The emergence of imaging technology in advanced prostate cancer

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Rapid advances in imaging technology have whetted our collective appetites for practical clinical applications to assist the physician and patient in therapeutic decisions. Current limitations of imaging technology are being addressed by the convergence of technology in materials science, the computer industry, and biology which have led to improvements of diagnostic imaging. Refinements in image acquisition, fusion of images, and outcomes data now suggest use for image-guided therapy. Novel imaging agents and technologies appear to provide improved capabilities to detect malignant lymph nodes. Future applications of optical coherence tomography, electron paramagnetic resonance imaging, nanotechnology, and other forms of molecular imaging promise further refinements to enhance our diagnostic armamentarium.

Key Words: prostate cancer, immunoscintigraphy, imaging, optical coherence tomography

Introduction

Despite a shift in prostate cancer demographics at time of presentation from an older population with a higher rate of advanced disease to younger men with smaller volume disease, the critical question of disease extent remains paramount. Our standard tools for initial diagnosis with digital rectal exam (DRE), serum prostate specific antigen (PSA), and transrectal ultrasound-guided (TRUS) biopsy help detect disease but do not allow accurate assessment of disease extent. Accurate prediction of local disease stage is aided by various nomograms based on biopsy information with serum PSA and DRE findings.[1,2] However, prediction of lymph node (LN) metastasis is less accurate because the nomograms only incorporate tissue samples from a limited area of possible lymphatic spread.

It has long been dogma that prostate cancer marches in an orderly fashion from the prostate through a small crossroad of the medial chain of the internal iliac lymphatic system before dispersal through the rest of the body. While this certainly is a common area for lymphatic involvement, this implies that prostate cancer differs from other cancers which follow various metastatic pathways. Yet accumulating evidence suggests that underestimation of nodal disease is higher than previously expected. Modest extension of LN dissection has resulted in a significant increase in patients with metastatic involvement. The potential for increased survival with extended pelvic LN dissection in patients with small volume metastatic nodal deposits is balanced by the 39% (4-year) and 43% (5-year) progression free rates, demonstrating the wider extent of the disease.[3,4] Stratification by risk category is useful for prognostication but nodal involvement is still underestimated even in the low risk prostate cancer population.[4] The same trend for increased positive LN detection is evident in the reports of scintigraphic sentinel LN sampling where over half of the 10% of low risk patients with LN metastases had disease outside of the sentinel nodes.[5] Very telling is a recent study of patients who underwent abdominoperineal resection for suspected LN-positive colorectal carcinoma where perirectal nodes contained prostate cancer in 4.5%.[6] The deep pelvic, presacral, and proximal common iliac LNs are not sampled in either standard or extended pelvic LN dissections.

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Various noninvasive imaging has been used to evaluate prostate cancer patients but the clinical utility of standard cross sectional imaging is limited because a relatively large volume of disease generally is required for detection. This unmet clinical need has spurred the search for new imaging modalities that incorporate molecular processes or tissue characteristics to enhance detection rates and provide further information about specific tumor biological activity.[7]

Conventional cross sectional imaging

The limitations of both computerized tomography (CT) and magnetic resonance imaging (MRI) to detect prostate cancer and nodal metastasis are recognized. Although LN size as a criterion for metastasis has low sensitivity, conventional CT and MRI use size criteria with threshold dimensions of greater than 10 mm in the short axis diameter of an elongated node or 8 mm if the lymph node is round. Sensitivity of CT for LN metastases using size criteria ranges from 25%-78%, with specificity of 77%-98%.[8-11] In one of the few studies with tissue confirmation of radiographic findings, CT sensitivity was 4% in a cohort of intermediate to high risk patients.[12] CT may fail to detect lymphadenopathy because nodes are beneath the size threshold for detection, may contain microscopic tumor deposits without enlargement, or because of technical performance of the scan and interobserver variability in interpretation.[13] When adenopathy is detected, CT does not distinguish between inflammatory and neoplastic involvement.[14] Therefore standard CT is best reserved for patients with clinical stage T3 or T4 disease and for radiotherapy pretreatment planning.[15] CT also remains useful as a conformal study for image coregistration.

