Imaging in the Diagnosis and Management of Prostate Cancer

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The current diagnosis and management of prostate cancer is largely based on the use of serum prostate-specific antigen (PSA) and pathologic risk factors such as Gleason score and clinical stage. The use of serum PSA in clinical practice has resulted in significant stage migration and, as such, imaging modalities historically utilized to stage prostate cancer are no longer able to reliably identify the small amounts of prostate cancer most often found at presentation. Molecular imaging techniques have focused on improving sensitivity and specificity for cancer detection through knowledge of specific attributes of disease biology. The evolution of imaging techniques has created a new role for imaging in the management of prostate cancer.
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Prostate cancer diagnosis and management has clearly been revolutionized by the clinical inception of prostate-specific antigen (PSA). Its use in clinical practice has allowed earlier detection, superior selection of candidates for curative therapy, and accurate monitoring of patients for relapse. Although PSA levels historically correlate with the presence of prostate cancer, this test provides little information regarding location and extent of cancer. Test limitations include poor specificity in cancer detection, poor sensitivity in detection of

extraprostatic disease at low PSA levels, and poor correlation with disease volume owing to the large contribution by the benign component of the gland.

As prostate cancer is diagnosed at progressively lower levels of serum PSA, clinicians have sought to identify better means of diagnosing, staging, and monitoring patients with the malignancy. The role of imaging in prostate cancer has historically been a confirmatory one. In men with low-risk disease parameters, imaging, which provides little information regarding stage, has generally not been utilized. In the high-risk patient, imaging generally confirms the presence of metastatic disease, but often the absence of disease on imaging does not greatly change choice of therapy or disease-related prognosis.

Technological advances in imaging have created a new role for various tests in the management of prostate cancers. Advances in imaging exploit the biology of the disease, and in doing so, allow more accurate detection of the location, extent, and aggressiveness of the malignancy. In this article, we review the current status of imaging in prostate cancer diagnosis, staging, and the monitoring of recurrence.

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Imaging in the Diagnosis of Prostate Cancer

The current diagnosis of prostate cancer is based on risk stratification by the combination of serum PSA and digital rectal exam (DRE). The vast majority of men presently diagnosed with prostate cancer have normal DRE, and as such, the likelihood of prostate cancer can generally be based upon PSA level. Recent evidence suggests that even at low levels of PSA, a risk for prostate cancer exists.

While a number of imaging modalities have been assessed for the ability to reliably detect cancer in men presenting with abnormalities of DRE or PSA, the routine integration of imaging as a screening tool has failed to gain popularity. Critical in analysis of the clinical value of an imaging modality is the determination of its ability to improve upon the current standard of care. In the case of prostate biopsy, this implies that the test must have the ability to significantly improve the yield of systematic biopsy either as a single modality or in combination with accepted tests such as PSA and DRE exam. Alternatively, a test may be of use if it can, through a high negative predictive value, allow one to do away with or decrease the number of negative biopsies in evaluation.

The use of imaging has historically provided inadequate resolution for identification of small volumes of cancer within the prostate. Efforts to utilize ultrasound for the detection of cancer have demonstrated poor specificity and poor negative predictive value. As such, within the current standard of care, transrectal ultrasound (TRUS) is used largely to guide biopsies rather than to identify the location and extent of cancer.

Newer imaging modalities such as endorectal coil magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI) offer the potential to detect cancers in the prostate. It remains to be seen, however, whether such modalities improve cancer detection rates when compared to systematic biopsy in unselected populations. The use of MRI/MRSI at present may be of value to those men with markedly elevated PSA levels and one or more negative biopsies.

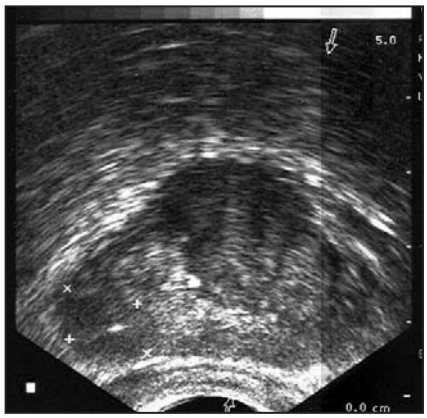

Figure 1. *Transrectal ultrasound (TRUS) demonstrating a right lateral hypoechoic lesion. The patient is a 46-year-old male presenting with a serum prostate-specific antigen (PSA) of 7.2 ng/ml and palpable induration of the right prostate lobe. Biopsy confirms the presence of Gleason 3+3/10 cancer in the right lateral tissue. Although obviously demonstrating a lesion consistent with prostate cancer, the TRUS added little to digital rectal exam (DRE), serum PSA, and systematic biopsy in this case.*

Transrectal Ultrasound (TRUS)

TRUS was initially developed as a means of guiding transperineal biopsies. In the pre-PSA era, it provided apparent superiority over DRE because of its ability to define the extent and location of cancers even in glands that were palpably normal. As biopsies were generally performed only in those patients who were very likely to have prostate cancer, the yield and accuracy of TRUS was quite good. In initial reports, Watanabe and colleagues reported an overall accuracy of 80%.[67] As the test was progressively evaluated, it became evident that cancers of the prostate were most often anechoic or hypoechoic (Figure 1), and so by directing biopsies to such regions instead of areas of capsular

bulge or anatomic distortion, earlier cancers could be identified.

With the advent of PSA screening, the ability to detect small volume, impalpable cancers arrived. As ultrasound abnormalities representing such cancers were often smaller and more equivocal, resulting in higher sensitivity of detection, the specificity and positive predictive value of TRUS declined as a result. Prostatitis and focal infarct have been reported to have the appearance of hypoechoic lesions on ultrasound, yielding a false positive result in a number of cases. Contemporary series report a positive predictive value of 34% when using standard ultrasound alone.[6,8]

Although TRUS often demonstrates hypoechoic lesions representative of cancers, the addition of lesion-directed cores to standard TRUS-guided systematic biopsy has added little yield. In a report by Hodge and colleagues, it was demonstrated that 80/83 cancers could be detected by systematic biopsy alone. Concordance between systematic and directed biopsies was seen in 86% of cancers while the addition of TRUS lesion-directed cores only increased yield by 5%.[1,2]

In recent years, a trend towards increased core numbers at biopsy, lower thresholds of PSA for biopsy, and younger age at screening has resulted in a declining role for hypoechoic lesion-directed biopsies in prostate cancer diagnosis. Although unlikely, in most cases, to identify cancers not detected by systematic sampling, TRUS remains critical for guiding transrectal biopsy as the location of biopsy sampling has become of critical importance in providing adequate negative predictive value (NPV) at the time of biopsy.

