Imaging Prostate Cancer: Current and Future Applications

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By Ehab A. El-gabry, MD [2], Ethan J. Halpern, MD [3], Stephen E. Strup, MD [4], and Leonard G. Gomella, MD [5]

Various treatment options are available for adenocarcinoma of the prostate—the most common malignant neoplasm among men in the United States. To select an optimum management strategy, we must be able to identify an organ-confined disease (in which local therapy such as surgery or radiation may be beneficial) vs prostate cancer beyond the confines of the gland (for which other treatment approaches may be more appropriate). At present, no standard imaging modality can by itself reliably diagnose and/or stage adenocarcinoma of the prostate. Standard transrectal ultrasound, magnetic resonance imaging (MRI), computed tomography, bone scans, and plain x-ray are not sufficiently reliable when used alone. Fortunately, advances in imaging technology have led to the development of several promising modalities. These modalities include color and power Doppler ultrasonography, ultrasound contrast agents, intermittent and harmonic ultrasound imaging, MR contrast imaging, MRI with fat suppression, MRI spectroscopy, three-dimensional MRI spectroscopy, elastography, and radioimmunoscintigraphy. These newer imaging techniques appear to improve the yield of prostate cancer detection and staging, but are limited in availability and thus require further validation. This article reviews the status of current imaging modalities for prostate cancer and identifies emerging imaging technologies that may improve the diagnosis and staging of this disease. [ONCOLOGY 15(3):325-342, 2001]

Introduction

Adenocarcinoma of the prostate remains the most common malignant neoplasm and the second cause of cancer-specific death among men in the United States.[1,2] For the year 2000, the number of new cases of prostate cancer in the United States is estimated to be 180,400, with 31,900 expected deaths.[1,2] Because early disease is usually asymptomatic, the need for reliable diagnostic modalities to identify patients with early-stage prostate cancer is essential if effective therapy is to be contemplated.

Determining the extent of disease in newly diagnosed patients is another critical issue. More than one-third of patients with apparent clinically localized prostate cancer already have extraprostatic disease.[3,4] Pretreatment identification of this group of high-risk patients is essential for the selection of an optimum therapy.[5] If the disease is confined to the prostate, it could be curable with definitive local therapy such as surgery or radiation. Conversely, if the disease extends beyond the confines of the gland, other treatment approaches may be more appropriate.[6]

Improvements in screening and diagnosing prostate cancer occurred with the use of prostate-specific antigen (PSA) and the development of gray-scale transrectal ultrasound (TRUS) biopsy techniques.[7-10] Years of experience have shown that TRUS-directed biopsy, while very useful, has several limitations.[11-13] Prospective TRUS imaging data have demonstrated that conventional gray-scale TRUS is slightly superior to random chance in detecting prostate cancer.[14] The present trend is to increase the number of biopsies in order to compensate for the limitations of imaging alone.

The traditional lesion-directed biopsy led to the development of the six-core or "sextant" biopsy technique. Today, the trend is to perform 8 to 10 biopsies to more adequately sample the prostate gland. These additional biopsies tend to be laterally directed.[15] This increase in the need for additional biopsies is partly due to current limitations in adequately identifying cancer with noninvasive imaging.

Imaging remains an essential part of specific management approaches to prostate cancer, such as the use of TRUS in prostate brachytherapy and cryotherapy. Imaging modalities used to diagnose
and stage prostate cancer include magnetic resonance imaging (MRI) and computed tomography (CT).[5,6] Bone scans and plain x-rays are used to detect distant metastasis.[6] However, the ability of these modalities to detect and stage prostate cancer is limited.[5]

The need for a more accurate imaging test has led to the development of new imaging technologies for both the diagnosis and staging of prostate cancer. These recent advances include Doppler imaging, contrast imaging,[16-20] MRI spectroscopy, and radioimmunoscintigraphy.[21-31] This article will review and critically assess the current status of prostate cancer imaging modalities, as well as discuss the evolving role of these newer imaging technologies.

**Ultrasound Imaging Modalities**

**Gray-Scale Transrectal Ultrasonography**

The role of gray-scale TRUS as an imaging modality for the prostate was firmly established in the 1980s with the introduction of high-frequency (7-MHz) transducers, the use of real-time ultrasound imaging, the development of biplanar probes, and the clinical applicability of outpatient transrectal biopsy. Gray-scale TRUS is frequently used to guide prostate biopsies (Figure 1) and for the evaluation of a patient with a palpably abnormal digital rectal examination or abnormal laboratory tests suggestive of prostate cancer (eg, elevated PSA). In some instances, TRUS may be used to monitor responses following a prostate cancer treatment in which the prostate was left in situ.

**Limitations of Gray-Scale TRUS:** Although gray-scale TRUS was a major achievement in improving the diagnostic yield of prostate cancer—especially in cases of nonpalpable disease (ie, stage T1c)—experience has shown TRUS to have several limitations. The subjective nature of the exam and the expertise of the clinician may affect the interpretation of images.[13] Interpretation of real-time, gray-scale TRUS images is also restricted by limitations of human visual perception. A recent study[13] showed that an expert user was not able to discriminate among images with more than 32 gray levels out of 256 displayed on a gray-scale image. Therefore, any technical improvement of ultrasound scanners may not always be perceived by human interpretation.

