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Imaging clinically localized prostate cancer

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For men residing within the United States, prostate cancer is second only to lung cancer in cancer mortality and second in incidence to nonmelanomatous skin cancers. The introduction in the 1980s of prostate-specific antigen (PSA) as a part of cancer screening protocols increased detection of clinically significant (and insignificant) prostate cancer, which has led to earlier identification of prostate cancer, at more treatable stages [1]. Given the substantial stage migration that has occurred, prostate cancer is rarely a systemically detectable disease at presentation. Therefore, clinicians have gone from using imaging-based staging to using clinical variables in combination (ie, serum PSA, T stage, Gleason score, and extent of disease on biopsy) as a more efficient means of assessing the likely extent of disease and the best initial treatment. Thus, there is significant controversy with regard to the optimal treatment of prostate cancer and the role of imaging in staging prostate cancer. This article explores the current literature with regard to the accuracy and utility of transrectal ultrasound (TRUS), modifications of TRUS, MRI and magnetic resonance spectroscopy (MRS), radiolabeled antibody imaging (ProstaScint) (Cytogen, Princeton, NJ), and CT in staging clinically localized prostate cancer.

Importance of imaging in staging

More accurate pretreatment staging of prostate cancer permits the appropriate selection of therapy and increases the likelihood of a favorable treatment outcome. Although there are many imaging techniques available to help assess stage, there is no clear standard modality that is uniformly accurate, sensitive, and specific, yet remains minimally invasive and cost effective.

An analysis of patients in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry—a longitudinal database of men with various stages of cancer—revealed that although utilization of imaging techniques between 1995 and 2001 has decreased, up to half of patients with clinically intermediate-risk tumors (PSA level between 10.1 and 15 ng/mL, Gleason score of 7, or clinical stage T2b) and a quarter of low-risk patients (PSA level less than 10 ng/mL, Gleason score less than 7, and clinical stage T1 or T2a) continue to undergo unnecessary radiographic examinations [2]. These findings underscore the importance of the critical evaluation of available data to reduce unnecessary utilization of resources.

Long-term cancer-free survival is determined by both the clinical extent of disease at the time of treatment and the type of treatment delivered. Understaging occurs in 30% to 60% of patients who undergo surgery for clinically localized disease [3]. The risk of understaging may be less than that noted previously, due to stage migration [4]. Therefore, an important goal of imaging is to distinguish those patients with either organ-confined prostate cancer (<pT2c) or limited extracapsular extension (ECE) from those with more advanced disease (Table 1).

Digital rectum examination (DRE) alone is insufficient for detecting the presence or extent of cancer [5]. This was noted by Jewett et al [6], who reported that 50% of palpable prostatic nodules were benign. Additionally, DRE alone has poor specificity in predicting pathologic stage of

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Table 1
TNM staging of prostate cancer

T stage: tumor
T2: tumor confined to prostate
T2a: tumor involves one lobe
T2b: tumor present in both lobes
T3: tumor extends through prostatic capsule
T3a: extracapsular extension present
T3b: tumor invades seminal vesicle
T4: tumor invades adjacent tissue
N stage: node status
Nx: nodal status cannot be assessed
N0: no regional node disease present
N1: single node; 2 cm or less at largest point
N2: single node, 2–5 cm at largest point, or multiple nodes no larger than 5 cm
N3: metastasis larger than 5 cm in any node
M stage: metastatic disease
Mx: metastasis cannot be assessed
M0: no metastasis present
M1: distant metastasis present
M1a: distant lymph nodes involved
M1b: distant bony metastasis
M1c: other distant site

disease, especially in patients with a low PSA. Over 60% of tumors staged by DRE alone are understaged [7].

Similarly, PSA alone has poor sensitivity and specificity in predicting tumor stage, particularly in patients who present with a PSA of less than 20 ng/mL. The accuracy of pretreatment staging is only moderately increased when PSA is combined with DRE [8]. The most accurate methods of estimating pathologic stage utilize PSA, DRE findings, and Gleason grade on prostate biopsy. By incorporating Gleason grade in preoperative staging, a good correlation can be made between clinical staging and pathologic staging through the recently updated Partin staging nomograms [9]. Data from CaPSURE suggests that incorporation of percent-free biopsies can increase the accuracy of preoperative staging in all risk groups compared with the use of serum PSA, T stage, and Gleason score [4].

Imaging may complement the use of clinical criteria as outlined above. Imaging aims to establish the local extent of disease and quantify other features of tumor that predict outcome, such as cancer location, volume, and grade [10]. The ideal imaging technique should be affordable and minimally invasive, with little variability in interobserver interpretation. In addition, the test should be able to predict tumor stage, volume, and location with high specificity and sensitivity. Although such a test does not currently exist for prostate cancer, many modalities are available that may provide valuable information that could impact clinical care.

Imaging techniques

Ultrasound

Gray-scale ultrasound

Although conventional gray-scale ultrasound imaging of the prostate can be performed in a variety of ways, TRUS provides the clearest view of the prostate. TRUS is the most common imaging test for the local staging of prostate cancer because it is used almost universally to assist in obtaining initial systematic and directed biopsies of the prostate. Additionally, many urologists have familiarity with this imaging technique, and the potential side effects of TRUS imaging and biopsy—although not uncommon—tend to be minor [11].

The optimal technique for TRUS involves placing the patient in a lateral decubitus position and obtaining axial and sagittal sections with a 7.5 MHz transducer. Any abnormality should be imaged in two planes and gland volume calculated. Benign prostatic hyperplasia (BPH) can complicate the TRUS image by compressing the peripheral zone where tumors are typically best visualized by TRUS. Tumors can appear hypoechoic (60%–70%), isoechoic (40%), or hyperechoic (rare) [12]. They may appear as a nodule, an infiltrating mass, or a combination of both or as benign processes such as prostatitis, focal atrophy, or prostatic infarcts. It has been shown, for example, that granulomatous prostatitis can appear as a focal hypoechoic area with a nodular appearance similar to prostate cancer [13]. There are some TRUS findings that are suggestive of the presence of extracapsular cancer extension. Protuberance and irregular borders at the capsule suggest the presence of ECE (T3 disease). The fat plane posterior to the prostate also can be visualized by TRUS and assessed for invasion by tumor. Additionally, invasion of the seminal vesicles (T3b disease) usually appears as a posterior thickening or loss of bulging of the seminal vesicle on gray-scale images. Unfortunately, ECE by small microscopic clusters of tumor cells may be impossible to see on TRUS.