Color Flow Doppler/Power Doppler

Attempts to improve the sensitivity and specificity of ultrasound in prostate cancer detection have included color Doppler, power ultrasound, and 3-dimensional (3-D) ultrasound. By identifying areas of increased blood flow relative to the surrounding tissue, one can theoretically identify isoechoic cancers not seen on grayscale ultrasound.[3] Additionally, blood flow characteristics may allow the distinction of cancer from benign lesions within hypoechoic areas.[4]

Reports of color Doppler have revealed mixed results, likely due to differences in patient selection and reader experience. Cheng and colleagues[3] reported on the routine use of color Doppler imaging in 500 patients undergoing biopsy: 11.7% of cancers were identified exclusively by color Doppler, whereas 76.9% of cancers with color Doppler abnormalities were moderately or poorly differentiated.[3] It is unclear what number of cancers found by color Doppler but missed on grayscale ultrasound would be detected by extended core systematic biopsy.

When directly comparing grayscale ultrasound to color Doppler, it is noted that the latter improves specificity, but in doing so decreases sensitivity. When combining the two modalities, a specificity of 97%, NPV of 84%, and positive predictive value (PPV) of 68% have been observed. Sensitivity, however, is reduced to 18%, from 90% for grayscale alone and 82% for color Doppler alone. As such, the use of color Doppler likely mandates concomitant systematic biopsy in order to maximize sensitivity.[5] Whether color Doppler greatly adds to the sensitivity of systematic biopsy alone is not clearly addressed in the literature.

Power Doppler allows detection of flow in smaller blood vessels than conventional Doppler.[6] As such, it theoretically carries a 3- to 4-fold greater sensitivity for areas of increased flow than color Doppler.[7] In a study of 170 men undergoing biopsy, a sensitivity of 98%, an NPV of 99% and a PPV of 59% were seen for power Doppler.[8] The same group eventually compared the performance of DRE, TRUS, and power Doppler in two cohorts from Japan and the US.[9] They observed superior performance of power Doppler in the Japanese men with both a superior sensitivity and specificity. The authors concluded that the power Doppler was of greater use in men with smaller prostates and larger tumor size relative to prostate volume. One could also conclude that operator experience lends greatly to the utility of the test.

Sauvain and colleagues[10] evaluated 282 men undergoing random prostate biopsy under TRUS guidance and compared histology to the results of power Doppler. Power Doppler improved the sensitivity and specificity results when compared to TRUS to 92.4% and 72%, respectively. Importantly, among 72 patients with negative systematic biopsies, 41 were found to have cancer. This suggests that for isoechoic lesions, or lesions not found on systematic biopsy, the use of power Doppler added greatly to cancer detection in this study. The addition of contrast infusion may improve the overall accuracy of power Doppler as well.[11]

In summary, it seems that in experienced hands, the use of color Doppler, and, particularly, power Doppler, may improve the specificity of lesion-directed biopsies compared to grayscale ultrasound. The use of these modalities in addition to systematic sextant biopsy will likely increase overall cancer detection. It remains to be seen, however, whether the use of color and power Doppler will truly add much to extended systematic biopsies of 10 to 12 cores as are currently performed in the US.

MRI/MRSI

MRI has been extensively studied for

its ability to detect prostate cancers. The use of endorectal coil MRI allows better visualization of prostate zonal anatomy and location and extent of tumor within the gland. Patients are imaged with both a whole body scanner with pelvic phased array coil and an endorectal coil, which consists of a magnetic coil placed directly into the rectum. T1 and T2 weighted images are obtained, but cancer visualization is generally performed on T2 weighted images where the cancer appears dark.

The use of MRI alone to detect prostate cancer has been evaluated in a limited fashion. In unselected patients, MRI carries a relatively poor sensitivity, due to a likelihood of isointense lesions on T2 weighted images, and a poor specificity.[12] Not unlike ultrasound, the addition of endorectal MRI to routing systematic biopsy would appear unlikely to greatly enhance cancer detection. In patients with previous negative biopsies and a markedly elevated serum PSA, endorectal MRI may allow an increased ability to stratify the risk of prostate cancer. In a study of 33 such patients, patients were grouped according to low, intermediate, or high risk of cancer on the basis of MRI.[13] At repeat biopsy, cancer was found in 1 of 18, 1 of 8, and 5 of 7 men considered to be low, intermediate, and high risk, respectively. In a prospective evaluation of 38 men undergoing endorectal MRI prior to repeat biopsy, a sensitivity of 83% and a PPV of 50% were reported.[14] Although this exceeded the sensitivity of both DRE and TRUS, it did not exceed the PPV of either. In retrospective evaluation of pathology, the correlation of endorectal MRI to histologic tumor location was poor.

