Imaging Prostate Cancer: A Multidisciplinary Perspective

The major goal for prostate cancer imaging in the next decade is more accurate disease characterization through the synthesis of anatomic, functional, and molecular imaging information. No consensus exists regarding the use of imaging for evaluating primary prostate cancers. Ultrasonography is mainly used for biopsy guidance and brachytherapy seed placement. Endorectal magnetic resonance (MR) imaging is helpful for evaluating local tumor extent, and MR spectroscopic imaging can improve this evaluation while providing information about tumor aggressiveness. MR imaging with superparamagnetic nanoparticles has high sensitivity and specificity in depicting lymph node metastases, but guidelines have not yet been developed for its use, which remains restricted to the research setting. Computed tomography (CT) is reserved for the evaluation of advanced disease. The use of combined positron emission tomography/CT is limited in the assessment of primary disease but is gaining acceptance in prostate cancer treatment follow-up. Evidence-based guidelines for the use of imaging in assessing the risk of distant spread of prostate cancer are available. Radionuclide bone scanning and CT supplement clinical and biochemical evaluation (prostate-specific antigen [PSA], prostatic acid phosphate) for suspected metastasis to bones and lymph nodes. Guidelines for the use of bone scanning (in patients with PSA level > 10 ng/mL) and CT (in patients with PSA level > 20 ng/mL) have been published and are in clinical use. Nevertheless, changes in practice patterns have been slow. This review presents a multidisciplinary perspective on the optimal role of modern imaging in prostate cancer detection, staging, treatment planning, and follow-up.

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The face of prostate cancer is changing. The widespread use of prostate-specific antigen (PSA) screening has led to a dramatic downstaging of prostate cancer at diagnosis (1,2). Data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results program demonstrate a remarkable decrease in the percentage of patients with distant metastatic disease at the time of diagnosis, from 20% for the period 1974–1985 to 5% for the period 1995–2000 (3,4). Similarly, in a single-institution study of patients with clinical stages T1 to T3NXM0 prostate cancer, the frequency of lymph node metastasis found at pelvic lymphadenectomy decreased from 23% in 1984 to 2% in 1995 (5). Earlier detection of prostate cancer has brought new challenges to clinical assessment and treatment selection—challenges that are compounded by the variability in natural history of the disease within the population at risk. The cancers detected today are smaller, lower stage, and lower grade than they were 20 years ago, but a wide range of aggressiveness remains. Our ability to predict biologic aggressiveness of tumors is still based on the histologic appearance of prostate cancer as assessed with the Gleason grading system, which has substantial limitations. A host of new biomarkers for prostate cancer are entering clinical practice and will undoubtedly alter treatment. Because men are being treated at a younger age, the long-term consequences of specific therapies merit increased consideration, since men may have to live with them for 20–30 years.

Prostate cancer is currently characterized by its clinical TNM stage, Gleason grade, and PSA serum level (1,6–8). PSA level is a strong indicator of stage and prognosis and is helpful in monitoring response to therapy. However, absolute PSA serum levels must be interpreted carefully with regard to the age of the patient, the size of the gland, and the presence of infection. Algorithms or nomograms that combine stage, grade, and PSA level to predict pathologic stage or prognosis (eg, progression-free probability after definitive local therapy) for the individual patient perform better than individual factors alone (9,10).

The thrust of cancer care in the new millennium is a risk-adjusted patient-specific therapy designed to maximize cancer control while minimizing the risks of complications. In the case of prostate cancer, such care requires accurate characterization of the tumor and selection of the optimal therapeutic approach from a bewildering array of alternatives: namely, deferred therapy (watchful waiting), androgen ablation, radical surgery (radical retropubic or laparoscopic prostatectomy), and various forms of radiation therapy (brachytherapy, external-beam irradiation, and combinations). Recently, focal ablative therapies (cryoablation, radiofrequency ablation, and focused ultrasound) have been added to the list of options (11,12). Imaging is becoming increasingly important in the assessment of prostate cancer because it can guide treatment selection, as well as treatment planning.