Whole body MR imaging for metastatic evaluation has improved with rapid sequence techniques for image acquisition but the limitation of size criteria for metastatic LN detection applies to MRI as well.[16] MRI for LN evaluation is enhanced by an imaging agent comprised of ultra small super paramagnetic iron oxide (USPIO) particles, first reported in a murine model in 1990.[17] The 20 nm hexagonal iron oxide cores coated with dextran (Combidex, Advanced Magnetics, Inc., Boston, MA) are injected intravenously and filtered through the lymphatic system. Normal LNs are laden with macrophages while areas of tumor deposit have very few. High intensity signal is noted in all nodes initially but macrophage phagocytosis in areas of normal LN architecture creates a very dark signal due to the nanoparticle paramagnetic properties and therefore eliminates the high intensity signal on repeat MRI. Nodes with metastatic disease demonstrate continued high intensity signal in areas of tumor. Sensitivity and specificity of MRI with lymphotrophic particles (96% and 99%) were improved compared to MRI alone (29% and 87%) in LNs between 5 mm and 1 cm.[18] Several noncontiguous positive LNs were detected, corroborating previous work that reported up to 17% of patients with a solitary iliac metastasis and 7% to 14% of patients with a solitary presacral or presciatic metastasis outside of the conventional area for lymph node dissection.[19,20] Again, this is also consistent with the findings that even modestly extended lymph node dissection detects unsuspected disease.[3,4] Imaging with this contrast agent is independent of tumor metabolic activity, unlike positron emission tomography, and relies on signal intensity which denotes functional activity regardless of size. This mechanism of functional activity makes this agent useful for many other tumor types in addition to prostate cancer. Unfortunately, this agent is not available for general use at this time.

Positron emission tomography (PET)

Positron emission tomography (PET) measures metabolism of a radio-labeled analog in tissue where the higher metabolic rate of neoplasia registers an increased scintigraphic signal, especially noted in rapidly progressive tumors. Although the most commonly used radiotracer for PET is ^{18}F-fluoro-2-deoxyglucose (FDG), this analog is not particularly useful in evaluation of prostate cancer.[21] In addition to an inability to use PET to differentiate between tumor and hyperplasia, PET is also less sensitive than bone scintigraphy for detection of osseous metastases.[21]

FDG-PET has shown variable results for lymph node assessment and its use may be hampered because of relatively low glycolytic rate in prostate cancer and its metastases.[22] However, some new positron-emitting agents have promise for prostate cancer imaging not solely based on tumor metabolism. Though the mechanism of action is incompletely understood, it appears that ^{11}C-acetate is incorporated into the lipid pool of neoplastic tissues with low oxidative metabolism and high rate of lipid synthesis while choline-derived agents undergo intracellular phosphorylation and incorporation into cell membranes.[23] The ^{11}C-methionine analog is incorporated in intracellular proteins and the ^{18}F-derivative of dihydrotestosterone uses a hormonal-based pathway.[24] The ^{11}C derivatives of methionine, acetate, and choline are also attractive because they avoid renal excretion, unlike ^{18}F-FDG. Therefore, the detection of juxtavesicular disease in the pelvis is not hindered by artifactual signal in the bladder as it is with ^{18}F-FDG.[23] A recent study using PET with

^{11}C-choline yielded a sensitivity of 80%, specificity of 96%, and accuracy of 93% without tissue confirmation in 67 patients.[25] Co-registration of PET images with anatomic CT data improves anatomic localization with many tumors. While encouraging, improvements in PET detection of prostate cancer await further studies and introduction of small high resolution PET scanners for the prostate.

Immunoscintigraphy

Immunoscintigraphy acquires images through use of a radiolabeled antibody that recognizes prostate tissue. Prostate-specific membrane antigen (PSMA) is expressed in prostate cells and upregulated in higher grade cancer, androgen insensitive cancer, and metastatic deposits.[26-30] The most intensively studied monoclonal antibody conjugate to PSMA is capromab pendetide (ProstaScint, Cytogen Corporation, Princeton, NJ) which is a 100 kd type II transmembrane glycoprotein that recognizes an intracellular epitope.[31] Several other candidates have been evaluated, including those to extracellular epitopes, but none have been approved for general use.[32] Despite controversy about the utility of an antibody to an internal epitope and the question of whether this antibody recognizes live tissue, capromab pendetide has been shown to bind to live cells and there are several studies with high correlation of pathological specimens to scan results.[12,33-35]

The pivotal clinical trial demonstrated a sensitivity of 63% (compared to 4% for CT and 15% for MRI) and a negative predictive value of 92% with tissue confirmation of scan results.[12] Despite these encouraging results, capromab pendetide scan results were variable primarily because gamma camera technology was not sensitive enough and, in other cases, areas of high signal intensity could not be localized well enough to anatomic structures. In the last 5 years, however, improvements in image acquisition and processing and the introduction of image co-registration have significantly enhanced resolution and localization. The fusion (co-registration) of the functional single photon emission tomography (SPECT) provided by the 7E-11 radioimmunoconjugate with anatomic images from CT or MRI has made a dramatic difference for prostate cancer detection.[35-37] Localization accuracy has doubled and tissue confirmation of scan results now demonstrate an accuracy of 83% with fused images.[36,37]