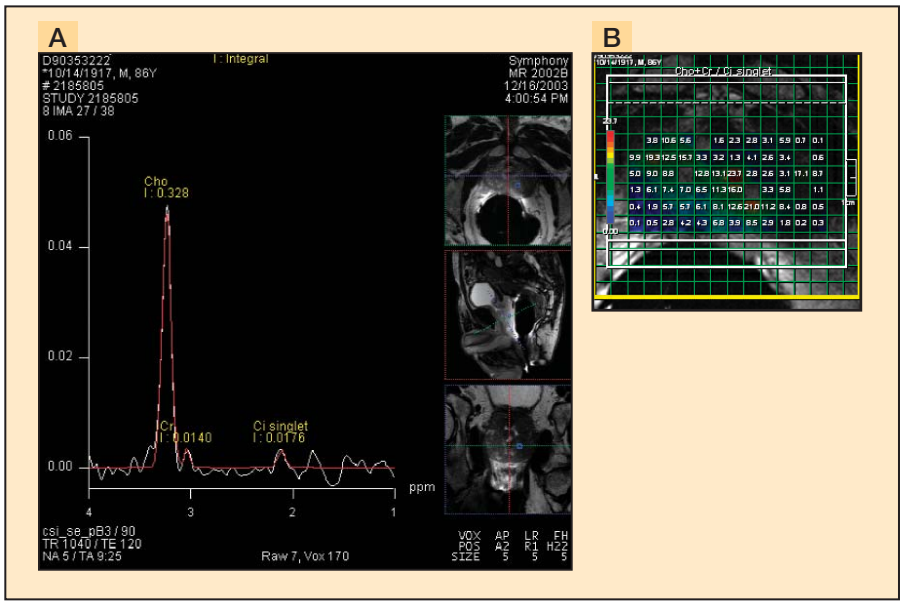

Figure 2. *Endorectal magnetic resonance spectroscopic imaging (MRSI) demonstrating the presence of extensive prostate cancer.* **(A)** *An illustration of the spectral display of metabolites within a single voxel (shown in the inset) of the prostate. In this case, the presence of high choline (large peak) and no citrate confirms the presence of prostate cancer.* **(B)** *Mapping of voxels over the whole prostate demonstrates diffuse cancer as evidenced by choline to citrate/creatine ratios > 0.8.*

In experienced hands, the use of color Doppler, and, particularly, power Doppler, may improve the specificity of lesion-directed biopsies compared to grayscale ultrasound.

MRSI is an MRI technique that attempts to identify cancer through the assessment of tissue metabolites.[15] As the hydrogen protons in different molecules have slightly different frequencies, MRSI provides a spatial map of signal intensity versus frequency as a spectral display of peaks (Figure 2a). Individual peaks are representative of metabolites within the tissue. The spatial mapping of the tissue is provided by analysis of individual areas of the image termed voxels, representing small volumes of prostate tissue (Figure 2b). The characteristic metabolite profile for prostate cancer is one of high choline and low citrate. Citrate and creatine are often combined due to the overlapping of their peaks. Areas of the prostate rich in choline but poor in citrate/creatine are likely representative of cancer (Figure 2b).

The addition of MRSI to MRI improves the accuracy of cancer detection through an increase in specificity.[15-17] In a study of 53 patients with known prostate cancer, MRI and MRSI were compared to step section histology. MRI alone had a sensitivity of 77% to 81% and a specificity of 46% to 61%. MRSI improved specificity to 70% to 80% but reduced sensitivity to 68% to 73%.[16]

On the whole, the addition of MRSI probably adds greatly to the evaluation of men suspected of prostate cancer despite negative biopsies. A clear potential problem of this application is the inability to accurately assess the transition zone for the presence of tumor.[18] As has been shown by many investigators, cancers identified on repeat biopsy are frequently

found in the lateral peripheral zone or transition zone.[19] The use of MRSI prior to repeat biopsy can allow targeted sampling of suspicious areas. As it is not likely or intended to replace systematic biopsy, its use in patients presenting for first time biopsy is limited. In those men in whom systematic biopsy demonstrates no cancer, but whose PSA remains markedly elevated, MRSI, if available, is a valuable diagnostic tool.

Imaging in the Staging of Prostate Cancer

In contemporary series, patients undergoing potentially curative surgery or radiotherapy for prostate cancer have experienced a profound stage shift towards earlier stage disease. As such, in most patients, the ability to accurately stage the disease prior to therapy has become more difficult. Treatment at lower PSA and disease volume inherently implies a much lower likelihood of demonstrable metastatic disease on conventional imaging. It is clearly desirable to accurately stage prostate cancer prior to therapy in order to 1) maximize the likelihood of treatment efficacy, and 2) offer emerging multimodal treatment strategies to patients at high likelihood of treatment failure.

Staging prostate cancer can be divided into local staging, for the purpose of identifying extracapsular extension (ECE), and distant staging, for the purpose of identifying lymph node and bone metastases. Both have the ability to impact greatly upon the selection of treatment.

Distant Staging

Bone scan. Bone scan remains the standard for identification of osseous metastasis. Since the late 1970s radioisotope bone scanning with a variety of isotopes has been demonstrated to provide an accurate means of detecting bone metastases in prostate cancer patients.[20-22] At present, Technetium 99m (99mT)-labeled diphosphonate is generally the isotope of choice. The presence of metastases on bone scan often precedes roentgenographic abnormalities by up to 4 years.[68] It offers greater sensitivity than x-ray, but on occasion must be correlated with MRI or bone biopsy in the event of solitary or equivocal areas of increased uptake.

Disease parameters can be very useful in selecting the appropriate candidates for bone scan, as the yield of the study will be quite low in the majority of patients. The median PSA level at which men with prostate cancer develop bone metastases is 40 ng/ml. In one study, all patients found to have metastases on bone scan had a serum PSA > 40 ng/ml. Several investigators have reported[27] that PSA allows accurate stratification of the risk of bone metastases.[23-31] Therefore, although bone scan remains the study of choice for identifying bone metastases in men being considered for surgery or radiation therapy, its judicious use is advised.

In one report of 521 men undergoing radionuclide bone scan at the time of prostate cancer diagnosis, the mean PSA of those with bone metastases was 158 ng/ml compared to 11 ng/ml in those without bone metastases ($P < .0001$).[23] Similarly, in a study by Oesterling,[25] the likelihood of bone metastases in men with PSA levels < 10 ng/ml was 0.5%. In those with levels < 20 ng/ml, the incidence of bone metastases was only 0.8%.[26] In a recent compilation of 23 studies evaluating bone metastases, bone scan identified metastases in 2.3%, 5.3%, and 16.4% of men with PSA levels of < 10 ng/ml, 10.1 to 19.9 ng/ml, and 20.0 to 49.9 ng/ml, respectively.[31] Albertsen and colleagues[28] reported that the yield of bone scan exceeded 10% only in individuals with PSA > 50 ng/ml or Gleason 8-10 disease and PSA > 20 ng/ml.

Based upon existing data, the use of bone scan has declined in recent years. Clearly, this is impacted, in part, by the observed stage migration of prostate cancer at diagnosis. Cooperberg and colleagues[30] have reported a 63% reduction in the use of staging tests in low-risk patients and a 25.9% reduction in intermediate-risk patients. The same group has previously reported excessive use of staging scans upon review of national trends.[32] While a reduction of test usage is a favorable trend in reduction of overall healthcare costs,[25] the absence of national guidelines makes it difficult for the clinician to adhere to a strict risk-based protocol.