TRUS images give limited information about the histology of prostate cancer; however, some

infrequently encountered tumors have characteristic appearances on TRUS. Comedocarcinoma appears as a multiple, small, hyperechoic lesions within a larger hypoechoic area [14], whereas lymphomas tend to appear as hypoechoic areas within the transition and peripheral zones [15].

TRUS alone has a relatively poor ability to detect palpable and nonpalpable prostate cancer [12] and predict disease outcome [16]. Its utility is affected by a number of factors. First, TRUS is operator dependent and, despite technical refinements, conventional ultrasound remains limited by the ability of the operator to distinguish subtle findings such as differences in gray scale [17]. Second, there are significant differences between the various ultrasound probes still commonly in use: older 3.5/4-MHz transducers do not depict zonal anatomy as well as do newer 5-MHz and 7.5-MHz transducers.

The ability of ultrasound to stage prostate cancer is influenced significantly by the pretest probability of local extension of the disease as determined by PSA, T stage, and cancer grade. In one series [18], patients with a PSA greater than 10 ng/mL had a risk approaching 50% of capsular penetration. Additional predictors of pathologic stage include PSA velocity (>0.75 ng/mL per year) [19], free-to-total PSA ratio, and PSA density (>0.1 ng/mL per milliliter of prostate). TRUS has a high specificity [20] and good interobserver reliability in estimating prostate volume [21]. Babaian et al [22] have shown that although the smaller tumors (defined as 0.51 cm^3 to 1.5 cm^3) tend to be less likely to have extraprostatic extension, a significant number (32%) of these small-volume tumors can have extraprostatic extension. Estimation of tumor volume may be useful clinically for brachytherapy, to aid in planning for prostatic shape and size [23]. Of interest, Ukimura et al [24] has suggested that the length of tumor in contact with the prostatic capsule by TRUS correlates with the likelihood of ECE.

Despite an initially positive report by Salo et al [25], subsequent data on TRUS for staging prostate cancer have been variable (Table 2). In 43 patients studied using a 4.0-MHz transducer, Hardeman et al [26] found a sensitivity of 54%, a specificity of 58%, a PPV of 62%, and a negative predictive value (NPV) of 50% (calculated from data presented) in predicting ECE. TRUS had a sensitivity of 60%, a specificity of 89%, a PPV of 67%, and an NPV of 86% (calculated from data) in predicting seminal vesicle invasion (SVI). In a multi-institutional, prospective trial of 230 patients [27], TRUS had a sensitivity of 66%, a specificity of 46%, a PPV of 63%, and an NPV of 49% in predicting ECE; and a sensitivity of 22% and 88% in predicting SVI. The poor utility was confirmed by Bates et al [28], who found a sensitivity of 23% and 33% in predicting ECE and SVI, respectively; and by Presti [29] who found that gray-scale TRUS had a sensitivity of 48%, a specificity of 71%, a PPV of 50%, and an NPV of 69% in predicting ECE; and 75%, 98%, 75%, 98%, respectively, in predicting SVI. In a prospective, multi-institutional study funded by the National Institutes of Health of 263 patients who underwent radical prostatectomy [30], preoperative clinical staging by TRUS and DRE was compared with pathologic staging. The staging accuracy of TRUS was correlated, in a nonstatistically significant manner, to tumor volume. Overall, TRUS was not significantly better than was DRE in predicting ECE. TRUS was noted to be better at staging posterior tumors than anterior ones [30].

In conclusion, although TRUS is useful for performing prostatic biopsies and providing a general anatomic assessment (eg, prostate volume), the overall low accuracy makes TRUS alone an imprecise technique for the local staging of prostate cancer [31].

Table 2
Utility of transrectal ultrasound in the literature

Author	Sensitivity	Specificity	PPV	NPV	Accuracy
Bates et al [28]					
ECE	23	86	—	—	—
SVI	33	100	—	—	—
Presti et al [29]					
ECE	48	71	50	69	—
SVI	75	98	75	98	—
Rifkin et al [27]					
ECE	66	46	63	49	58
SVI	22	88	—	—	—
Hardeman et al [26]					
ECE	54	58	62	50	56
SVI	60	89	67	86	82
Salo et al [25]					
ECE	86	94	92	89	90
SVI	29	100	100	75	77

Abbreviations: ECE, extracapsular extension; SVI, seminal vesicle invasion; PPV, positive pedictive value; NPV, negative predictive value.

Color Doppler, power Doppler, and contrast agents

Modifications to TRUS have attempted to increase its utility. Color Doppler TRUS (CDUS), which was described in 1993 as a means of differentiating cancer from benign growth, utilizes reflected sound waves to evaluate blood flow through prostatic vessels. Early studies showed that cancers that are not revealed in gray scale, such as in isoechoic hypervascular tumors, may be visualized by imaging vascular flow (Fig. 1). Initial enthusiasm was heightened by research on angiogenesis that indicated that prostate cancer tissue has a higher microvessel density than does benign prostatic tissue [32].

Unfortunately, there is little data on the ability of CDUS to stage localized disease. Color signals from vessels in CDUS can obscure the gray-scale image of the capsule, making local staging difficult. Only one study has presented data on staging by CDUS; Cornud et al [33] evaluated 94 patients with T1c prostate cancer who underwent radical prostatectomy and found that ECE and SVI were present more often in tumors that could be visualized by CDUS than in those that could not be visualized. The data of Cornud et al [33], however, did not compare the CDUS with conventional gray-scale ultrasound. Nonstaging data has shown that CDUS may not detect more tumors than gray-scale ultrasound [34]; however, Kelly et al [35] found that only 1 patient out of 158 had a tumor detected by CDUS that was not found on conventional TRUS. Other studies [36,37] have shown better utility for CDUS in detecting prostate cancer when accounting for traditional predictors of pathologic stage such as Gleason grade.