Perhaps the most troubling aspect of standard gray-scale TRUS is the nonspecific, echogenic nature of the tumor itself. Very early studies[7,9] suggested that prostate cancer was associated with hyperechogenicity. Presently, prostate cancer is believed to have an echogenicity that is less than that of normal prostate gland tissue (hypoechoic), with some series reporting 60% to 97% of cases as hypoechoic.[32,33]

Hyperechoic cancers are now considered very rare, and some authors have even questioned their true existence. If present, hyperechoic prostate cancers are usually carcinomas of the comedo type or cancers that have invaded areas of calcification or corpora amylacea. Egawa et al[34] reported hyperechogenic prostate cancer to account for 1.3% of cases in a contemporary series.

Up to 25% of tumors are reported to be isoechoic (the same echogenicity as the normal prostate tissue).[34] Isoechoic tumors are almost impossible to detect because a clear distinction between the tumor and surrounding prostate gland tissue cannot be made on the basis of echogenicity. In such cases, the presence of secondary signs—such as glandular asymmetry, capsular bulging, and areas of attenuation—might prove helpful.

Echogenic discrepancies may again be a useless diagnostic criterion in cases where the tumor diffuses and totally replaces an entire zone or the entire gland. Overall, the presented data suggest that gray-scale TRUS alone is unreliable in diagnosing prostate cancer and must always be performed with a biopsy to evaluate for cancer.

Early studies generated enthusiasm about the role of TRUS in improving the staging of locally advanced prostate cancer.[7] However, this enthusiasm soon faded when other studies failed to demonstrate that TRUS was better than a digital rectal exam for the detection of local extension.[35] The ability of TRUS to detect a neurovascular bundle or seminal vesicle involvement is operator dependent and is associated with a high false-positive rate for seminal vesicle involvement.[5]
In general, an accurate assessment of locally advanced disease is frequently difficult; available ultrasound units do not have adequate resolution to detect the microscopic extension associated with many cases of locally advanced disease. This was reflected in staging studies that reported low predictive values of gray-scale TRUS ranging from 18% to 60%. For these reasons, gray-scale TRUS is considered by most to be a nonreliable tool for staging locally advanced disease.

**Doppler Imaging**

The Doppler shift frequency is an effect that applies to all wave motion. Discovered by Austrian physicist Christian Doppler (1803-1853), the effect refers to a change in wave frequency caused by the motion of a wave source, receiver, or reflector. Acoustic Doppler effect is frequently experienced in our daily life, for example, with approaching and receding sirens or train whistles. Mathematically, this effect is represented by the following formula:

\[
f = 2fv \cos \theta / c
\]

where \( f \) is the Doppler frequency shift, \( f \) is the incident frequency, \( v \) is the flow velocity, \( c \) is the speed of sound in tissue, and \( \theta \) is the angle between the ultrasound beam and flow direction. Simply put, this equation measures the difference in frequency of returning echoes and emitted frequency.

**Principles of Use in Medicine:** Doppler ultrasound is mainly used in medicine to detect the presence or absence of blood flow in vessels, its direction, and its characteristics. In urology, this technology has been frequently applied to detect the velocity of renal blood flow, penile vasculature, and to assess neovascularity in renal, testicular, and prostate tumors.

Flow can be detected either by pulsed-wave Doppler (which displays the frequency shift or velocity as spectral waves) or color Doppler imaging, also known as color-flow imaging. Color-flow imaging provides a two-dimensional (2D), cross-sectional, real-time, color-coded Doppler shift that is superimposed on the real-time gray-scale anatomic display. It displays the range of the mean frequency shift or velocities of red blood cells within flowing blood as colors of the spectrum. Flow toward the transducer is depicted in various shades of red, and flow away from the transducer is characterized by shades of blue.

Normally, the prostate gland should demonstrate symmetrical, low-to-absent color-flow signal intensity, with the periurethral area exhibiting some flow and the outer gland showing minimal to no flow. Several studies have demonstrated that malignant prostate tissue can sometimes be associated with abnormal vascular patterns. Detection of these abnormal blood flow patterns within prostatic tumors is the main application of Doppler ultrasound in prostate cancer imaging.

**Early Clinical Results:** Early results using pulsed Doppler were disappointing, and slightly better results were reported later with the use of color Doppler imaging. Rifkin et al reported their experience in 619 patients in whom color Doppler imaging was used as an adjunct to gray-scale TRUS. Using TRUS biopsies of foci lesions identified with gray-scale imaging or from sites showing flow abnormality on color Doppler imaging scans, they confirmed the presence of 132 cancers in 121 men. A total of 123 men (93%) had corresponding gray-scale abnormalities, and 114 men (86%) demonstrated abnormal flow on color Doppler imaging. Nine patients (7%) showed no obviously identifiable abnormality on gray-scale scanning but had distinctly abnormal flow on color Doppler scanning.

Kelly and associates reported a sensitivity of 96% for TRUS alone and 87% for color Doppler imaging. The addition of color Doppler imaging increased the positive-predictive value (PPV) from 0.53 using TRUS alone to 0.77 but at a cost of reduced sensitivity. In only 1 case out of 158, color Doppler imaging suggested the diagnosis of malignancy independently of TRUS. The authors concluded that color Doppler imaging improves the PPV of TRUS, but has no demonstrable value over TRUS alone in the diagnosis of prostate cancer.
Correlation With Biopsy Findings: Newman and coworkers[50] correlated color Doppler imaging results with the histologic findings from site-specific transrectal core biopsies. In this study, color Doppler imaging had a sensitivity of 49%, specificity of 93%, and PPV of 62%, and was able to detect at least one focus of carcinoma in seven patients with no gray-scale abnormalities. The findings indicated that focal peripheral zone hypervascularity on color Doppler imaging is associated with an increased likelihood of prostate cancer or inflammation on biopsy[50] often without a focal gray-scale abnormality. Although the authors suggested that color Doppler imaging may help identify an appropriate site for biopsy, they stated that a negative color Doppler imaging scan should not preclude biopsy, since it has a limited sensitivity in the detection of all sites of cancer.