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Computerized tomography (CT)/MRI. Historically, the major application of CT in pretreatment evaluation of prostate cancer has been for the identification of abnormally enlarged lymph nodes. The sensitivity of detection of enlarged nodes depends upon the size threshold utilized for defining abnormal. A fundamental shortcoming of CT in detecting lymph node metastases is its inability to detect architectural changes within normal-sized (< 10 mm) lymph nodes. As the majority of surgically detected lymph node metastases are microscopic in contemporary

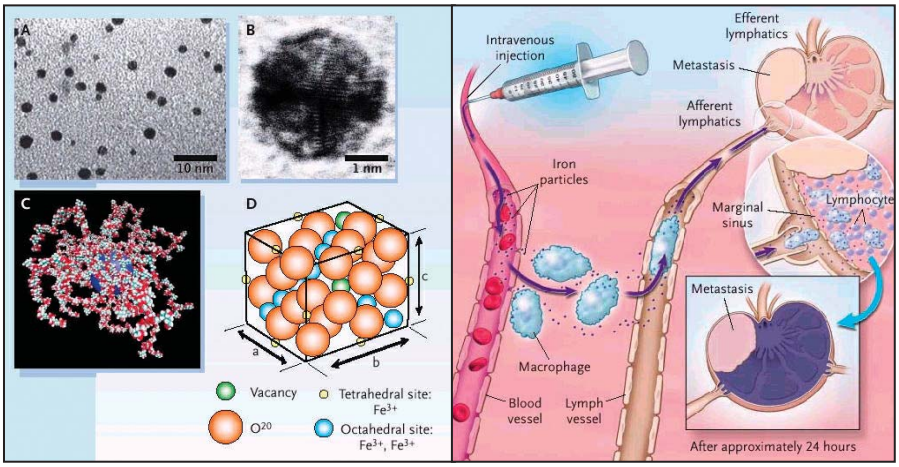


Figure 3. *The systemically injected long-circulating particles gain access to the interstitium and are drained through lymphatic vessels. Disturbances in lymph flow or in nodal architecture caused by metastases lead to abnormal patterns of accumulation of lymphotropic superparamagnetic nanoparticles, which are detectable by MRI. (Reprinted with permission from Harisinghani MG, Barentsz J, Hahn PF, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer.* N Engl J Med. *2003;348:2491-2499.[38] Copyright © 2004 Massachusetts Medical Society. All rights reserved.)*

series, the sensitivity of CT scanning is reduced.

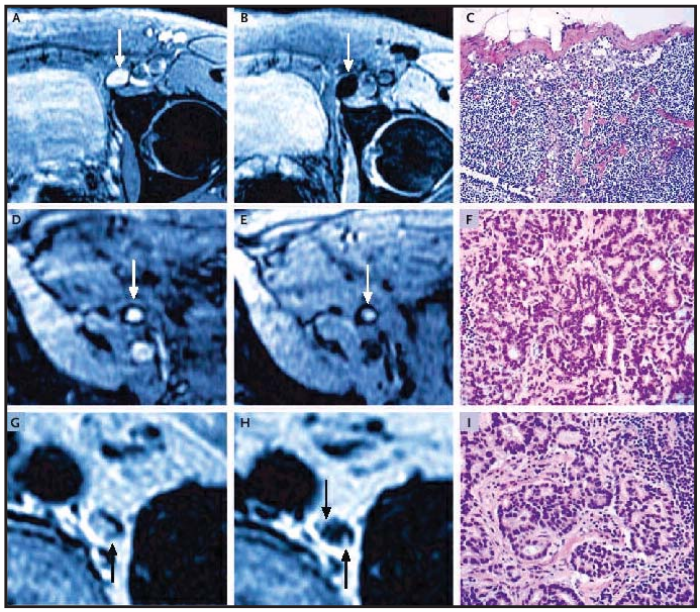
Early series of CT evaluation of lymph nodes demonstrated sensitivity of 14% to 30% in the detection of metastases.[33-35] In contemporary series incorporating patients with smaller volume disease, the likelihood of detecting such lymph nodes is even smaller. The specificity of lymph node detection is affected by the inability to distinguish inflammatory lymph nodes from metastatic lesions when the node is enlarged. Improved accuracy is noted when the size cutoff for abnormality is reduced and the CT is combined with fine needle aspiration. When utilizing such a strategy, authors have reported sensitivity of 50% to 77.6% and a specificity of up to 96% to 100%.[36,37]

MRI for detection of lymph node metastases suffers from similar limitations to CT. While, in some reports, 3-dimensionally (3-D) reconstructed T1-weighted images may define larger foci of metastatic disease within lymph nodes, the inability to discern cancer within smaller lymph nodes remains. In a study of 134 patients with either bladder or prostate cancer, 3D T1-weighted images were used to predict lymph node metastases and correlated to pathologic or cytologic findings. MRI achieved a sensitivity of 75%, specificity of 98%, accuracy of 90%, and PPV of 94%. In 11 patients with metastases deposited in normal lymph nodes, MRI was unable to identify metastatic disease.[69]

Similar to bone scan, the use of CT/MRI for the evaluation of lymph nodes offers limited yield in the vast majority of patients undergoing therapy for localized prostate cancer. Given the low prevalence of lymph node metastases in men with low-risk disease, the use of CT/MRI may be best reserved for individuals with high-risk disease. In a recent review of 25 studies, CT was found to identify lymph node metastases in 0% of men with PSA < 20 ng/ml and in 1.1% of men with PSA > 20 ng/ml.[31] Detection rates rose to 12.5% and 19.6% of patients with Gleason score ≥ 8 ng/ml or locally advanced disease, respectively.