The emergence of clinical outcomes data related to PSMA and capromab pendetide scan results strengthens the case for the use of this radioimmunoconjugate. Patients with prostate cancer that overexpress PSMA in the prostate gland have been shown to have twice the recurrence rates and a faster time to recurrence compared to those with normal expression in the gland.[38] Overexpression in the gland was shown to be the only statistically significant predictor of PSA recurrence in 450 patients (aside from actual positive LNs) in a recent study.[39] In a study with similar implications for intraprostatic PSMA expression, correlation of saturation biopsy pathological results with scans revealed an 80% overall accuracy.[40]

The question of high intensity signal on fused scans in areas distant from the prostate is now much more clearly answered as well, Figure 1. First, there is a

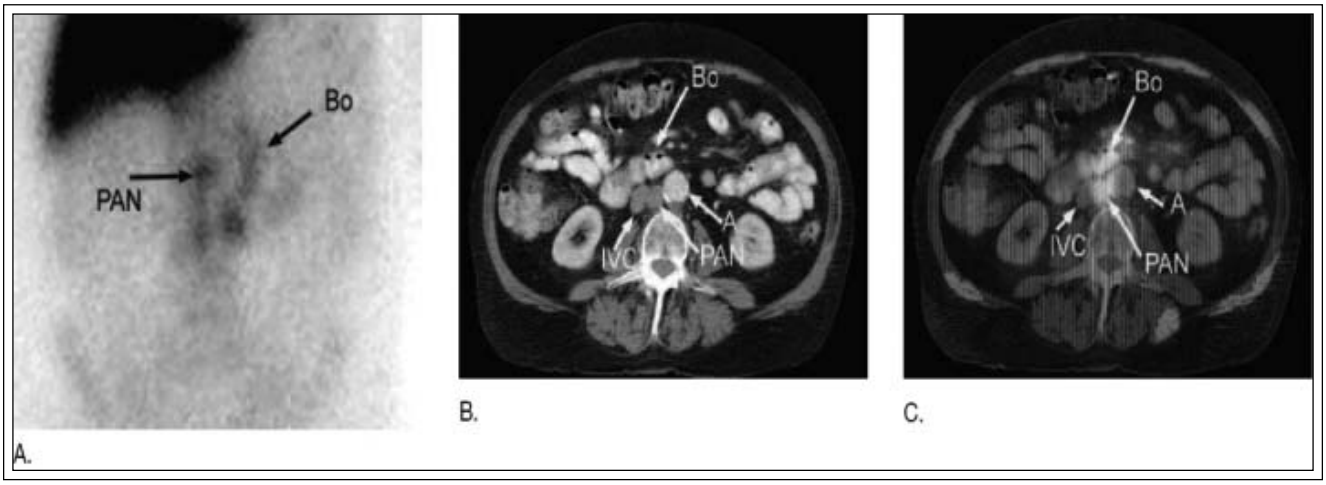

Figure 1. Capromab pendetide and CT scan fused demonstrating high intensity signal in both the intestine, which is the normal excretion of the immunoconjugate, and the para-aortic lymph nodes (PAN). (Courtesy of R. McDonald, MD Anderson Cancer Center, Orlando, FL).

growing recognition that prostate cancer may not progress orderly from the pelvis to the rest of the body which is strongly supported by autopsy data. Two distinct patterns of LN metastasis occur in prostate cancer: the commonly accepted progression from pelvic LNs on to abdominal sites and beyond, and a second pattern with little or no pelvic LN involvement but a predominant central abdominal pattern of involvement.[41] The 7-year follow up data on 239 patients undergoing brachytherapy where fused scans were used demonstrated strongly statistically significant survival for patients with no distant high signal intensity.[42] Patients with the fused capromab pendetide scans positive outside of the pelvis showed a three-fold increase in biochemical disease recurrence regardless of risk category. In another large recently published study, patients with a central abdominal pattern in a cohort of 341 were found to have ten-fold greater prostate cancer-specific death rates than those without such a pattern.[43] These findings were independent of use or timing of intervention with androgen ablation. This suggests that the scan results can be used both to predict better outcomes on the basis of the absence of distant signal intensity.

Patients with a rising PSA after prostatectomy have also been evaluated with capromab pendetide. Reports have shown mixed results with some authors demonstrating a durable complete biochemical response rate to external beam radiotherapy over a nearly 5-year period while others claim there is no advantage for the use of the scan.[44-47] However, studies with no advantage have not used fused images and generally have used older camera technology. In the modern era with fused images from higher resolution cameras, investigators report the value of immunoscintigraphy.[48] These suggest that the fused scans will be more suitable for patient selection and localization for targeted therapy.

The future of prostate cancer imaging: technologies on the horizon

Some quite fascinating imaging technologies are under development with application to prostate cancer imaging.