Imaging has played a critical role in prostate cancer staging since the development of radiography of the axial skeleton, but precise indications for and sensitivity and specificity of conventional imaging methods such as radionuclide bone scanning, computed tomography (CT), magnetic resonance (MR) imaging, ultrasonography (US), and combined positron emission tomography (PET)/CT remain under debate. The literature is replete with controversy about the value of imaging, ranging from enthusiastic endorsement to serious skepticism. Data from the Cancer of the Prostate Strategic Urologic Research Endeavor show that from 1995 to 2002, there was a national shift...
toward fewer imaging studies in all risk categories; the proportion of patients receiving any staging imaging test decreased by 63% in low-risk patients, by 25.9% in intermediate-risk patients, and by 11.4% in high-risk patients (13). The most precipitous decreases occurred in bone scan utilization rates, which decreased by 68.2%, 24.6%, and 11.1% in the low-, intermediate-, and high-risk groups, respectively. To some degree, these changes reflect the more appropriate use of imaging in response to the downward stage migration caused by PSA screening, but it is clear that some high-risk patients are proceeding to treatment without appropriate imaging evaluation (ie, work-up for metastases) (13).

Optimal use of imaging is not easy to define. However, this review will provide a multidisciplinary perspective on the optimal role of imaging in prostate cancer detection, staging, treatment planning, and follow-up by incorporating supporting evidence-based data when available.

**Imaging Guidelines, Patterns of Care, and Practical Points of Technology**

The selection of an imaging modality for prostate cancer should be based on the questions that need to be answered for a particular patient. The menu of available imaging options is continuously evolving in response to changes in clinical care, scientific discoveries, and technologic innovations. Transrectal US, MR imaging, CT, radionuclide bone scanning, and PET each have advantages, disadvantages, and specific indications. The Table summarizes the recommendations for imaging test utilization published in reports supported by the American Urological Association, the American Joint Committee on Cancer, and the American College of Radiology (8,14,15). In the following sections, we will review each of the major modalities for their utility in the detection of prostate cancer, local and distant staging, and tumor monitoring. We will also consider future developments that may improve the utility of each method.

**Transrectal US**

Transrectal US is the most widely used clinical imaging method, and it is the essential imaging tool for prostate cancer biopsy guidance. When prostate cancer is suspected, the diagnostic test of choice is a systematic needle biopsy with US guidance. Before biopsy, the patient is prepped with an enema and antibiotics (quinolone analogs). With the patient in the decubitus position, the transrectal US probe is placed in the rectum, the prostate and seminal vesicles are visualized, and the images are recorded in transverse and sagittal planes. A needle guide is used to systematically obtain 18-gauge cutting-needle biopsy cores from all parts of the prostate by using a spring-loaded handheld biopsy gun. Each specimen is identified and labeled according to its location and is sent for pathologic interpretation. From these labeled cores, biopsy “maps” are created that reflect the locations in the involved prostate. Even with such systematic sampling, underdiagnosis of the extent of prostate cancer can occur with transrectal US-guided biopsy.

Cores are typically obtained from six areas, or sextants, of the peripheral zone: left and right apex, left and right midgland, and left and right base. In addition, cores should be obtained from any sonographically suspicious (eg, hypoechoic) areas. A single biopsy session has a sensitivity of 70%–80% for the detection of cancer (16). To minimize the need for repeat biopsy sessions, many physicians obtain more cores the first time (17). There is growing evidence that 10 or 12 cores obtained from the medial and lateral apex, middle and base peripheral zones (the medial aspect of the peripheral zone seems to yield the least) of each side increases the sensitivity (15%–30% more cancers detected) (17,18). Biopsies become increasingly painful after six to eight samples, so many urologists and radiologists inject a local anesthetic (1% lidocaine without epinephrine) (19) around the nerves laterally at the junction of the seminal vesicles and base of the prostate and wait 10 minutes before obtaining samples. Separate samples of the anterior prostate (or transition zone) are usually not obtained unless previous biopsy sessions have failed to find a suspected cancer (eg, in a patient with a high PSA level, abnormal findings at digital rectal examination [DRE], and multiple negative peripheral zone biopsy specimens), or imaging with transrectal US or MR suggests an anterior cancer.