Albertsen and colleagues[28] reported a total positive test rate of 12% for men with PSA between 4 and 20

Figure 4. *MRI nodal abnormalities in 3 patients with prostate cancer. As compared with conventional MRI (Panel A), MRI obtained 24 hours after the administration of lymphotropic superparamagnetic nanoparticles (Panel B) shows a homogeneous decrease in signal intensity due to accumulation of lymphotropic superparamagnetic nanoparticles in a normal lymph node in the left iliac region (arrow). Panel C shows the corresponding histologic findings (hematoxylin and eosin, x125). Conventional MRI shows a high signal intensity in an unenlarged iliac lymph node completely replaced by tumor (arrow in Panel D). Node signal intensity remains high (arrow in Panel E). Panel F shows the corresponding histologic findings (hematoxylin and eosin, x200). Conventional MRI shows high signal intensity in a retroperitoneal node with micrometastases (arrow in Panel G). MRI with lymphotropic superparamagnetic nanoparticles demonstrates two hyperintense foci (arrows in Panel H) within the node, corresponding to 2-mm metastases. Corresponding histologic analysis confirms the presence of adenocarcinoma within the node (Panel I, hematoxylin and eosin, x200). (Reprinted with permission from Harisinghani MG, Barentsz J, Hahn PF, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer.* N Engl J Med. *2003;348:2491-2499. Copyright © 2004 Massachusetts Medical Society. All rights reserved.)*



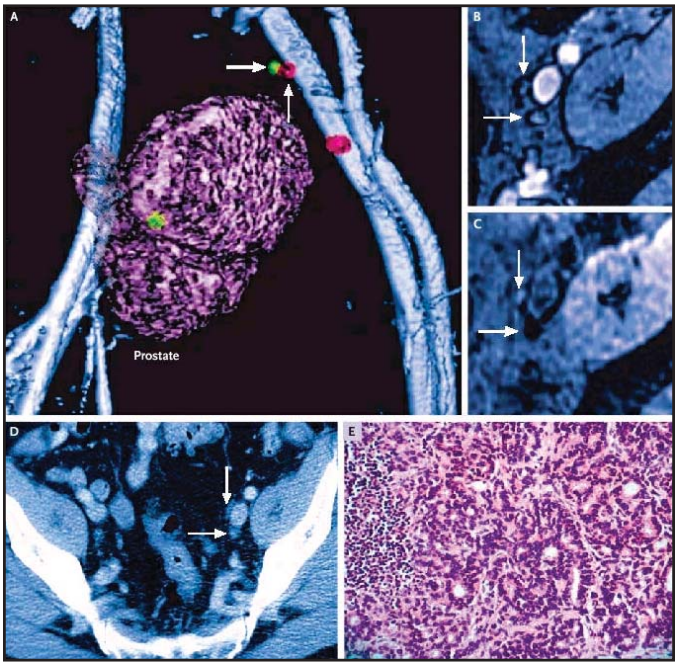


Figure 5. *Three-dimensional (3-D) reconstruction of pelvic lymph nodes (Panel A), conventional MRI (Panel B), MRI with lymphotropic superparamagnetic nanoparticles (Panel C), abdominal CT (Panel D), and histopathological findings (Panel E). Panel A shows a 3-D reconstruction of the prostate, iliac vessels, and metastatic (red) and nonmetastatic (green) lymph nodes, to assist in the planning of surgery and radiotherapy. There is a malignant node (thick arrow) immediately adjacent to the normal node (thin arrow) posteromedial to the iliac vessels. In Panel B, conventional MRI shows that the signal intensity is identical in the two nodes (arrows). In Panel C, MRI with lymphotropic superparamagnetic nanoparticles shows that the signal in the normal node is decreased (thick arrow) but that it is high in the metastatic node (thin arrow). In Panel D, abdominal CT fails to differentiate between the two nodes (arrows). In Panel E, histopathological examination of the malignant lymph node reveals sheaths of carcinoma cells (hematoxylin and eosin, x200). (Reprinted with permission from Harisinghani MG, Barentsz J, Hahn PF, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer.* N Engl J Med. *2003;348:2491-2499. Copyright © 2004 Massachusetts Medical Society. All rights reserved.)*

ng/ml.[28] Clearly the patient make-up of the study cohort predicts the overall risk. This group concluded that yields of > 20% were achieved only in individuals with PSA > 50 ng/ml or Gleason ≥ 8 and PSA 20 ng/ml. Based upon these observations, the overall utilization of CT in pre-treatment evaluation has declined.[30]

Lymphotropic magnetic nanoparticle infusion prior to MRI (Combidex®). As the primary limitation of cross-sectional imaging techniques to identify lymph node metastases is the inability to identify disease within smaller (5 mm to 10 mm) lymph nodes, investigators have attempted to identify molecular means of discerning normal lymphatic tissues from malignant deposits (Figure 3). One such method is the infusion of supermagnetic nanoparticles that reach lymph node tissue through interstitial lymphatic fluid transport. Combidex® (Cytogen Corp., Princeton, NJ) is an investigational agent (ferumoxtran-10) consisting of iron oxide nanoparticles, which, when infused prior to MRI, potentially allow the distinction between cancer and lymphoid tissues within a lymph node (Figure 4).

When tested in 80 men with stage T1-3 prostate cancer, Combidex improved the detection of nodal metastases by high resolution MRI. Of 334 lymph nodes resected at surgery, 63 nodes in 33 men were found to contain metastatic disease on histologic analysis. Only 15 of 33 patients with lymph node metastases were detected by conventional MRI size criteria, while all 33 were detected upon Combidex infusion.[38] Overall, 90.5% of all positive lymph nodes, and 96.4% of metastases in lymph nodes 5 mm to 10 mm in size were identified by Combidex infusion. Only a 5% false positive rate was observed. Given the great promise of the technique to identify metastases even in normal sized (< 10 mm) lymph nodes, the agent is currently under review for approval by the FDA (Figure 5).

Indium 111 capromab Pendetide-Scanning (ProstaScint®). The ProstaScint® (Cytogen Corp., Princeton, NJ) scan utilizes a radiolabeled monoclonal antibody to prostate-specific membrane antigen (PSMA) to identify prostate cancer metastasis. The test is approved by the FDA for the imaging of prostate cancer patients. Patients receive an intravenous infusion of 5 mCi of radiolabeled antibody followed by planar and cross-sectional single photon emission computerized tomography (SPECT). Repeat images are obtained 3 to 5 days later in order to allow wash-out of the isotope from blood vessels and bowel.

