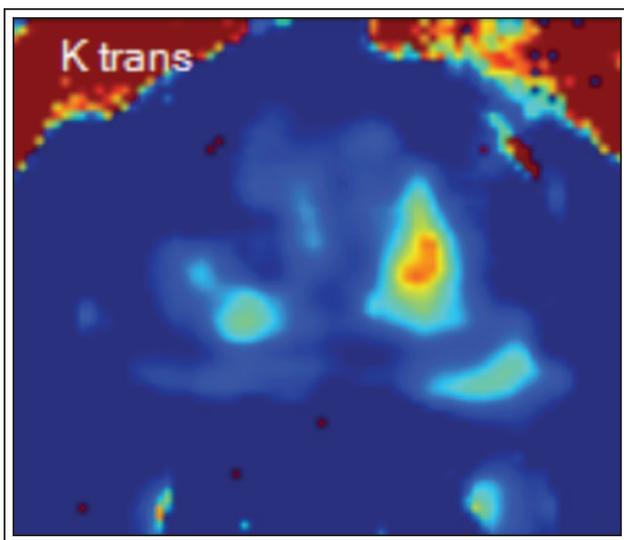


Figure 3. Parametric image of K_{trans} , a measure of vascularity in a prostate. The red area represents a high Gleason prostate cancer.

infiltration by prostate cancer; the abnormal marrow has higher values of a semi-quantitative parameter that measures flow.³⁷ Diffusion weighted imaging has been used both to characterize metastases³⁸⁻⁴⁰ and as a predictive⁴¹ and pharmacodynamic^{42,43} biomarker.

Hyperpolarized nuclei have properties that permit MRI with extremely high sensitivity, and carbon-13 is a hyperpolarized nucleus that has been successfully studied in humans labeled to pyruvate. Hyperpolarized C-13 labeled pyruvate has shown promising results in imaging prostate cancer,⁴⁴ and studies are underway to address its utility.

Timing

When should imaging be carried out? The only consensus document for CRPC in this regard is unclear.⁴⁵ Bone scans should be repeated preferably only after the end of a course of therapy. A bone scan that shows progression may represent a flare response, and thus unless there are multiple new lesions (usually two or more) that persist in a follow up scan obtained at least 6 weeks later, the scan cannot be considered to be progression. Bone scans moreover rarely demonstrate a reduction in uptake intensity or lesion number following successful therapy, and hence cannot be used to reliably document response.

Metabolic and receptor imaging, particularly with PET and MRI, may have an important role in assessment of therapy response. These techniques have been shown to be extremely promising, but there are few studies that have systematically evaluated these novel methods, and the cost constraints of most modern imaging techniques preclude their widespread utilization especially given the low cost of currently available biomarkers for estimation of extent of disease.

Biochemical change is however not rapid. The ultimate value of the novel imaging biomarkers may therefore be not in their utility as pharmacodynamic biomarkers, but as predictive or prognostic of aggressive disease, or indeed as EARLY pharmacodynamic biomarkers. This last may be particularly useful as costly and unnecessary therapy may well be avoided by an early indication of the futility of a particular therapy.

Conclusion

Imaging castration resistant prostate cancer is still in its infancy. In particular, bone metastases remain non-measurable, evaluated by bone scans that are sensitive but not specific. Novel imaging techniques that assess extent of disease in the whole body are limited to molecular imaging, particularly PET/CT. MRI can carry out assessment of individual lesions, with predictive and

pharmacodynamic potential. The development of an accurate imaging biomarker is fraught with difficulties, both economic and logistic. There is increasing necessity, however, for the development of imaging tools that can characterize the cancer phenotype, since imaging permits assessment of lesions throughout the body. Proper application and development of the range of available imaging modalities and techniques will lead to more rapid identification and appropriate modification of targeted therapies in this prevalent disease with a grim prognosis.

Disclosure

Dr. David Leung, Saravanan Krishnamoorthy and Lawrence Schwartz have no potential conflict of interest. Dr. Chaitanya Divgi has received honoraria from Bayer AG and Willex AG. □

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