In cases of incongruent findings between color Doppler and conventional Doppler, other conditions (such as prostatitis, which can show increased flow on CDUS), should be considered [38]. Of interest, preliminary studies have suggested that CDUS may predict the behavior and aggressiveness of cancer (Gleason grade and rate of relapse) [39] as well as the growth of prostate cancer after hormonal therapy [40]. Additional studies are required to assess the true utility of CDUS over conventional techniques.

Other modifications of ultrasound that attempt to increase the specificity of TRUS include power Doppler, 3-dimensional (3D) Doppler, and the use of new contrast agents. Power Doppler imaging (PDI) detects small differences in blood flow and can image alterations in flow in very small tumor vessels [41]. PDI has a threefold to fourfold higher sensitivity compared with color Doppler alone [42]. There is no data on PDI for staging prostate cancer. In detecting tumors, Okihara et al [43] reported a sensitivity of 98% and an NPV (98%) that was superior to

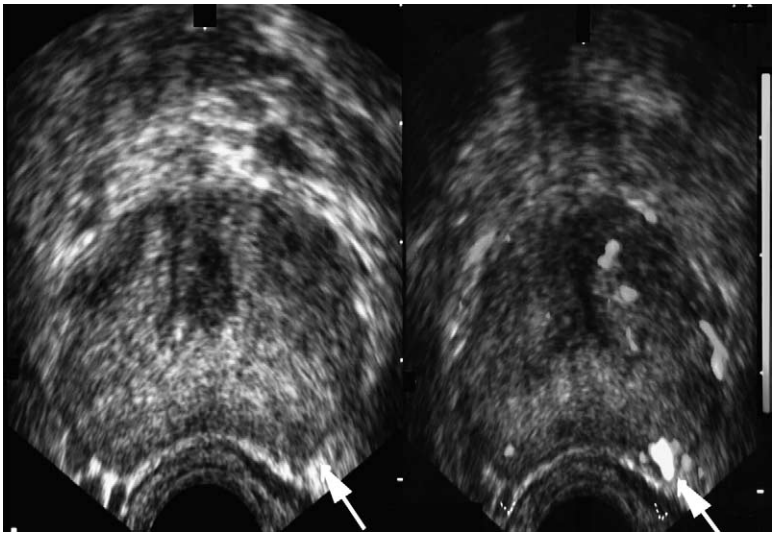

Fig. 1. (*Left*) Conventional gray-scale TRUS of prostate. The *solid arrow* points to area of prostate cancer. (*Right*) Doppler Color ultrasound shows significant hypervascularity of this area as indicated by the *solid arrow*. Assessment of extracapsular extension is difficult. Directed biopsy of this region showed intermediate grade adenocarcinoma.

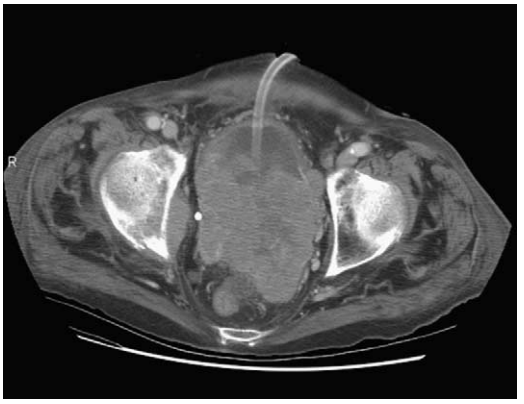

Fig. 2. CT scan demonstrating T4 adenocarcinoma of the prostate. Biopsy confirmed the presence of high-grade cancer. Of note, a suprapubic tube is in place to manage urinary retention.

conventional TRUS, but a PPV of 59%, which was not superior to conventional gray-scale TRUS. In a separate paper, Okihara et al [44] found that PDI better detected tumor vascularity in Japanese men than in American men. They hypothesized that this was secondary to the Japanese men having smaller prostates and proportionately larger tumors than did the American men. Moreover, they found that PDI added little new information to increase the efficacy of biopsies compared with standard gray-scale TRUS [44].

3D color Doppler permits a 3D image to be constructed from a series of 2D images by a computer algorithm. It may decrease the interobserver and intraobserver interpretive variability of conventional 2D TRUS and provide more accurate information with regard to the site, size, and extent of cancer [45]. In a pilot study of 3D TRUS (without color or power Doppler) in 36 patients with newly diagnosed prostate cancer, Garg et al [46] found that 3D ultrasound had an overall sensitivity of 80%, a specificity of 96%, a PPV of 90%, and an NPV of 96% in predicting ECE. The staging accuracy of 94% compared favorably with 72% for conventional 2D TRUS; the 22% improvement in staging accuracy was statistically significant ($P < 0.05$). The advantage,