Patel and Rickards[51] investigated the discriminative value of the amount of color flow on Doppler ultrasound within the peripheral zone of the prostate. The histologic outcome of 274 guided biopsies was correlated with the grade of color flow on ultrasound hard-copy images. They noted that normal color flow was seen with both normal and abnormal prostate biopsies. Results of the study demonstrated that with the greatest color flow, specificity for the diagnosis of an abnormal prostate (either cancer or prostatitis) is very high, and that with prostatitis, a markedly increased color flow reflects the severity of inflammatory cellular reaction. Nevertheless, the authors concluded that grading the amount of color flow with Doppler ultrasound is of limited diagnostic usefulness.

Predictive Value of Tumor Vascularization: The prognostic significance of detecting an increased flow within a given tumor has also been investigated. Findings of several studies have indicated that tumor vascularization may correlate with its potential for rapid growth and distant metastasis.[44-47] Brawer et al[46] demonstrated that the histologic determination of microvessel density in prostatic carcinoma is an independent predictor of pathologic stage, and, hence, malignant potential.

Thus, quantification of tumor angiogenesis may guide prostate cancer treatment strategies. This issue was partly addressed in a study by Littrup et al,[52] in which cancers with a high color flow had significantly higher mean Gleason scores than cancers without demonstrable color flow, particularly in African-American men.

Our group previously demonstrated that color-coded Doppler flow within the tumor correlates with both tumor grade and stage, and that increased flow is associated with a higher Gleason score and higher incidence of seminal vesicle invasion. Our study findings also indicated that increased flow noted on color Doppler imaging is independently predictive of the likelihood of biochemical relapse following radical prostatectomy.[53]

Drawbacks of Color Doppler Imaging: Although studies suggest that color Doppler imaging has potential prognostic significance, it still has two major pitfalls: overlap with prostatitis and low sensitivity in the detection of tumor blood flow within a prostatic carcinoma. Its failure to detect tumor blood flow may be partly attributed to the fact that the presence or absence of tumor flow may be influenced by tumor size or volume, with tumors smaller than 2 mm in diameter being avascular and those at least 1 cm possessing vascularity.[54] Other technical factors may also contribute to the failure of tumor blood flow detection: (1) The limited spatial resolution on color Doppler makes it difficult to detect blood flow in very small vessels, and (2) low-volume flow results in frequency shifts below the noise level, and consequently, cannot be detected.[13]

Power Doppler: More recently, the amplitude or power of the Doppler shift (known as power Doppler) has been encoded into color Doppler and used to detect flow. The main advantage of power Doppler is its ability to detect slower flow with less reliance on the Doppler angle.[55]

Our group recently compared the accuracy of gray-scale TRUS, color Doppler imaging, and power Doppler imaging in the detection of prostate cancer, and then assessed the influence of operator experience on test results.[14] Our study indicated that gray-scale TRUS and Doppler imaging are minimally effective in prostate cancer detection, that there is no benefit of power Doppler over color Doppler imaging, and that there is no apparent benefit from increased operator experience with Doppler imaging. We did, however, observe that with gray-scale TRUS or Doppler, foci abnormalities were 2.5 times more likely to contain cancer than adjacent tissues with normal ultrasound findings.
While Doppler flow studies may provide some prognostic data, the routine use of this technique for the diagnosis of prostate cancer does not appear to be warranted at the present time.

**Modern Advances in Ultrasound Imaging**

### Ultrasound Microbubble Contrast Agents

Gramiak and Shah first introduced vascular microbubble ultrasound contrast agents in 1968.[56] Using agitated saline injected through a catheter into the ascending aorta during echocardiographic examinations, they noted that the acoustic mismatch between free-air microbubbles in the saline and surrounding blood led to the production of strong echoes within the heart.

Nevertheless, microbubbles produced by agitation are both large and unstable, and they diffuse back into solution within 10 seconds.[57] It was only after the development of contrast agents that were stable enough to last through multiple cardiac cycles that these agents became suitable for further clinical applications such as prostate imaging.[13]

In distinct contrast to gadolinium enhancement in MRI—which appears in the interstitial space as well[58]—ultrasound microbubble contrast agents are confined to the intravascular space.[59] Using microbubbles (of an average diameter of 2 to 5 µm) would lead to a marked enhancement of signal-to-noise ratio and enhanced visualization.[57]

Significant increases in the Doppler signal demonstrated a relationship with bubble concentration in a linear fashion.[60] Some contrast agents demonstrate Doppler enhancement only, whereas others demonstrate both gray-scale and Doppler enhancement. Several vascular ultrasound agents are being studied for their use in prostate imaging (Table 1).

### Contrast-Enhanced Biopsy

To date, only a few studies have investigated contrast enhancement in the human prostate.