Diagnostically, transrectal US is used to measure the volume of the prostate gland (20), an important factor in computing “PSA density” (serum PSA level in nanograms per milliliter divided by the volume of the prostate in cubic centimeters). Moreover, the volume as measured with transrectal US can be used in staging and in predictive nomograms (21). Cancer, depending on its size, grade, and location, usually appears hypoechoic relative to the normal peripheral zone of the prostate (only approximately 1% are hyperechoic) (22). As a diagnostic test for cancer, transrectal US without biopsy is as accurate as DRE and complements the physical examination. Some palpable cancers are not visible at US, and some visible cancers are not palpable (23–25). With the

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**Use of Imaging in Staging Prostate Cancer**

<table>
<thead>
<tr>
<th>Source*</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>American College of Radiology, 2000 (14)</td>
<td>Bone scanning, CT, or MR imaging; PSA level &gt; 10.0 ng/mL; Gleason score &gt; 6.</td>
</tr>
<tr>
<td>American Urological Association, 2001 (15)</td>
<td>Bone scanning, PSA level &gt; 20.0 ng/mL unless prostate cancer is poorly differentiated or high grade (stage T3 or higher). CT or MR imaging, PSA level &gt; 25.0 ng/mL. Utility of endorectal MR and MR spectroscopic imaging not determined.</td>
</tr>
<tr>
<td>American Joint Committee on Cancer, 2002 (8)</td>
<td>Bone scanning or cross-sectional imaging, PSA level &gt; 20.0 ng/mL, Gleason score &gt; 7–8.</td>
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</table>

* Numbers in parentheses are reference numbers.
shift toward smaller, early-stage cancers, many cancers detected at biopsy are not visible at US (low sensitivity) and many hypoechoic areas do not prove to be malignant at biopsy (low specificity); therefore, transrectal US alone, without the addition of biopsy, has limited value in the detection of cancer.

Transrectal US has been used for local staging of prostate cancer in some studies but is generally considered insufficient (Fig 1). The criteria for identifying extracapsular extension (ECE) on transrectal US scans are bulging or irregularity of the capsule adjacent to a hypoechoic lesion (Fig 2). The length of the contact of a visible lesion with the capsule is also associated with the probability of ECE (26). Seminal vesicle invasion (SVI) is heralded by a visible extension of a hypoechoic lesion at the base of the prostate into a seminal vesicle or by echogenic cancer within the seminal vesicles (27). Asymmetry of the seminal vesicles or solid hypoechoic masses within the seminal vesicles are indirect indicators of disease extension. When extraprostatic extension into the seminal vesicles is suspected, additional transrectal US-guided biopsies of the seminal vesicles can be performed.

Authors of studies performed in the 1980s, when cancers tended to be larger (stage T3) and more readily palpated, reported sensitivity in the range of 80% for detecting ECE and SVI at transrectal US (28). Accuracy improved when US findings were interpreted in concert with DRE findings and PSA level to estimate the likelihood of extraprostatic extension (29). Today, however, tumors are smaller and local extension is uncommon. Modern nomograms more accurately help estimate the probability of ECE, SVI, and lymph node metastases from standard clinical data (stage, grade, and PSA level) (30). Nevertheless, these algorithms provide no information about the location of the cancer or the site of ECE. There has been renewed interest in the use of transrectal US with the advent of color duplex Doppler and color power Doppler US to identify cancer in hypervascular areas, with only modest improvements in sensitivity and specificity (31–33).

Transrectal US continues to play an important role in therapy. Worldwide, transrectal US is the modality of choice for directing brachytherapy seeds into the prostate (34). Cryotherapy of the prostate also requires US guidance as does high-intensity focused ultrasound, which, coupled with US targeting, is used for focal ablation of prostate cancers (36,36). New treatment approaches such as hyperthermia, photodynamic therapy, direct injection of oncolytic viruses, tumor vaccines, and gene therapy also depend on transrectal US for easy access to cancers of the prostate (37). While guidance techniques using MR imaging and other modalities are being developed, transrectal US will continue to play a major role in the management of prostate cancer, not least because of its wide availability and relatively low cost. Of course, the advantages of transrectal US (flexibility and relatively low cost) are balanced by its limited ability to define the prostate cancer in situ. The latter makes evaluation of US-guided therapies difficult, because recurrence could result either from the tumor being missed during treatment or from the inability of the treatment modality to kill the tumor.