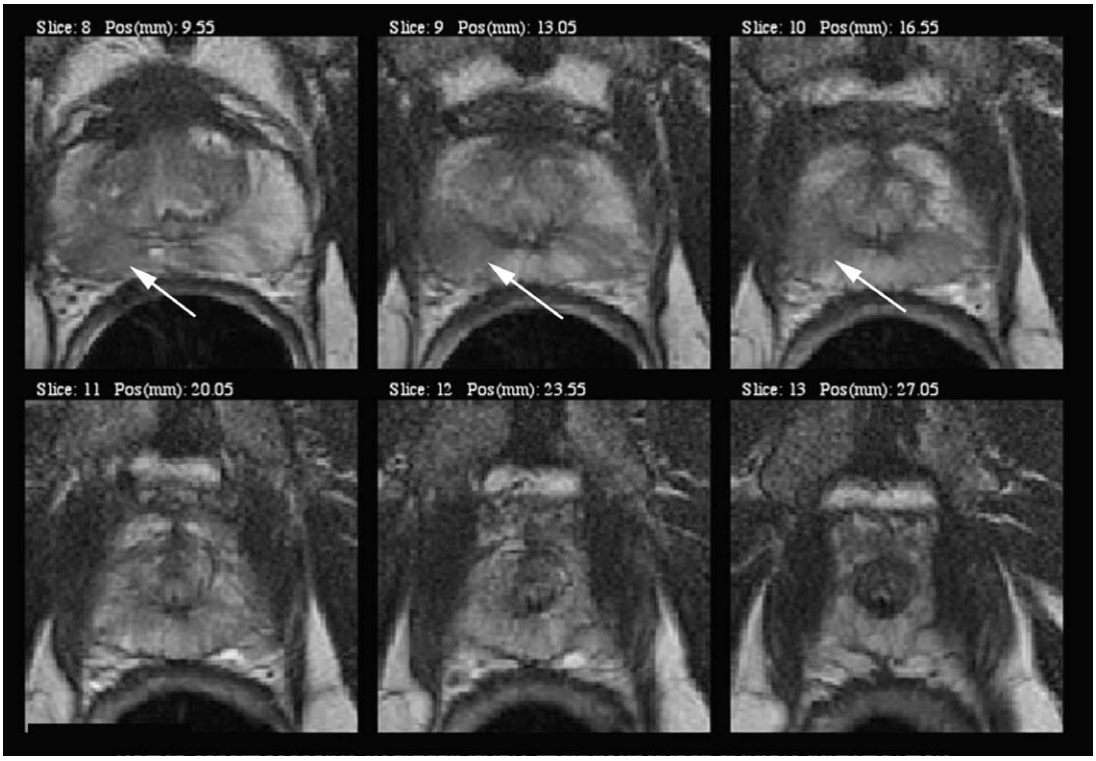

Fig. 3. MRI image of the prostate in a patient with a PSA of 3.2 and known Gleason 3 + 3 right-sided adenovarcinoma. Arrows in MRI demonstrate a clear-cut metabolic abnormality in the right midgland extending into the right apex. (Courtesy of Aliya Qayyum, MD, Department of Radiology, University of California—San Francisco.)

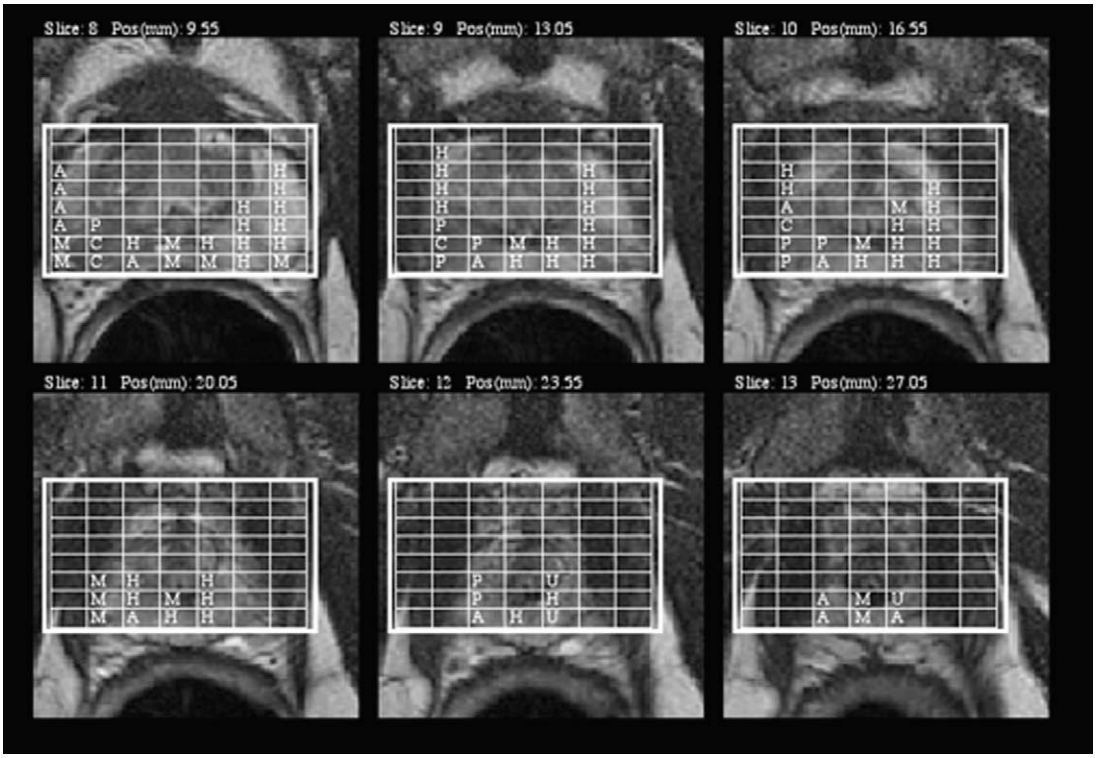

Fig. 4. This abnormality is confirmed on MRS. Voxels (0.34 cm^3 per voxel) showing the letter "C" on MRS image denotes area with metabolite ratio suspicious for cancer. P, probable for cancer; H, healthy tissue; A, atrophy.

they noted, was present only when tumors were hypoechoic [46]. The study, although well designed, was hampered by the relatively small number of subjects. Additionally, their study did not include power or color Doppler ultrasound techniques, which are likely to be used in future applications. Some data have suggested a modest improvement in yield of biopsies with 3D Doppler [47]. Other data have shown that 3D ultrasound may increase sensitivity at the cost of a significant decrease in specificity, with cancer correctly identified by two experts 49% and 57% of the time, respectively [48].