The staging ability of the ProstaScint scan has been evaluated by a number of investigators. A fundamental necessity of the scan is experience in the interpreter. As the findings of the study are often subtle, with a high risk of false positive due to bowel or blood vessels overlying the lymph nodes, there may be an improvement in interpretive accuracy as the reader becomes more experienced. In the hands of experienced readers, the scan does appear to offer a valuable tool for staging of prostate cancer.

In most studies to date, the predictive ability of ProstaScint is superior to that of CT/MRI in detecting lymph node metastases prior to therapy.

The importance of reader experi-

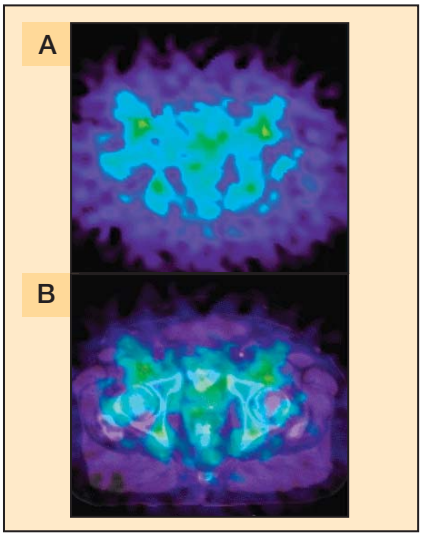


Figure 6. *Patient presenting with localized prostate cancer and intermediate risk features of Gleason 3+4 cancer and serum prostate-specific antigen (PSA) of 13 ng/ml.* **(A)** *Staging ProstaScint® demonstrates uptake in the region of the left prostate lobe and inguinal/iliac lymph nodes.* **(B)** *Fusion of the image with cross-sectional imaging anatomically localizes uptake to the prostate and defines the inguinal uptake as overlying femoral blood vessels.*

ence in interpretation of ProstaScint scans is made evident by the reported data regarding staging. The PPV of the study varies in published reports from 11% to 66.7% in patients selected for radical prostatectomy (RP).[39-42] In those series evaluating high-risk patients, the PPV was improved, probably due, in part, to the increased prevalence of metastatic nodal disease. In most studies to date, the predictive ability of ProstaScint is superior to that of CT/MRI in detecting lymph node metastases prior to therapy.

In a study of 160 men with high-risk disease defined by Gleason score, PSA, and clinical stage, 152 were studied with ProstaScint prior to surgical staging.[59] Of 64 patients with positive lymph nodes, 40 were read as positive by ProstaScint scan (PPV = 62%). Of 88 patients without lymph node metastases, 63 were read as negative by ProstaScint (specificity = 72%). Overall, the sensitivity for detection of lymph node metastases was 62%. In this study, CT and MRI demonstrated PPV of only 4% and 15%, respectively.[59]

Given the poor sensitivity and predictive value of CT/MRI in predicting extraprostatic disease, many clinicians rely upon algorithms or nomograms to predict the risk of lymph node metastases. Polascik and colleagues[70] compared the ability of several clinical algorithms and ProstaScint scans to predict lymphatic metastases in 198 men with clinical T2-3 disease undergoing radical prostatectomy. A total of 39% of patients in this high-risk cohort were found to have lymph node metastases at surgery. From 40.5% to 45.4% of lymph node positive patients were predicted by clinical algorithm compared to 66.7% by ProstaScint alone. When integrating ProstaScint with clinical algorithms based upon Gleason score, disease volume, and pre-operative PSA, a PPV of 72.1% could be achieved. As such, in evaluating patients prior to treatment, the use of ProstaScint scan may be particularly useful in staging individuals in the intermediate- to high-risk category.

In the emerging age of multimodal treatments for prostate cancer, the knowledge of advanced stage prior to therapy might alter decision making regarding choice of treatment.

Although limited by its risk for false positive readings in inexperienced hands, the ProstaScint scan offers a useful tool for detection of lymph node metastases in newly diagnosed prostate cancer. Its use in high-risk disease allows the appropriate selection of candidates for potentially curative therapies. Current efforts to further improve specificity (described below) include fusion of the SPECT acquired images with 3D reconstructed MRI or CT[42] (Figure 6).

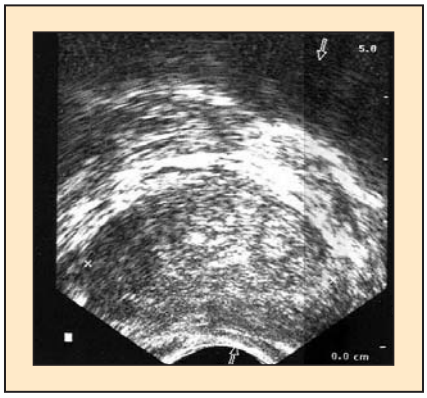


Figure 7. *A staging ultrasound in a patient presenting with a question of locally advanced prostate cancer. The patient is a 63-year-old male with serum prostate-specific antigen (PSA) of 8.2, a palpable nodule in the left prostate, and Gleason 3+4 disease in multiple biopsy cores. Transrectal ultrasound (TRUS) demonstrates cancer extending to the prostate capsule, but no clear extraprostatic extension is seen. At surgical resection, the patient was confirmed to have extracapsular disease.*

Local Staging

In selecting patients for local therapy (either surgery or radiation), it remains highly desirable to provide accurate staging prior to treatment. Individuals with extracapsular extension (ECE), invasion of the seminal vesicles (SV), or large volume disease are at higher risk of treatment failure. In the emerging age of multimodal treatments for prostate cancer, the knowledge of advanced stage prior to therapy might alter decision making regarding choice of treatment.

Currently, best estimates of locally advanced disease are provided by assessment of local disease features such as Gleason score, clinical stage, and pretreatment PSA. Disease volume on biopsy, presence of perineural invasion, and location of tumor within the gland may also, to a lesser extent, predict the likelihood of disease outside the prostate at presenta-

tion. Imaging utilized for pre-operative assessment of disease stage includes TRUS and MRI/MRSI. Both modalities offer the ability to identify ECE, but are heavily influenced by the disease volume and the pretest probability of ECE based on other disease parameters. In individuals with high-risk disease, TRUS may allow localization of SV invasion and can guide biopsy and sampling of the SV for confirmation.