Future developments in transrectal US include the use of microbubble contrast agents and targeted imaging. Microbubbles are relatively large, micrometer-sized, gas-filled bubbles that can be seen with exquisite sensitivity with real-time US. Indeed, by using harmonic imaging and encoded phased imaging, single microbubbles can be detected (38). Moreover, microbubbles can be coated with surface ligands, which preferentially target tumor neovascularity. Because of their large size (>1 μm), these agents are mostly confined to the vascular space and hence provide information primarily about large-vessel microvascularity but nonetheless could play a major role in improving cancer detection in the future.

CT Imaging

Although CT continues to be widely used in patients with newly diagnosed prostate cancer, it has virtually no role in prostate cancer detection or primary tumor staging. On CT scans, the separation between the prostate and the levator ani muscle is poorly defined, and intraprostatic anatomy is not well demonstrated. However, because of increased temporal resolution, multidetector CT, when properly performed, can more clearly depict intraprostatic anatomy. The major role of CT is in the nodal staging of prostate cancer, for which it is limited. Nomograms based on clinical data (PSA level, Gleason grade, DRE findings) provide risk stratification estimates that guide the appropriate ordering of imaging tests, including CT. For instance, it is recommended that CT should be performed only in patients with a PSA level grater than 20
ng/mL, Gleason score greater than 7, and/or clinical tumor stage T3 or higher (39). This is because the criterion for detection of positive nodal disease at CT is based on node size (> 1 cm diameter), and nodal enlargement due to metastases occurs relatively late in the progression of prostate cancer (Fig 3). Since nodal metastases are often microscopic, neither CT nor standard MR imaging can be used to reliably rule them out. Reported CT sensitivity for the detection of lymph node metastases varies, but it is typically in the range of 36% (40). One study published in 1980 reported an 85% sensitivity and 67% specificity (41), while another published in 1988 reported specificity of as low as 25% (42), which reflects the changes in the presentation of prostate cancer. Oyen et al (43) found a sensitivity of 78% and a specificity of 97% by using a size criterion of 0.6 cm or larger. The same study also reported a specificity of 100% for CT combined with CT-guided fine-needle aspiration biopsy. The smaller size criterion (0.6 cm) and use of fine-needle aspiration have not been widely adopted. It should be noted that the reported sensitivity and specificity of CT are highly dependent on the proportions of high-, medium-, and low-risk patients in the population studied.

Overutilization of CT in the past may have been due in part to the emergence of widespread PSA testing and the resultant rapid shift toward detection of early-stage disease. Currently, the majority of patients with newly diagnosed localized prostate cancer are at low risk for metastases, and the diagnostic yield of CT is low in these patients (40). However, unusual or discrepant clinical data may prompt imaging even if an individual’s risk falls below the recommended thresholds.

CT can be useful as a baseline examination in high-risk patients with clinically apparent, grossly advanced local disease (gross extracapsular disease, gross SVI, or invasion of the surrounding structures, including bladder, rectum, levator ani muscles, or pelvic floor). These patients will almost always fall above the cutoff recommendations for the appropriate use of CT imaging on the basis of DRE findings, PSA level, and Gleason grade; they will also be at risk for lymph node metastases, which may be assessed concurrently (Fig 4).

Metastatic lymph nodes (stage M1) are nodes that lie outside the confines of the true pelvis as outlined earlier, with enlarged nodes typically measuring more than 1.0 cm in the short axis. Nodal disease often progresses in a step-wise fashion, such that retroperitoneal or mediastinal nodal disease is most often accompanied by pelvic lymphadenopathy in the obturator regions (44). Metastases to the pelvic lymph nodes, thought to be uncommon in patients with early-stage prostate cancer, are reported in only 2%–5% of patients (5,45), but there is some uncertainty about the adequacy of pelvic lymphadenectomy in those series (46,47). Removal of grossly enlarged nodes has not been shown to have therapeutic value in prostate cancer (48). However, removal of microscopically positive pelvic lymph nodes during prostatectomy does provide long-term cancer control in 15%–20% of patients (49,50). The cancer-specific survival rate for patients with positive pelvic lymph nodes is excellent (83% ± 3 at 10 years for patients with lymph node metastasis found at pelvic lymphadenectomy) (51).