Attempts to place contrast into the prostate to enhance visualization of cancer have been moderately successful. A microbubble contrast agent in the prostate, with a mean half-life of 5 to 10 minutes, has been created by injecting an intravenous aqueous fluorocarbon that releases 2-micron to 5-micron microbubbles that traverse prostatic capillaries in proportion to blood flow. These microbubbles may improve the signal-to-noise ratio in Doppler sonography and enhance visualization of smaller vessels that would otherwise not be seen by Doppler alone [49]. Preliminary data indicate that microbubbles may enhance the sensitivity (to around 80%) and possibly the specificity of cancer detection by power Doppler [50,51] A prospective study of 230 patients by Frauscher et al [52] evaluated the efficacy of contrast-enhanced color Doppler relative to conventional gray-scale TRUS for cancer detection. Patients underwent both a conventional TRUS with 10 systematic biopsies and color Doppler imaging (CDI) with contrast using five or fewer directed biopsies. The rate of cancer detection was statistically equivalent: 24.6% by contrast-enhanced CDI and 22.4% by conventional TRUS. Each contrast-enhanced CDI-directed biopsy was 2.6 times more likely to contain tumor than was a conventional systematic TRUS biopsy [52]. There are no similarly well-designed studies on the ability of contrast-enhanced TRUS to improve cancer staging. Future TRUS directions may include image enhancement by elastography—which calculates differential properties of tissues (eg, prostate cancer and normal prostatic tissue) under strain (through the use of a

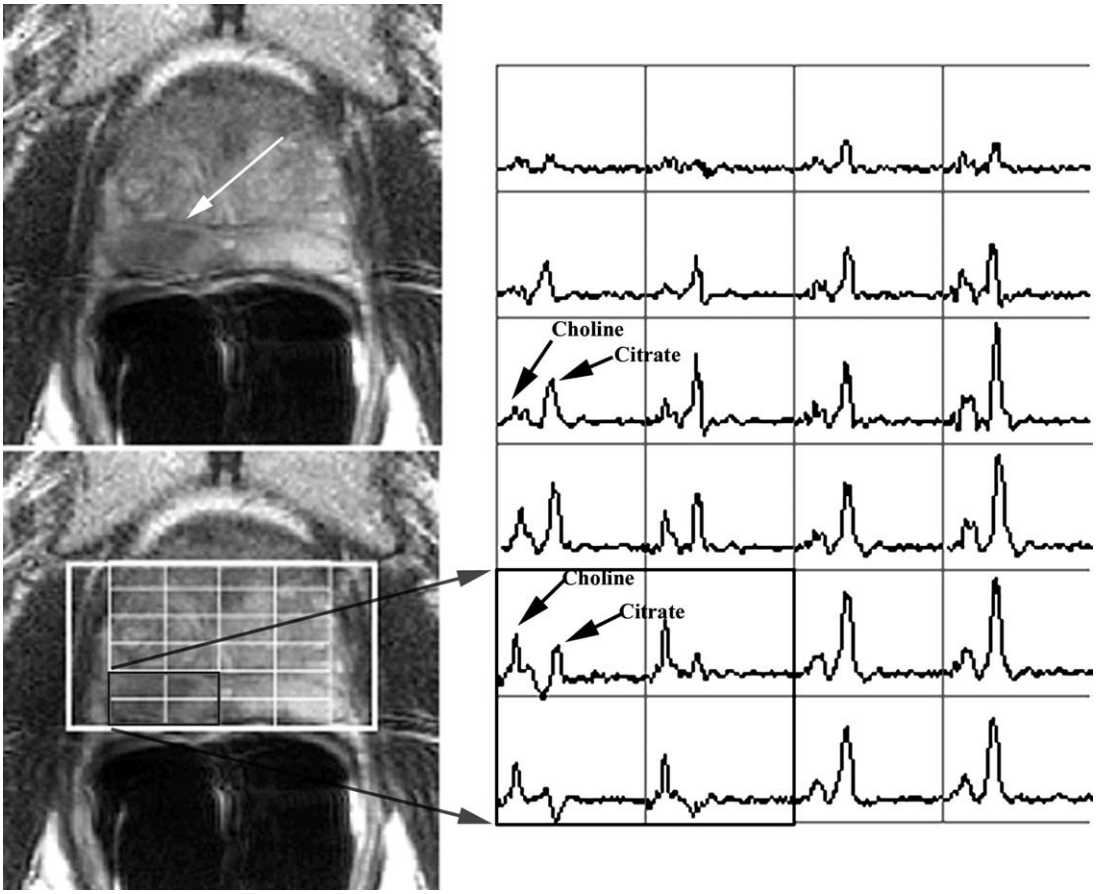

Fig. 5. MRI (*upper left image, white arrow*) shows a suspicious area on MRI. Combined MRI/MRS data suggests a high probability of cancer.

transrectal balloon) [53]—and further mechanical refinements to improve image clarity.

CT

Abdominopelvic CT scans were evaluated for staging of prostate cancer and were found to be of little value in low-risk and intermediate-risk patients. Problems included a lack of visualization of the prostatic capsule, the inability to accurately distinguish BPH nodules from cancer, and poor soft tissue resolution. Staging for locally advanced cancer may be possible when tumor invades periprostatic fat. In 1997, the National Comprehensive Cancer Network recommended using CT to help in the assessment of stage for patients with clinical stage T3 and T4 disease (Fig. 2) [54]. In patients with stage B and C prostate cancer, however, Hricak et al [55] found little difference in the accuracy of CT (65%) over clinical staging (61%) when comparing the results with pathologic findings after radical prostatectomy. In a study published in 1987 of 38 patients who underwent a radical prostatectomy, Salo et al [25] found preoperative CT to have a sensitivity, a specificity, a PPV, and an NPV of 25%, 89%, 67%, and 59%, respectively. In ECE, the ability of CT to predict SVI was slightly better: 36%, 96%, 80%, and 76%, respectively [25]. Other studies [56,57] have found sensitivities ranging from 2.5% to 75% and specificities ranging from 60% to 92% in predicting ECE, and sensitivities ranging from 5.8% to 33% and specificities ranging from 60% to 99% in predicting the presence of SVI. Data have shown that CT adds little in the way of preoperative staging for patients with clinically low-stage disease [58–60]. Even in higher risk patients, CT scans may have limited clinical utility