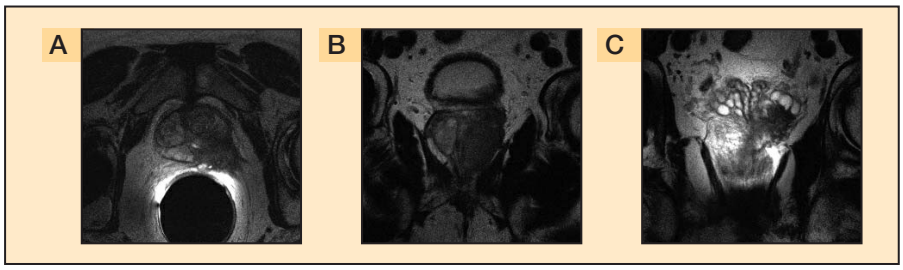


Figure 8. *Staging endorectal MRI at time of prostate cancer diagnosis.* **(A)** *Evidence of left extraprostatic extension with invasion to the region of the left neurovascular bundle. The tumor appears darker than the remainder of the prostate on T2-weighted image. The leading edge of the cancer is irregular and is seen infiltrating into the periprostatic fat.* **(B)** *A coronal section demonstrates cancer within the entire left lobe and significant bulge of the capsule.* **(C)** *The tumor also exhibits seminal vesicle invasion.*

TRUS. TRUS allows the detection of disease extending beyond the prostate capsule only in those cases in which cancer is visible as a hypoechoic lesion. As previously discussed, as a number of cancers are isoechoic or too small for easy detection, TRUS, in these cases, would be of little use in detecting ECE. In a prospective evaluation of 230 patients, TRUS carried a 66% sensitivity and a 46% specificity for the detection of ECE.[44] While the PPV of 63% was favorable, the NPV of 49% was concerning, which suggests little ability to influence decision making. In the same study, TRUS demonstrated a sensitivity of only 22% in predicting SV invasion (Figure 7).[44]

Others have confirmed the relatively poor overall sensitivity of TRUS in detecting ECE.[45-48] In combination with conventional predictors such as PSA, Gleason score, and disease volume, it would appear to add relatively little. In a prospective study of 263 patients undergoing radical prostatectomy, TRUS and DRE were compared to surgical pathology. TRUS staging did not significantly correlate with pathologic tumor volume, and TRUS was deemed no better than DRE for staging.[48]

MRI/MRSI. The local staging ability of whole body and endorectal MRI has been extensively evaluated. Of all modalities, it is clear that endorectal MRI, and now MRSI, have the greatest ability to improve local staging prior to therapy. Difficulties may arise in interpreting MRI due to postbiopsy hemorrhage, and as such it is generally recommended to wait a minimum of 7 to 8 weeks after the biopsy before proceeding with a staging study. As most surgical treatment is generally delayed from 4 to 6 weeks postbiopsy for similar reasons, such a delay should not impact upon disease related outcomes.

MRI as a sole staging modality carries a 22% to 95% sensitivity for detection of ECE, and a 49% to 82% specificity.[44,46,49,50] Overall performance in the detection of SV invasion is worse, with a sensitivity of 28% to 50% and specificity of 88% to 94%. The wide variability is likely due to the lack of clear criteria for ECE as well as the threshold of the reader in calling the finding. In cases of SV invasion, higher specificity is likely reflective of a more clear radiologic appearance of the finding. In defining ECE, most readers look for bulge or irregularity of the capsule, or clear evidence of invasion into surrounding fat or neurovascular bundle (Figure 8). Although capsular irregularity is well defined, its frequent presence is poorly correlated with pathologic findings of extracapsular disease. Among a cohort of 100 men undergoing RP, 28% were found to have capsular irregularity, but only 55% of these were noted to pathologic ECE.[51]

As is the case in other modalities, the low prevalence of ECE in the majority of patients undergoing curative intent therapy results in little usefulness for staging MRI when widely applied. In a multivariate analysis of factors predicting ECE, endorectal MRI was found to be independently predictive of ECE ($P = .0001$) and SV invasion ($P < .0001$) when compared to the use of Gleason score, clinical stage, and PSA.[52] Likewise, the prediction of ECE on MRI appears to predict a higher likelihood of biochemical failure after local therapy.[52-54]

Endorectal MRI and MRSI have the greatest ability to improve local staging prior to therapy.

The key to improving the clinical utility of staging with endorectal MRI may be proper patient selection. In a group of 335 high-risk patients defined by disease volume and PSA > 10 ng/ml, MRI alone carried a 95% specificity and a sensitivity of 69% in the detection of ECE.[58] In a recent study, surgeons assessed the need for neurovascular bundle excision on

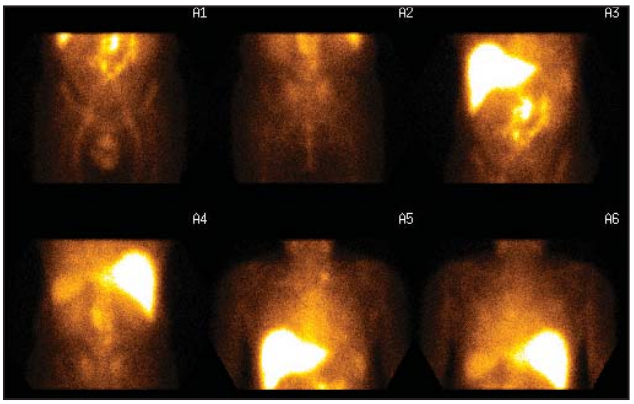


Figure 9. *ProstaScint imaging in an individual with rising prostate-specific antigen (PSA) after radical prostatectomy. Intense uptake is noted in the para-aortic nodes suggesting metastatic recurrence.*

the basis of endorectal MRI among 135 patients undergoing nerve resection.[56] Overall, it was assessed that MRI findings altered the surgical plan with regard to nerve resection in 39% of patients, but in 36 patients considered to be high risk for ECE, the surgical plan was affected in 78%.

The addition of MRSI has improved the staging ability of MRI by allowing better delineation of the extent of cancer and distinction between the cancer and surrounding structures. In doing so, there may be a reduction in interobserver variability, thereby increasing the true utility of the test in general practice. Yu and colleagues[71] demonstrated a 46% to 54% sensitivity, 93% to 96% specificity, and 85% to 88% NPV in the prediction of ECE prior to prostatectomy.