Electron paramagnetic resonance

Electron paramagnetic resonance (EPR) correlates tumor presence with hypoxia and localized prostate cancer is characterized by marked hypoxia and significant heterogeneity in oxygenation.[49-51] Overhauser-enhanced magnetic resonance imaging (OMRI) combines two spectroscopic techniques, nuclear magnetic resonance (NMR) and electron paramagnetic resonance (EPR) to provide high resolution MR images at low magnetic fields (~ 10 mT). While NMR detects species with magnetic nuclei such as water protons, EPR detects species with unpaired electrons such as paramagnetic molecules. Infusion with the paramagnetic agent before scanning with both the EPR frequency and the NMR frequency yields MR images with high spatial resolution.[50] The very small probes used require about 650-fold less energy than standard MRI. In vivo studies demonstrate that tumor accumulates significant amounts of the contrast agent yet large areas of the tumor are severely hypoxic. This unique, small, portable OMRI technique is capable of providing anatomically co-registered images of oxygen distribution, again demonstrating the value of image fusion.

Optical coherence tomography (OCT)

Optical coherence tomography (OCT) is an intriguing application of reflectance spectroscopy which employs continuous wave light (instead of sound waves) to obtain images in a manner analogous to B-mode ultrasonography. However, OCT does not require a conducting medium and can therefore image through air or water with far greater resolution than ultrasound.[52] Reflected light, generated in the near infrared spectrum by a superluminescent diode, is measured by interferometry to produce two-dimensional images. OCT images tissue *in situ* and in real time, providing resolution on the order of five to twenty microns, which is comparable to traditional confocal microscopic analysis. OCT is relatively inexpensive, portable, and can be used with existing endoscopic instrumentation.[53]

OCT imaging of human genitourinary tissue first occurred in 1997 demonstrating differentiation between the prostatic urethra and prostate, visualization of the neurovascular bundle and the prostate-adipose border, visualization of the prostatic capsule, and differentiation of the anatomic layers in the bladder and ureter.[54] A recent report has demonstrated the feasibility and high sensitivity for determination of early bladder tumor invasion.[55] OCT is currently being used to evaluate effects on prostate tissue from ionizing radiation and to locate neurovascular tissue during radical prostatectomy, Figure 2. Improvements in the ability to obtain OCT images strongly suggest that greater depth of tissue penetration will be possible with greater implications for solid tissue evaluation.

Technology convergence

The very dynamic changes in imaging technology are exciting but translation to clinical application presents obstacles to rapid integration into practice. The real value of these interesting imaging technologies will

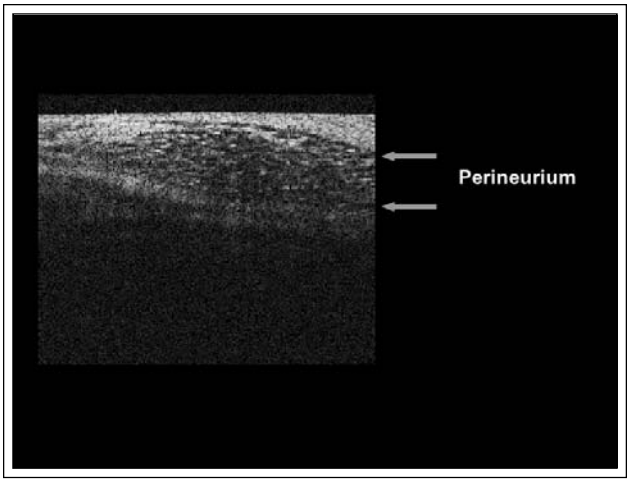

Figure 2. Optical coherence tomography of human prostate neurovascular tissue demonstrating the presence of the nerve in tangential view. (Courtesy of Imalux Corporation, Cleveland, OH).

be the fusion of information from them to provide a composite picture of a biological system and differences in signal in both normal and diseased tissues when perturbed. Fortunately, computer technology currently under development or in use will provide that opportunity due to logarithmic improvements in the ability to process signal. The ability to process the signal in real time and provide that information to the clinician is very intriguing. Capturing the data, combining it with pre-existing image information, and projecting it into the operative field is a worthy goal. We are not far from the day when we can do exactly that. Imagine the combination of archived CT, MRI, and sonographic images, combined with archived or real time immunoscintigraphy, OCT images, and anatomic data from existing databases. Technology to project that information into the surgical field exists currently with three-dimensional images with magnification in a head-mounted display, Figure 3. Image projection using a GPS chip to maintain anatomical position is now possible in a system which provides augmented reality for the surgeon.[56] One can envision a day in the not too distant future where the surgeon can respond affirmatively to the weary joke about "cutting on the dotted line" because of dramatic changes in true image-guided therapy.

Figure 3. Three-dimensional head mounted surgical display into which images can be imported or presented in real time as imaged. (Courtesy of Viking Systems, Inc., La Jolla, CA).

Disclosure

Dr. Michael J Manyak is an employee of Cytogen Corporation. He is on the Science Advisory Board for Imalux Corporation and Endocare. □

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