**Echogen:** Ragde et al[18] studied the potential benefit of EchoGen (perflanapent injectable emulsion) for improving prostate cancer detection, especially in patients with rising serum PSA levels and prior negative biopsies. The study consisted of 15 patients, all of whom had rising PSA levels, with 14 patients showing a prior negative biopsy. Color Doppler TRUS was performed before and after the administration of Echogen, with correlation of sextant biopsies. Abnormal microvessel patterns were noted in eight patients, two of whom proved to have malignancies and two, benign tissue. One patient was diagnosed with prostatitis, and false-negative results were observed in three patients.

**Levovist:** Watanabe[19] reported the use of the contrast-enhancing agent Levovist in nine cases of prostatic cancer. In their study, blood flow images were enhanced in all cases. In cases of localized cancer, blood flow images were clearly visualized in the cancer lesion. In both studies, the authors concluded that contrast color Doppler imaging is a promising technique that may allow for better imaging of blood flow and a more accurate detection of early malignant lesions.

Bogers et al[20] was the first to report on the use of contrast-enhanced, three-dimensional (3D) power Doppler angiography in the human prostate. Using Levovist as a contrast agent, 18 patients with suspicion of prostate cancer were evaluated. In this study, sensitivity of the enhanced images was 85%, compared with 38% for unenhanced images and 77% for gray scale. Both enhanced and unenhanced images had a specificity of 80%. Of the six patients who showed no B-mode abnormalities, four patients were judged to have abnormal prostatic vascular patterns, of which three were malignant. Findings of the study indicated that contrast-enhanced power Doppler and 3D image reconstruction are useful imaging tools that have considerable potential for improving prostate cancer detection in the future.

**Imavist:** We have recently reported the results of our initial experience using Imavist (formerly known as Imagent) as a prostate contrast agent.[61] A total of 26 subjects with an elevated PSA
and/or abnormal digital rectal examination were studied. Continuous gray-scale, intermittent gray-scale, phase-inversion gray-scale, and power Doppler sonography of the prostate were performed and correlated with sextant biopsy results. Our study demonstrated a significant visible enhancement ($P < .05$) after the administration of Imavist.

**Limitations of Contrast-Enhancement Imaging:** In general, two issues may be considered limitations of contrast-enhancement imaging: time and cost. The additional examination with a contrast agent increases the standard TRUS examination time. It is also relatively more expensive than standard TRUS imaging, with an average cost of approximately $75 for ultrasound agents.[20] Nevertheless, contrast-enhanced prostate imaging appears to be a promising technology. Further research is needed to fully investigate its potential for improving the early detection of prostate cancer. A contrast-enhanced ultrasound image is demonstrated in Figure 2.

**Intermittent Ultrasound Imaging**

Adequate enhancement of ultrasound imaging using microbubble contrast agents can only be achieved if these agents can safely traverse the tumor neovascularity without being destroyed. Unfortunately, conventional ultrasound systems frequently deliver power levels that are sufficient to destroy microbubbles. A potential solution to this problem is the use of intermittent imaging, also known as transient-response imaging. Studies have demonstrated that intermittent imaging increases the enhancement provided by the ultrasound contrast agents.[62-64] Enhancement with intermittent imaging is dependent upon flow rate, acoustic power output, and frequency of insonation.[65]

A conventional gray-scale ultrasound image is refreshed at 30 frames per second. Thus, the amount of contrast agent available for each frame is that which enters the imaging plane in one-thirtieth of a second. This short period of time is usually not sufficient for contrast agents to enter small diameter vessels. With intermittent imaging, the ultrasound beam is turned off for longer periods between each frame, thereby allowing more contrast material to enter the imaging plane during the interscan period. This technique also provides more time for the contrast agents to traverse further into the capillary bed. Thus, intermittent imaging demonstrates a quantitative increase in contrast enhancement, as well as a qualitative difference in the enhancement pattern that may be related to contrast in smaller vessels (Figure 3).

Findings of our initial experience[61] with 26 subjects indicated that intermittent imaging might provide enhanced visualization of the prostate cancer neovascularity. Two patients in our series demonstrated a clear enhancement of tumor foci that were not detected by conventional gray-scale TRUS and Doppler imaging.

**Harmonic Imaging**

Harmonic imaging is another advance in contrast-enhanced ultrasound imaging.[66-68] When contrast agents are imaged with ultrasound, the reverberations created by the microbubble may resonate at frequencies that are different from the insonating frequency. Various harmonics of the insonating frequency are produced by the contrast and can be imaged. Normally, ordinary tissue would reflect ultrasound at the frequency of insonation, and thus, most harmonic signals are reflected by the contrast agents. This leads to a reduction of background signal from surrounding structures and improves contrast material imaging.

Our group is investigating the combination of intermittent imaging with wide-band harmonic imaging. A combination of these two modalities is expected to yield an improved signal-to-noise ratio for visualization of the neovascular bed.

**Magnetic Resonance Imaging**

The mechanism of MRI is primarily based on the nuclear properties of the human body’s hydrogen ions, which have a nucleus that consists of a single proton. All nuclei with an odd number of protons generate a small magnetic field with a particular vector that is randomly oriented. When a strong
magnetic field is applied, the nuclei of the hydrogen ions align in a parallel or antiparallel fashion to the applied field. Once in alignment, a radiofrequency coil antenna applies a pulse of energy that generates a higher potential energy state of the nuclei. When the radiofrequency pulse stops, the nuclei return to their original energy level after emitting the absorbed energy. This energy is received by the coil and transformed into an image pattern.