Detection of Recurrent Disease

In patients presenting with recurrent prostate cancer, clinical decision making is essential in both defining the nature of the relapse and selecting the appropriate intervention. At the time of relapse after RP or radiation, patients commonly present with a rising PSA. Clearly, this is representative of local recurrence, metastatic relapse, or both, or may represent residual benign elements in the prostate or prostate bed. Numerous definitions exist for relapse after primary therapy, but within the context of this discussion, the critical element remains defining the nature of the relapse.

In the case of RP, men with rising PSA believed due to isolated local recurrence can undergo salvage radiotherapy as an option for curative therapy. Overall rates of response to salvage radiotherapy suggest that the majority of men with relapse have metastatic disease at presentation. Typically, local recurrence is not identified by local imaging until adequate disease volume for detection exists. Biochemical relapse after RP does not usually occur when serum PSA levels are below 1.0 ng/ml.

While it was previously in vogue to consider fossa biopsy at the time of recurrence after RP, it has been realized that the presence of fossa recurrence on biopsy does not rule out metastatic relapse, nor does negative biopsy rule out isolated recurrence. In fact, those patients likely to respond favorably to salvage radiotherapy would generally not have sufficient disease volume to reliably detect recurrence on biopsy.

As such, although reports of ProstaScint, MRI, and MRSI suggest a promising ability to detect local recurrences after both radiation and surgery, it remains critical to rule out occult metastatic disease at presentation of relapse. Conventional imaging studies such as MRI and CT rarely demonstrate measurable disease upon relapse in the setting of low (< 1.0 ng/ml) serum PSA levels, and as such, molecular imaging studies such as ProstaScint and positron emission tomography (PET) may offer the greatest ability to detect extraprostatic recurrence.[57-59]

As in the case of staging prior to therapy, extraprostatic disease detection is, in part, a function of the experience of the reader, but ProstaScint is able to identify nodes both within the pelvis and retroperitoneal regions (Figure 8). Elgamal and colleagues[60] reported on the follow-up of 100 patients with recurrence after primary therapy and a mean PSA of 55.9 ng/ml. An isolated local recurrence was seen in 42.9% of patients; lymph node metastases were identified in 49%. When tested against the pathologic outcome of lymph node sampling, the test displayed 89% sensitivity and 67% specificity. In a similar evaluation of patients at recurrence, ProstaScint identified extraprostatic recurrence in 42% of evaluated patients.[61] In a larger cohort of patients followed for primary or recurrent disease, ProstaScint outcomes correlated significantly ($P < .033$) with the likelihood of isolated fossa recurrence.[62]

It remains critical to rule out occult metastatic disease at presentation of relapse.

Perhaps the best means of assessing the accuracy of ProstaScint in evaluating local recurrence is in comparing

its outcome to that of salvage radiation. Wilkinson and Chodak[63] evaluated 42 patients with biochemical relapse and proceeded with salvage radiotherapy in 15 who had evidence of isolated local recurrence. The initial and durable responses to radiation were 66.7% and 46.7%, respectively.

In our institution, we have utilized a technique of fusing the ProstaScint scan to a 3-D reconstructed MRI or CT (Figure 6). In doing so, several false positive uptake areas observed due to overlying blood vessels and bowel can be avoided. In our preliminary analysis, the specificity of the test in predicting response to salvage radiotherapy was doubled (Kramer and Taneja, unpublished data). In an evaluation of 58 men with rising PSA after primary therapy, 74 of 161 positive sites prior to fusion were found to be negative. As such, we believe that anatomic localization may improve performance of the test.[43]

PET has been studied in a limited fashion for the detection of occult metastases in patients with recurrent prostate cancer. Its utility appears limited using conventional tracers such as 18F fluorodeoxyglucose.[64] Newer tracers utilizing 11C-choline appear to offer more promise in future imaging of prostate cancer.[65, 66]

Conclusions

Although the imaging of prostate cancer has made tremendous advances in recent years, difficulty remains in identifying small volumes of prostate cancer both in the gland and metastatic sites. The use of molecular imaging techniques such as MRSI, ProstaScint, Combidex infusion MRI, and PET offer a great opportunity to better identify the progression of prostate cancer and progress our understanding of its biology. Careful selection of patients for the appropriate imaging tests is essential and relies upon knowledge of the ability and limitations of each study. In the diagnosis, staging, and monitoring of prostate cancer, the clinical usefulness of a test is heavily dependent upon the prevalence of the desired outcome. Careful assessment of risk, along with training of radiology staff, will allow increasing application of the emerging imaging modalities. Further technological advancement will undoubtedly increase the use of imaging in all aspects of prostate cancer care. ■

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Main Points

- With the progressive downward stage migration of prostate cancer, those imaging modalities historically utilized in diagnosis and staging are of decreasing clinical utility.
- Although prostate-specific antigen (PSA) values correlate well with the presence of cancer, the ability to determine the stage, location, and volume of cancer is relatively poor.
- Innovations in prostate imaging exploit the biology of prostate cancer and thereby offer the potential for superior detection of the location, extent, and aggressiveness of smaller volumes of prostate cancer.
- Despite the fact that endorectal magnetic resonance spectroscopic imaging (MRSI) improves the accuracy of local cancer detection over conventional imaging techniques, it does not greatly improve the detection of cancer over systematic biopsy alone.
- The main application of MRI/MRSI is likely limited to individuals with markedly elevated serum PSA and multiple negative biopsies, and the use of standard bone scan and computed tomography (CT) staging should be limited to individuals at high risk of metastasis on the basis of other disease parameters.
- At lower levels of serum PSA, ProstaScint® scanning offers superior sensitivity to CT/MRI in the detection of lymph node metastases; the infusion of supermagnetic nanoparticles (Combidex®) prior to MRI offer the greatest potential to detect metastasis in even normal-sized lymph nodes.
- In individuals with recurrent disease after local therapy, CT/MRI generally are unable to identify extraprostatic disease, and, therefore, molecular imaging such as ProstaScint and PET scanning may be of greatest clinical value.

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