CT has been used to monitor bone metastases, but bone scanning and MR imaging are superior to CT in the diagnosis of bone metastases (52,53). Lytic and blastic bone metastases will com-
monly be visible at CT, however, and should not be overlooked. CT scans may be normal in cases of metastatic disease detected at radionuclide bone scanning, but CT allows more accurate distinction of malignant from benign causes of increased radioisotope uptake at bone scanning (54). Individual osseous metastases are more accurately defined as individual lesions on a CT scan than on a bone scan and, therefore, clear changes in osseous lesions seen at CT can be used to monitor responses to systemic therapy. Caution should be exercised in interpreting all osteoblastic lesions as metastases, as CT typically depicts the effects of tumor cells on normal osteoblasts rather than directly reflecting metastases, and bone changes in response to therapy may lag behind therapeutic effects.

**MR Imaging**

MR imaging can be used for prostate cancer detection, although it is recommended only if cancer is suspected despite negative transrectal US and biopsy findings. MR imaging can also aid in local and distant staging. Although it is a highly versatile technique, MR imaging has gone through several phases of popularity. Overall, its use has not shown a marked increase in recent years, but at centers that offer the technique the number of prostate MR examinations performed per month ranges from one to 150, which reflects a lack of consensus about the still-evolving role of this modality.

At present, optimal MR imaging of prostate cancer for detection and local staging requires the use of an endorectal coil in conjunction with a pelvic phased-array coil on a mid- to high-field-strength magnet. Thin (3-mm) sections and a small (14-cm) field of view are required to obtain submillimeter-resolution T2-weighted images necessary for local staging (55). The use of an endorectal coil at 3 T is more controversial, as the improved signal-to-noise ratio of the high-field-strength systems can compensate for the lack of signal from an endorectal coil, providing images of a similar quality to those obtained with 1.5-T endorectal MR imaging. However, it is expected, though not yet proven, that the use of an endorectal coil at 3 T will allow better prostate cancer detection. The detection of prostate cancer depends on the type of imaging sequence used. On T1-weighted images, the prostate demonstrates homogeneous medium signal intensity and tumors are impossible to discern. On T2-weighted images, cancer most commonly demonstrates decreased signal intensity relative to the high-signal-intensity normal peripheral zone (56) (Fig 5).

While detection of prostate cancer at MR has been most effective for tumors located in the peripheral zone, MR imaging, especially when combined with MR spectroscopic imaging, can also be used to detect tumors in the transition zone (57). Tumors in the transition zone and those located in the anterior part of the peripheral zone should be carefully sought during MR interpretation in patients with increasing PSA levels and multiple biopsies with negative findings, since these areas often are not routinely sampled or targeted during transrectal US-guided biopsy. Findings supporting the diagnosis of a transition zone tumor include (a) a homogeneous low-signal-intensity region in the transition zone (especially in the absence of a dominant peripheral zone tumor), (b) poorly defined or spiculated lesion margins, (c) lack of a low-signal-intensity rim (seen commonly in association with benign adenomatous nodules), (d) interruption of the surgical pseudocapsule (transition zone–peripheral zone boundary of low signal intensity), (e) urethral or anterior fibromuscular stromal invasion, and (f) lenticular shape (58) (Fig 6). A recent study evaluated the performance of two experienced readers of prostate MR images in the detection of transition zone tumors with endorectal MR imaging; sensitivity and specificity were 75% and 87%, respectively, for reader 1 and

**Figure 5**

*Images in 45-year-old man with prostate cancer stage pT2b and presurgical PSA level of 5.1 ng/mL. (a) Transverse, (b) coronal, and (c) sagittal unenhanced T2-weighted fast spin-echo (repetition time msec/echo time msec of 5000/96 [effective]) MR images demonstrate a low-signal-intensity area (arrow) in the peripheral zone of right posterolateral midgland and apex. Tumor appears confined to the gland, as outer margin in all planes is smooth.*
80% and 78%, respectively, for reader 2, and detection improved significantly when tumor volume was 0.77 cm³ or greater (P = .001) (58).