The MRI pulse can be manipulated to provide maximal tissue contrast based on proton density, T1 and T2 times, and pulse duration,[69] where T1 and T2 refer to the time constants that describe magnetic relaxation (return of the excited ions to their previous equilibrium). The degree of contrast depends on the distance between the coil and the tissue that is being imaged. The recent development of endorectal surface coils has significantly improved imaging capabilities by decreasing this distance.[70]

On T1-weighted images, the prostate has a homogeneous appearance with intermediate signal intensity. The zonal anatomy of the prostate, however, can be well demonstrated on T2-weighted images. The peripheral zone has a higher signal intensity because of the larger proportion of glandular elements. The central zone shows a lower signal intensity because of the higher proportion of striated muscle and connective tissue storm. The transitional zone has a signal intensity similar to the central zone and thus differentiation between these two zones is primarily based upon anatomic location.

**Conventional Body Coil MRI**

Approximately 70% of prostate cancers arise in the peripheral zone. Detection of prostate carcinoma with MRI is limited primarily to these tumors. In 1991, Carter and associates[71] conducted a study to define the role of body coil MRI in detecting nonpalpable tumors of the prostate. Body coil MRI showed a sensitivity of 58% and a specificity of 48% in detecting nonpalpable prostate tumors. Nevertheless, it had a sensitivity of 85% for anterior, nonpalpable lesions. However, in the same study, body coil MRI was 96% sensitive in detecting palpable cancers. Its inability to detect central-gland tumors and small tumors might explain its lower sensitivity and specificity in detecting nonpalpable lesions.

Other studies have attempted to differentiate between benign prostatic hyperplasia (BPH) and prostate cancer using body surface coils.[72-74] Studies have generally shown that body coil MRI is not a reliable tool in differentiating BPH and organ-confined cancer.[73,75] Quint et al[76] measured tissue optical density on whole-mount prostate sections in a study of 28 patients who had undergone a preoperative MRI examination. A total of 30 lesions were identified as cancer on MRI (on the basis of low signal intensity [SI] on T2-weighted images). However, only 21 lesions proved to be cancer, with 9 representing benign tissue. Additionally, a pathologic examination revealed 31 cancers, of which preoperative MRI had missed 10.

**Body Coil MRI to Delineate Stage:** A number of published studies have reported on the capabilities of body coil MRI in differentiating stage B from stage C disease. Schiebler et al[77] conducted a study of 100 patients who underwent radical prostatectomy. In this study, they compared preoperative MRI readings with postoperative step-section pathology findings. The criterion for extracapsular disease was the presence of low T2 SI disease that transgressed the capsule or periprostatic venous structures adjacent to the peripheral zone; the criterion for seminal vesicle invasion was low T2 SI in the seminal vesicles. Since the presence of hemorrhage has been considered a confounding factor in interpreting MRI images of a previously biopsied prostate tumor, the T1 scan was used as a check to exclude the possibility of hemorrhage being responsible for the low T2 seminal vesicle SI.

Results of the MRI images were interpreted by four radiologists. Pathologic examination of the whole-mount prostate sections revealed extracapsular disease in 61% of patients, with 20% of these having more than a 3-mm penetration. An overall agreement of 70% was found among the four radiologists. The overall accuracy of detecting stage C disease was only 55%, just slightly more than a chance guess.

The same group conducted a further analysis of the same patient population data,[78] comparing
the efficacy of preoperative PSA value and MRI in identifying stage C adenocarcinoma. In this study, they found no statistical significance between the two parameters. Thus, preoperative PSA measurement is equivalent to body coil MRI in staging stage C prostate cancer. In another study by McSherry et al,[79] body coil MRI proved to be a poor staging modality with a predictive value of 30% for organ-confined tumors and 66% for extracapsular disease. Both these results were lower than that obtained by digital rectal examination and TRUS.

**Body Coil MRI to Determine Tumor Volume:** Since the correlation between tumor volume and disease stage has been reported in several studies,[80-82] Quint and associates[76] have reported their experience using body coil MRI for tumor volume determination. Using a voxel summation technique, they compared preoperative MRI tumor volumes to pathologically outlined tumor volumes. The pathologist also noted the presence of extracapsular disease. In this study, body coil MRI predicted the pathologic tumor volume in 10% of cases (only 2 of 20). Seven tumor volumes were overestimated by 50%, while another five were underestimated by 50%. As a consequence of the false-volume estimation, a marked overlap was noted between MRI tumor volume ranges and the presence of extracapsular penetration.

Using external phase-array coils with a fast spin-echo technique, Sommer and associates[83] reported a better correlation between MRI predication and pathologic mapping ($P < .001$). However, the authors stated that this correlation would still be unacceptable as a reliable base upon which to make clinical decisions.

**MRI to Detect Neurovascular Bundle Invasion:** Determining neurovascular bundle invasion is another factor to take into consideration if curative surgery is chosen; an attempt to spare the nerves should not be made if the neurovascular bundle is invaded by the tumor. Tempany and associates[84] conducted a retrospective study to investigate the role of MRI in evaluating the status of neurovascular bundle invasion. Using T1 weighting to assess the periprostatic fat plane and outline the neurovascular bundle, and using T2 weighting to identify prostate cancer, the accuracy of MRI evaluation of neurovascular bundle invasion was 64%.