Table 3
Utility of MRI in the literature

Author	Sensitivity	Specificity	PPV	NPV	Accuracy
Tuzel et al [84]					
ECE	37.5	87	75	69	65
SVI	20	92	50	73	70.5
Ikonen et al [64]					
ECE	13	97	—	—	91
SVI	59	84	—	—	80
Deasy et al [85]					
ECE	55	91	—	—	77
SVI	83	96	—	—	94
Presti et al [29]					
ECE	91	49	51	90	—
SVI	50	94	40	96	—
Bartolozzi et al [62]					
ECE	95	82	—	—	82
SVI	80	93	—	—	—
Perrotti et al [63]					
ECE	22	84	—	—	64
SVI	23	93	—	—	77
Rifkin et al [27]					
ECE	77	57	71	63	69
SVI	75	98	75	98	—
(MRI + MRS) Yu et al [86]					
ECE	46–54	93–96	65–81	85–88	—
SVI	—	—	—	—	—

Abbreviations: ECE, extracapsular extension; SVI, seminal vesicle invasion; PPV, positive predictive value; NPV, negative predictive value.

in predicting nodal involvement by tumor [57]. Levran et al [59] showed that only 1.5% of 861 patients with a PSA level of more than 20 ng/mL were noted to have suspicious lymph nodes on CT. Although CT scans may have little utility for preoperative staging in low-risk patients, radiation oncologists often use CT for pretreatment radiation dosage planning [61] and CT-guided brachytherapy [62].

MRI/MRS

MRI has been used to improve staging in low-grade to intermediate-grade tumors. Endorectal MRI utilizes a magnetic coil placed in the rectum to better visualize the zonal anatomy of the prostate and better delineate tumor location, volume, and extent (stage). Patients are imaged in a whole-body scanner using a pelvic phased array coil combined with an inflatable, balloon-covered, endorectal surface coil positioned in the rectum. Both T1-weighted and T2-weighted spin-echo MRI images are required to evaluate prostate cancer. The prostate appears homogenous on T1-weighted images; on T2-weighted images, cancer appears as an area of lower signal intensity surrounded by a normal area of higher intensity. The prostatic capsule often can be visualized by MRI. Distinctions between normal and pathologic tissue may be hampered by postbiopsy hemorrhage, which can appear as a high-signal intensity area on T1-weighted imaging. MRS has been used with MRI to increase the accuracy of radiographic assessment. MRS detects metabolic activity and may differentiate normal from cancerous prostate tissue based on the ratios of creatine, choline, and citrate production and consumption (Figs. 3–5).

The data on the ability of MRI alone to predict stage are variable (Table 3). Presti et al [29] found endorectal MRI to be 91% and 50% sensitive and 49% and 94% specific in predicting ECE and SVI, respectively. Rifkin et al [27] presented similar data showing a sensitivity of 77% and 28% and a specificity of 57% and 88% in predicting ECE and SVI, respectively. Bartolozzi et al [60] evaluated 73 patients who underwent endorectal MRI and radical prostatectomy. MRI had a -sensitivity of 95% and a specificity of 82% in diagnosing the presence of ECE; analysis of the data presented showed a PPV of 90% and an NPV of 92% for ECE [60]. Perrotti et al [63] found endorectal MRI to have a sensitivity of 22% and a specificity of 84% in predicting ECE. Ikonen et al [64] also found that endorectal MRI was much more likely to detect tumors over 10 mm in size (89% detection) than those that were 5 mm in size (5% detection) and was more specific than sensitive (97% versus 13%) in predicting ECE. These differences have been attributed to the lack of diagnostic criteria and interobserver variability in scan interpretation. May et al [65] found significant differences in MRI accuracy between two radiologists whose training was not specified (93% by one and 56% by another); the authors also reported that MRI had a lower specificity but a better sensitivity than did TRUS.

More careful selection of patients may increase the utility of MRI. Using a multivariate analysis

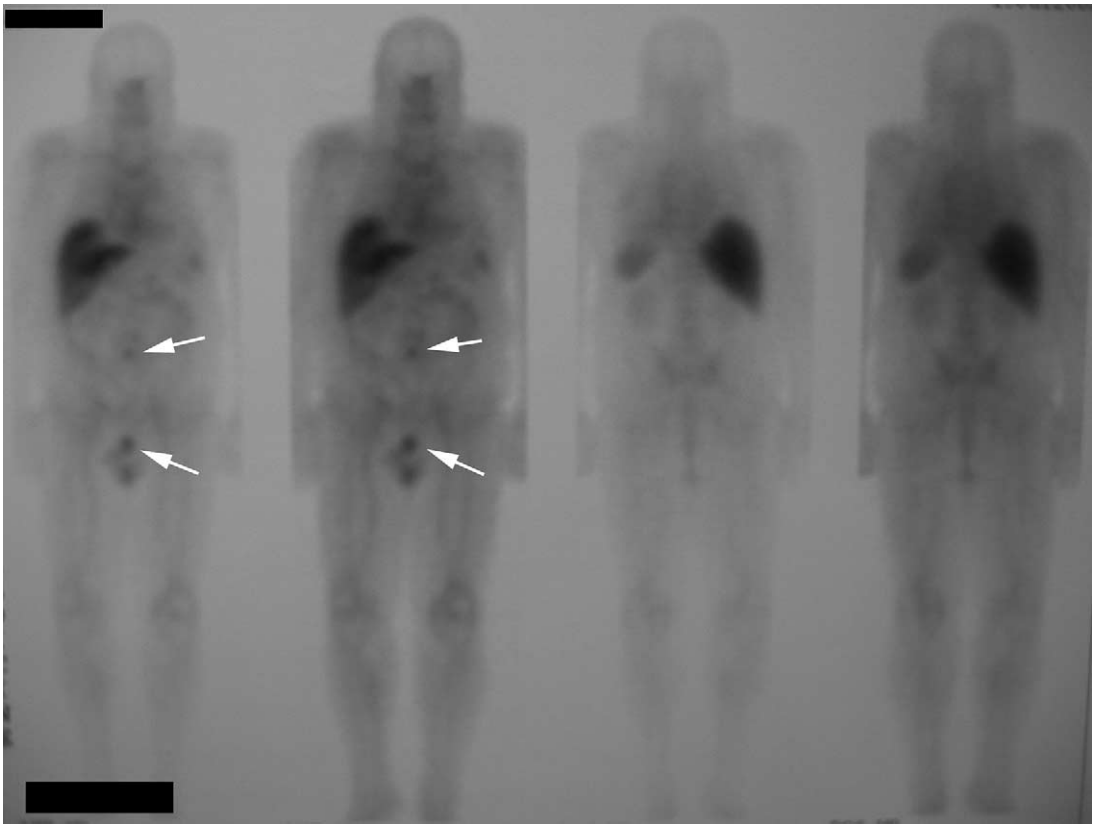

Fig. 6. Whole-body ProstaScint scan demonstating prostate with abnormal areas of uptake (*arrows*) at the prostate and near the aortic bifurcation consistent with nodal disease.