Postbiopsy hemorrhage may hamper tumor detection in the prostate, leading to either under- or overestimation of tumor presence and local extent. The imaging appearance depends on the length of time between the biopsy and MR imaging. Previously, a delay of 3–4 weeks between biopsy and MR imaging was considered sufficient; however, in the past 10 years, the typical number of biopsy cores has increased, and, therefore, a longer delay of 6–8 weeks is recommended (59–61). The reported accuracy of prostate cancer detection on MR images varies widely, and controversy persists regarding recommendations for the use of MR imaging in the initial diagnosis of high-risk patients or in patients with previous negative biopsy findings but persistently high PSA level (62). Nevertheless, MR imaging has been shown to contribute significant incremental value to both DRE and transrectal US-guided biopsy (P < .01 for each) in cancer detection and localization in the prostate (63).

MR imaging also permits detection of the presence and location of ECE and SVI, and its use in staging prostate cancer is gaining acceptance at select centers around the world (64–66). On endorectal MR images, criteria for ECE include asymmetry of the neurovascular bundle, tumor envelopment of the neurovascular bundle, an angulated prostate gland contour, an irregular or spiculated margin, obliteration of the rectoprostatic angle, capsular retraction, a tumor-capsule interface greater than 1 cm, and a breach of the capsule with evidence of direct tumor extension (65,67,68) (Fig 7). In the evaluation of extracapsular invasion, transverse sections are essential and a combination of transverse and coronal images is ideal. The addition of sagittal images facilitates evaluation of tumor located at the apex and base.

The features of SVI on endorectal MR images include disruption or loss of the normal architecture of the seminal vesicle, focal low signal intensity within the seminal vesicle, focal low-signal-intensity mass effect within the seminal vesicle, enlarged low-signal-intensity ejaculatory ducts, enlarged low-signal-intensity seminal vesicle, obliteration of the angle between the prostate and the seminal vesicle (best seen on sagittal images), and demonstration of direct tumor extension from the base of the prostate into and around the seminal vesicle (64). The combination of tumor at the base of the prostate that extends beyond the capsule and low signal intensity within a seminal vesicle that has lost its normal architecture is highly predictive of SVI (64) (Fig 8). Combined transverse, coronal, and sagittal sections facilitate evaluation of seminal vesicle and bladder neck invasion.

MR imaging has been reported to have 13%–95% sensitivity and 49%–97% specificity for detection of ECE and 23%–80% sensitivity and 81%–99% specificity for detection of SVI (64,69–76). Two studies (77,78) of the same patient population that used pathologic findings from a radical prostatectomy specimen as the standard of reference found that endorectal MR contributed significant incremental value to clinical variables in the prediction of ECE, although the contribution of MR was only significant when MR interpretation was performed by specialists in genitourinary MR as opposed to general body MR radiologists (Fig 9).

Reports of the accuracy of MR imaging in staging prostate cancer have ranged from 54% to 93% (36,62,68,70,73,79), raising concerns about interobserver variability. On the whole, the accuracy of endorectal MR in local staging has improved with time, most likely due to the maturation of MR technology (eg, faster imaging sequences, more powerful gradient coils, and postpro-
cessing image correction), better understanding of morphologic criteria used to diagnose ECE or SVI, and increased reader experience.

In the evaluation of lymph node metastases, unenhanced MR imaging has no advantage over CT. However, promising results have been reported for the use of ultrasmall superparamagnetic iron oxide particles as an aid to diagnosing lymph node metastasis at MR imaging. This technique is discussed later in the Future Prospects for MR Imaging section.