In a large, prospective, multi-institutional analysis,[35] the Radiological Diagnostic Oncology Group (RDOG) reported a specificity of 57% for MRI for the prediction of gland-confined disease, a sensitivity of 77% for extraglandular disease, and a sensitivity of 18% for detecting seminal vesicle invasion, with an overall staging accuracy of 69%.

**MRI Enhancements:** In a trial to further enhance MRI prostate imaging, Kier et al[85] investigated the advantage of combining fast spin-echo pulse sequences with a pelvic phased-array multi-coil. Image quality obtained with the combination of the fast spin-echo sequence and the multi-coil was judged to be superior to that obtained with either the conventional spin-echo sequence and the multi-coil or the fast spin-echo sequence and the body coil MRI. This finding led the authors to conclude that fast spin-echo imaging with a pelvic phased-array multi-coil may obviate an endorectal coil for the detection, localization, and staging of prostatic carcinoma. Other new MRI technologies, such as the endorectal surface coil, fat suppression, and MRI spectroscopy, were also investigated for their value to improve the overall role of MRI as an imaging tool for prostate cancer.

**Modern Advances in MRI**

**Endorectal Surface Coils**

High-resolution images of the prostate provided by endorectal MRI[70,86] have led many authors to investigate its potential in improving the accuracy of MRI of the prostate. In a comparison of retrospective, blind readings of endorectal coil and body coil images, Schnall and colleagues[87] reported a 16% improvement in accuracy of staging prostate cancer with endorectal coil images (Figure 4).[87-91] Another study by Chelsky et al[92] showed an overall staging accuracy of 68%, a 74% accuracy rate in staging advanced disease, and a 91% accuracy rate for depicting seminal vesicle involvement. Failure to recognize microscopic extracapsular disease was responsible for the majority of staging inaccuracies in this study.
**Detecting Extraprostatic Extension:** Our group assessed the accuracy of using several criteria to evaluate endorectal coil MRI for extraprostatic extension in 30 patients with prostate cancer.[93] Blinded images were interpreted by several experienced readers, and their evaluations were compared with whole-mount pathologic findings. Our data indicated that the sensitivity and specificity were generally low for the diagnostic criteria that determined extraprostatic extension. The usefulness of endorectal coil MRI in staging prostate cancer may be limited by the lack of diagnostic signs that uniformly identify extracapsular penetration.

**Inversion-Recovery Sequences:** The value of inversion-recovery sequences in the diagnosis and staging of prostatic carcinoma with MRI was investigated by Parivar and colleagues.[94] A total of 26 patients with carcinoma of the prostate were imaged with an endorectal surface coil, a variety of inversion-recovery sequences, and a set of spin-echo sequences for comparison. The authors concluded that the addition of the inversion-recovery sequence to MRI with the endorectal coil might improve the usefulness of this examination.

**MRI Techniques Compared:** In an attempt to define the role of endorectal coil MRI, the RDOG conducted a study comparing body coil MRI alone, body coil MRI with fat suppression, and endorectal coil MRI.[90] These investigators reported an overall accuracy of 61% for conventional body coil, 64% for fat-suppressed body coil, and 54% for endorectal coil MRI. Findings of the study suggested that no technique was highly accurate for staging early prostate cancer. Nevertheless, individual radiologists did achieve a high degree of staging accuracy with the endorectal coil and body coil combination.

**Contrast MRI**

In an effort to improve endorectal prostate imaging, Mirowitz et al.[95] studied 13 patients using spin-density, T2-weighted, and gadolinium-enhanced and unenhanced T1-weighted MRI performed with an endorectal surface coil. Results suggested that gadopentetate dimeglumine is not warranted for routine use in endorectal MRIs of the prostate, but may be useful for evaluation of the seminal vesicles in selected patients.

In another study by Quinn et al.[91] a prospective evaluation of 70 patients with known prostate cancer using an endorectal surface coil and MRI were compared with whole-mount sections. Gadopentetate dimeglumine was administered to 40 patients. The addition of the contrast agent provided no benefit in the diagnosis or staging of prostate cancer.

**MRI With Fat Suppression**

Tsuda et al.[96] conducted a recent 79-patient study comparing the efficacy of fat-suppressed and non-fat-suppressed fast spin-echo endorectal MRI in the detection of extracapsular extension of prostate cancer by both experienced and inexperienced radiologists. A total of 21 patients were imaged with frequency-selective fat suppression, and 58 were imaged without fat suppression. An independent, retrospective review of all images was performed by two readers (with different levels of experience) who were blinded to clinical and pathologic findings. Compared with MRI without fat suppression, the use of frequency-selective fat suppression did not produce any significant improvement in the diagnosis of extracapsular extension, for either the experienced (area under the receiver operating characteristic curve \( [Az] = 0.81 \text{ vs } 0.79 \)) or the inexperienced (\( [Az] = 0.76 \text{ vs } 0.68 \)) reader.

In another study, body coil MRI alone was compared to body coil MRI and fat suppression.[90] Results showed no clear advantage in using fat suppression. The role of MRI with fat suppression for improving the diagnostic yield of prostate cancer awaits further validation.