of 336 high-risk patients (greater than three cores positive on sextant biopsy, positive DRE, and PSA level >10 ng/mL) who underwent radical prostatectomy, Cornud et al [66] found that MRI alone yielded a specificity of 95% and a sensitivity of 50% to 69% for detecting pT3 disease. As experience among radiologists grows, it is likely that MRI will be used more often, but at this time there are no data to suggest that it should be used routinely to assess prostate cancer.

In 1996, Kurhanewicz et al [67] reported on significant differences among BPH, prostate cancer, and normal prostate tissue that were seen on MRS of metabolites. Cancer is associated with proportionately lower levels of citrate and higher levels of choline and creatine compared with BPH or normal prostate tissue [68]. The combined metabolic and anatomic information provided by MRI and MRS may allow for a more accurate assessment of cancer location and stage than does MRI alone. MRS is currently undergoing technical refinements to increase its resolution, in the hopes of increasing accuracy. Yu et al [69] examined 53 patients who had undergone combined MRI/MRS prior to radical prostatectomy and observed that MRS reduced intraobserver variability and increased staging accuracy. Combined MRI/MRS had a sensitivity of 46% to 54%, a specificity of 93% to 96%, a PPV of 65% to 81%, and an NPV of 85% to 88% (the range of values reflects differences between two different readers) in predicting the presence of ECE [69]. The numbers of patients in the series was small and a larger follow-up study is needed to confirm these results.

Of interest, there is some evidence that MRI/MRS also may predict higher grade of cancer. It has been reported that early enhancement may signal more aggressive tumors, with poorly differentiated tumors showing the earliest and most rapid enhancement [70]. Additionally, increasing the staging capability of MRI/MRS may

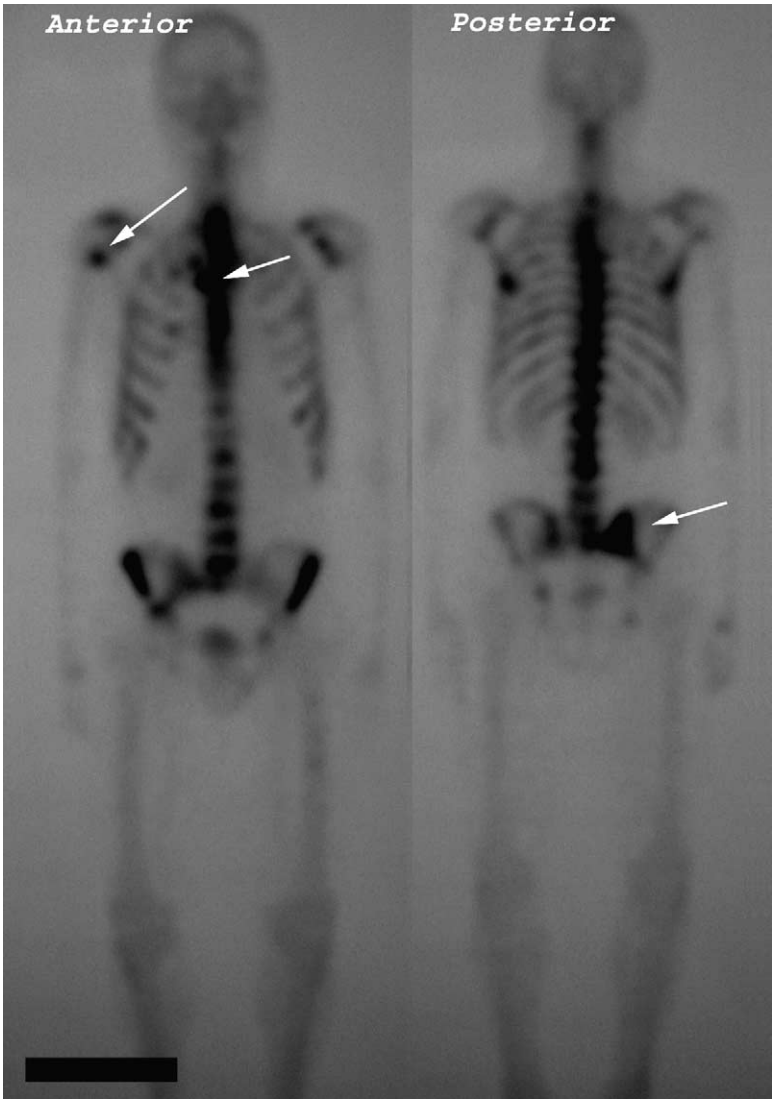

Fig. 7. Whole-body bone scintigram. *Arrows* point to the most prominent areas of enhancement consistent with metastatic disease.

have some utility for preoperative selection and treatment planning in patients undergoing brachytherapy [71].

Antibody imaging

ProstaScint is a murine monoclonal antibody to an intracellular component of the prostate-specific membrane antigen that is conjugated to 111 indium. After infusion of the antibody, single photon emission CT images usually are obtained at 30 minutes to access vasculature and at 72 to 120 hours. ProstaScint has been approved by the Food and Drug Administration for use in the evaluation of patients prior to undergoing treatment for their primary disease and for detecting the site of recurrent disease in patients who have biochemical relapse after radical prostatectomy (Fig. 6). Three possible clinical uses for ProstaScint have been enumerated by Lange [72]: the detection of lymph node metastases, the site of relapse in those with a detectable PSA after prostatectomy, and detecting occult metastasis prior to primary therapy. In his 2001 editorial, he

Table 4
Imagine recommendations

Modality	Recommendation
Transrectal ultrasound	All patients eligible for biopsy Assessment of volume Consider color Doppler for directed biopsies
Bone Scan	PSA > 15 ng/mL High-risk patients Elevated alkaline phosphatase Bony pain
CT	Negative bone scan in very high-risk patients
MRI/MRS	Select intermediate and high-risk patients

Low risk: PSA<10 ng/mL or clinical stage T1c, T2a-disease, or Gleason grade 2–6 with no component over 3.