**MRI Spectroscopy**

Accumulation and secretion of extraordinarily high levels of citrate are unique functions of the normal prostate's secretory epithelial cells.[97,98] Studies have demonstrated an association of prostate cancer with low citrate levels,[30,99,100] which were attributed to loss of the characteristic ductal morphology of the gland[73,101] and changes in cellular function.[97,98] Prostate cancer is
also associated with significantly decreased levels of phosphocreatine and increased levels of phosphomonoesters as compared to healthy prostates.[30,41,102]

The evolution of magnetic resonance (MR) spectroscopy[103,104] and its recent applications in prostate imaging have broadened the ability of prostate cancer detection beyond the anatomic information obtained with conventional MRI, by enabling detection of the cellular metabolites citrate, creatine, and choline.[30,105-107] Kurhanewicz et al.[30] stimulated echo-proton spectroscopy in conjunction with endorectal surface coils to obtain water-suppressed hydrogen-1 spectra from regions of the normal prostate’s peripheral zone, BPH, and prostate cancer. Results were correlated with pathologic areas identified on T2-weighted endorectal coil MRI and histologic study of the step-sectioned gland following surgery. Significantly lower mean citrate/creatine-plus-choline peak-area ratios were noted for regions of cancer (0.67 ± 0.17), compared with BPH (1.21 ± 0.29) and normal peripheral zone (1.46 ± 0.28). This demonstrated the potential role of citrate as an in vivo marker for discriminating prostate cancer from surrounding regions of the normal peripheral zone and BPH.

In another study by the same group, citrate levels were shown to be low in primary prostate cancer and even lower in metastatic disease.[108] Kaji et al.[109] conducted a retrospective study to assess the value of MR spectroscopic imaging for improving localization of prostate cancer in postbiopsy hemorrhage cases. They reported that the addition of MR spectroscopic imaging to MRI significantly (P < .01) increased the accuracy (52% to 75%) and specificity (26% to 66%) of tumor detection.

3D MRI Spectroscopy: The application of 3D hydrogen-1 MR spectroscopic imaging is yet another advancement in the field of MR spectroscopic imaging of the prostate. Kurhanewicz et al.[27] performed combined, phased-array, endorectal MRI and 3D MR spectroscopic imaging in 9 young, healthy volunteers, 5 patients with BPH, and 85 patients with prostate cancer and BPH. Images were compared with postoperative pathologic histology findings. Results of the study suggest that a 3D MR spectroscopic imaging examination added to a clinical MRI examination may help define the presence and spatial extent of prostate cancer.

In 1999, Scheidler et al.[29] reported the findings of a retrospective cross-sectional study in which MRI and 3D MR spectroscopic imaging examinations were performed in 53 patients with biopsy-proven prostate cancer and subsequent radical prostatectomy with step-sectioned histopathologic examination. They noted that the addition of 3D MR spectroscopic imaging to MRI resulted in a significant improvement in tumor localization and provided better detection of prostate cancer in a sextant of the prostate than can be achieved with MRI alone.

Computed Tomography

Computed tomography has not proven to be useful in the diagnosis or staging of locally advanced prostate cancer. Although CT scan may delineate gland size, density, and symmetry, separation of individual zones is not possible. Moreover, differentiation of prostate cancer from BPH is frequently difficult. Due to the fact that most of the extension of local prostate cancer is microscopic or low volume, the CT scan holds little value in local staging. Based on the recommendations of O’Dowd and associates,[110] the use of CT in the evaluation of newly diagnosed prostate cancer should be restricted to patients with PSA levels > 20 ng/dL, Gleason scores of 8 to 10, or clinical stage T3 to T4 disease.

Elastography

Localized changes in tissue elasticity or stiffness are frequently associated with an underlying tissue abnormality such as cancer. Simply put, the palpable lesion detected upon a digital rectal examination is due to changes in the elasticity of the tumor relative to the surrounding tissue. Numerous attempts have been made to generate images of the parameters of tissue elasticity. However, no known modality is capable of imaging the elastic properties of tissue directly.

Indirect methods using ultrasonography to measure local tissue response to deformations produced by an external mechanical stimulus have been reported. Data before and after slight compression
are compared, and a measurement of the difference in the tissue’s mechanical properties is viewed as a 2D, cross-sectional, gray-scale image. Since elastography reflects shear properties that are determined by a higher level of tissue organization (which is most likely altered by cancer and other diseases), it has a greater potential to detect early tissue pathology than conventional ultrasound imaging (which is based on bulk properties determined by the molecular composition of tissue).

Most elastography work to date has been performed upon breast lesions. However, its applications for prostate pathology are rapidly evolving. Recent studies[111-113] attempting to investigate the mechanical behavior of prostate tissue and to define elastographic features of the prostate have shown this technique to be a promising imaging tool.

Detection of Distant Prostate Cancer

CT or MRI to Detect Lymph Node Disease

Early studies indicated that CT was unreliable in the detection of lymph nodes less than 2 cm.[114] Modern CT technology can now detect nodes between 1 cm and 1.5 cm. However, since most patients currently present with a small volume of metastatic disease,[115,116] CT resolution is still unacceptable. Current CT technology has several other limitations, including variability in interobserver interpretation[117] and the inability to distinguish between inflammatory and neoplastic pathology without fine-needle aspiration.[118] Accordingly, few patients with high-volume, lymph node disease might benefit from CT staging.

Since the ability of MRI to detect lymph node metastasis is dependent on the volume of nodal disease, its applications in this regard are also limited, with an overall sensitivity of 42% and specificity of 98%.[5] In general, although MRI is more useful than CT in detecting local extension, neither of these modalities is reliable in detecting lymph node disease. However, they may prove to be useful in detecting other organ (eg, liver) involvement.