Intermediate risk: PSA between 10 and 20, Gleason 7, or T2b disease.

High risk: PSA > 20 ng/ml, Gleason > 7 or clinical T2c, T3 disease or higher.

Abbreviation: MRS, magnetic resonance spectroscopy; PSA, prostate - specific antigen.

noted that prior studies have shown only a 60% to 70% sensitivity and specificity in predicting nodal disease. Other studies [73] have indicated that ProstaScint may serve as a useful adjunct with PSA levels, Gleason score, and bone scan in predicting stage of disease. In a study of 275 patients receiving treatment for prostate cancer with nodal disease or metastatic disease determined by either surgery or bone scan, respectively, Murphy et al [74] found that incorporation of ProstaScint, PSA level, and bone scan results into artificial neural networks indicated that ProstaScint results were a significant prognostic variable for nonlocalized cancer. In the same study [74], however, ProstaScint did not have any significant value for local (T) staging of disease. In another study, Elgamal et al [75] evaluated 100 patients, with an average PSA level of 55.9 ng/mL, who underwent definitive local treatment and developed local recurrence; ProstaScint correctly identified only 43% of local recurrences and 49% of nodal disease. ProstaScint's utility for predicting nodal disease was reported by Polascik et al [76], who evaluated 198 patients and found that compared with pathologic findings, ProstaScint had a sensitivity of 67%, a specificity of 80%, a PPV of 75%, and an NPV of 73%. Combining the clinical algorithms with the results of ProstaScint improved the PPV of lymph node involvement [76].

Although ProstaScint results may reinforce the predictive capacity of the other clinical tests such as PSA level, the significance of an incongruent positive or negative result is not clear. At this time, ProstaScint does not appear to be an important part of the initial assessment of most patients; certainly those with low-risk to intermediate-risk profiles and most with even high-risk features.

Other tests

Traditionally, radionuclide bone scintigraphy (bone scans) has been utilized for the initial staging of prostate cancer and was reported to be a sensitive method of detecting metastatic lesions in bone (Fig. 7) [77]. Analysis of CaPSURE data indicates high utilization rates even among men in low-risk (18.6%) and intermediate-risk (50.9%) categories [2], despite the findings of Oesterling [78] that less than 1% of men with a PSA level of less than or equal to 20 ng/mL have positive scans. In a study of 111 Dutch patients who had positive bone scans, Wymenga et al [79] noted that bone scans may initially be more useful if patients present with elevated alkaline phosphatase levels (>90 U/L) or bone pain. In

Table 5
Summary of data on prediction of extracapsular extension

Imaging test	Sensitivity	Specificity	PPV	NPV
Transtrectal ultrasound	23%–91%	46%–71%	50%–63%	49%–90%
Color Doppler	No data	No data	No data	No data
Power Doppler	No data	No data	No data	No data
3D Doppler	80%	96%	90%	96%
MRI	13%–95%	49%–97%	51%–90%	63%–92%
MRI + MRS	45%–54%	93%–96%	65%–81%	85%–88%
CT scan	2.5%–89%	25%–92%	67%	59%
ProstaScint	No data	No data	No data	No data

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; MRS, magnetic resonance spectroscopy.

Table 6
Summary of data on prediction of seminal vesicle invasion

Imaging test	Sensitivity	Specificity	PPV	NPV
Transrectal ultrasound	22%–75%	88%–100%	67%–75%	86%–98%
Color Doppler	No data	No data	No data	No data
Power Doppler	No data	No data	No data	No data
3D Doppler	No data	No data	No data	No data
MRI	20%–83%	92%–98%	40%–75%	73%–98%
MRI + MRS	No data	No data	No data	No data
CT scan	5.8%–96%	36%–99%	80%	76%
ProstaScint	No data	No data	No data	No data

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; MRS, magnetic resonance spectroscopy.

a multivariate analysis of 631 patients who had a bone scan and prostate biopsy, Lee et al [80] found that bone scans were not useful as an initial staging tool but could assist in determining the existence of metastatic disease in men with a Gleason grade greater than 7, a PSA level of greater than 50 ng/mL, or clinical stage greater than T3 disease. Although in their study, Lee et al [80] had defined high risk as patients with a PSA level of greater than 50 ng/mL, a PSA level of greater than 15 to 20 ng/mL is more commonly categorized as the cutoff point for obtaining a bone scan.

Data have shown that positron emission tomography (PET) scan, occasionally used for depicting metastasis in prostate cancer, does not have utility for the routine staging of prostate cancer [81]. The development of new tracers for PET scan—such as labeled 11C-choline [82] and 11C-acetate [83]—may assist in detecting and staging prostate cancer, although data on this is currently lacking.

Summary

At this time there is no highly sensitive and specific widespread radiographic test for local staging of prostate cancer. Future developments will likely require a combination of imaging modalities with utilization guided by risk-stratification models (Table 4). Staging data for all imaging tests discussed in this article are summarized in Tables 5 and 6.

Clinically, conventional gray-scale TRUS remains the most frequently used tool because of its utility in guiding prostatic biopsies. Modifications of TRUS—including power and color Doppler, 3D imaging, and new ultrasound contrast agents and elastography—show promise in increasing the accuracy of ultrasound.

Endorectal MRI may have some value for staging selected patients. The addition of prostatic MRS, which images the differential activity of metabolites, may increase the specificity of MRI. Newer techniques with finer voxel resolution may prove to be clinically useful. A large well-designed study evaluating the utility of MRI/MRS is currently being planned.

Cross–sectional imaging of the pelvis with either MRI or CT should be used selectively as should radionuclide bone scans. Similarly, ProstaScint scans should be ordered selectively, either before or after primary therapy, rather than routinely in all patients.

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