Nuclear Scans to Detect Lymph Node Disease

In 1983, Goldenberg et al[119] first reported on radioimmunoscintigraphy of prostate cancer using an iodine-131-radiolabeled polyclonal antibody to prostatic acid phosphatase. In a later study, Dillman et al[120] reported on the use of indium-111-labeled monoclonal antibodies to PSA in four patients, in whom 14 of 21 disease sites were detected. Advances in monoclonal antibody technology have further improved the recognition of prostate cancer-associated antigens such as prostate-specific membrane antigen (PSMA)

Recently, a radioimmunoconjugate based on PSMA, known as capromab pendetide (ProstaScint), was introduced for use in high-risk, newly diagnosed cancer patients and in patients with biochemical failures after definitive treatment. A recent multicenter study[22] using indium-111 capromab pendetide in radioimmunoscintigraphy was carried out in 51 patients with prostate carcinoma who were at high risk for metastatic disease. Correlation with the histologic evaluation of removed tissue was performed and results were also compared with other standard methods for diagnosing patients prior to surgery.

Out of 51 patients, 19 showed evidence of lymph node involvement with radioimmunoscintigraphy. Of these, 15 showed pathologic evidence of cancer in the biopsied lymph nodes. Sensitivity was 75%; specificity, 86%; accuracy, 81%; and the PPV for detection of extraprostatic disease was 79%. Ultrasound, CT, and MRI of the pelvis demonstrated a combined accuracy of only 48% in detecting lymph node disease. Results of the study indicated that radioimmunoscintigraphy had an impact on patient management through its detection of occult disease in more than 50% of the patients with prostate carcinoma.

In another study, the ability of several predictive models (based on preoperative PSA, biopsy Gleason score, and clinical stage) to predict lymphatic metastases in 198 men with clinical T2- or T3-classified, bone-scan-negative prostate carcinoma was compared to an indium-111 capromab pendetide scan prior to staging lymphadenectomy. Results of both modalities were correlated with
the pathologic examination of the lymph nodes. The PPV of the monoclonal antibody scan (66.7%) was significantly better than the PPV of the clinical predictive model algorithms (40.5% to 46%). When the radiolabeled monoclonal antibody scan was combined with clinical predictive models, a PPV of up to 72.1% was obtained. These data suggest that the use of a radiolabeled monoclonal antibody scan, alone or in combination with the algorithms, can improve the ability of predicting lymph node involvement in patients with prostate carcinoma at high risk of regional disease spread.

**Radiographic Detection of Osseous Disease**

**Plain Radiographs**

In patients with advanced prostate cancer, the skeleton is the most frequent site of metastases.[121] Plain radiographs have been shown to have low sensitivity in the detection of osseous metastases; at least a 50% change in bone density is required for plain films to detect the lesion.[122] Furthermore, most of the detected lesions are osteoblastic, and osteoclastic lesions are usually missed. Thus, a negative plain film is not a reliable modality to indicate that a given patient is free from osseous metastatic disease.

In 1979, Paulson[123] studied 454 patients with prostatic adenocarcinoma who were assigned a preliminary clinical stage on the basis of serum acid phosphatase, routine bone survey, and physical examination. Results were correlated with findings of radioisotopic bone scanning, lymphangiography, and staging pelvic lymph node dissection. He noted that 23% of patients with negative skeletal surveys would demonstrate bony involvement upon scintigraphy. In addition, 16% of patients who had been diagnosed as having stage A, B, or C disease would be further upstaged upon additional radionuclide scanning. Accordingly, plain radiographs are not a reliable imaging tool in detecting bone disease and have been widely replaced by bone scintigraphy.

**Bone Scintigraphy**

In the pre-PSA era, most men underwent radionuclide imaging of their bony skeleton as part of their initial metastatic work-up for prostate cancer. In these cases, nearly 25% of them would have osseous metastasis.[123] After the introduction of PSA and after the correlation was made between PSA levels and incidence of metastasis, indications for bone scintigraphy were then refined.[124] Current data suggest that bone scans should be reserved for patients with bone pain or a PSA level above 10 to 15 ng/mL upon initial presentation.

Technetium-99m and phosphonates are the most frequent agents used in this setting. These agents are taken up by metabolically active bone after intravenous injection. Bone scans are highly sensitive but nonspecific, and thus, equivocal positive findings should be correlated with plain radiographs of the abnormal area. False-negative examinations reportedly account for approximately 8% of all such tests[125] and are usually associated with a lack of osteoblastic activity or diffuse high activity throughout the skeleton. Although other imaging modalities, such as MRI or capromab pendetide, can detect bone lesions not detected by bone scan, none of them is recommended as part of the initial work-up for skeletal metastasis.

**Conclusions**

Current prostate imaging modalities for both the diagnosis and staging of prostate cancer are limited, and the need for new or improved technologies cannot be overemphasized. Modern advances in the fields of ultrasound and MRI, particularly the use of intermittent, contrast-enhanced ultrasound imaging, combined MRI spectroscopy, or endorectal MRI, are very promising.

However, their role in the routine care of patients awaits further validation. Radioimmunoimaging has considerable potential to enhance the detection of soft-tissue disease. Future advances in imaging prostate cancer may provide additional clinical information that may alter our treatment approach to the disease.
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