**MR Spectroscopic Imaging**

Prostate MR spectroscopic imaging adds specificity to MR imaging in the detection of prostate cancer and allows assessment of tumor metabolism. MR spectroscopic imaging displays the relative concentrations of chemical metabolites within a small volume of interest or voxel. In vivo proton spectroscopy of the prostate in cancer detection is aimed at determining the levels or concentrations of the metabolites citrate, creatine, and choline, making use of the differences between the normal prostate gland tissue, which contains (secretes) citrate, and prostate cancer, which shows high levels of choline and often diminished citrate levels (Figs 7, 7).

**Figure 7**

Images in 58-year-old man with prostate cancer clinical stage T2a. (a, b) Transverse unenhanced T2-weighted fast spin-echo (5000/96 [effective]) MR images with corresponding spectroscopic data show large low-signal-intensity lesion in the right side of peripheral zone with a focal bulge (arrowhead) and obliteration of the rectoprostatic angle (arrow) in addition to broad (>1 cm) capsular contact. Findings are indicative of ECE, which was proved at surgery (stage pT3a). Abnormal spectra (elevated choline and decreased citrate level) suspicious (SC) or very suspicious (VC) for prostate cancer are seen in voxels containing tumor (+). A = artifactual, ED = ejaculatory duct, H = healthy prostate tissue, ND = nondiagnostic. (c) Corresponding pathology step section shows tumor (outlined) and site of established ECE (arrow). (Hematoxylin-eosin stain.)
The differences in the concentrations of metabolites are believed to be due to enhancement of the phospholipid cell membrane turnover associated with tumor cell proliferation, increased cellularity, and growth.

The addition of MR spectroscopic imaging to MR imaging can significantly ($P < .001$) improve tumor localization within the peripheral zone (80). In the diagnosis of ECE, the combined use of MR imaging and MR spectroscopic imaging significantly increases the accuracy of less-experienced readers and decreases interobserver variability (66). Furthermore, MR spectroscopic imaging can provide an indication of prostate cancer aggressiveness. A study (81) in which MR imaging and MR spectroscopic imaging data were compared with step-section surgical histologic examination in 94 patients found that tumor detection using MR spectroscopic imaging was dependent on the Gleason grade. For Gleason grade 6, tumor depiction was 44%, and it increased to 90% for Gleason grades 8 and 9. A correlation between metabolic abnormality detected at MR spectroscopic imaging and cancer aggressiveness (Gleason grade) at surgical pathologic examination was suggested by the data, although MR spectroscopic findings overlapped at various Gleason score levels (81).

While combined use of MR imaging and MR spectroscopic imaging is typically used to evaluate clinically high-risk cancers, it may also prove useful for evaluating clinically low-risk cancers to assess suitability for deferred therapy. An initial retrospective study of 220 patients with prostate cancer (82) found that in the prediction of insignificant cancer (pathologically defined as organ-confined tumor 0.5 cm$^3$ or less in volume with no element of Gleason grade 4 or 5 cancer), a nomogram model incorporating MR imaging and MR spectroscopic imaging findings with clinical variables yielded an area under the receiver operating characteristic curve of 0.854 and was significantly more accurate than previously published nomogram models that incorporated only clinical variables ($P < .001$). New nomograms incorporating MR imaging and MR spectroscopic imaging data with clinical variables for the prediction of very low-risk cancer are being designed.

Findings from proton high-resolution magic-angle spinning nuclear MR spectroscopy and histopathologic examination can be correlated with preoperative MR imaging and three-dimensional (3D) MR spectroscopic imaging to reveal spectral patterns associated with mixtures of different prostate tissue types and cancer grades, as well as molecular markers (83). Preliminary evidence obtained from prostate cancer tissue profiles supports the role of key molecular markers as a way to improve histologic prediction of prostate cancer aggressiveness. Examples include cellular proliferation markers, apoptosis markers, a variety of serum biomarkers, and molecules associated with key signal transduction pathways (35–37, 40, 84). For example, the tumor cell proliferation marker Ki-67 has shown utility in the prediction of tumor progression, treatment outcome, and biochemical recurrence (41, 42, 85). Research is underway in which MR imaging and MR spectroscopic imaging

Figure 8

Unenhanced T2-weighted fast spin-echo (5000/96 [effective]) endorectal coil pelvic MR images in 61-year-old man with clinical stage T2a prostate cancer. (a) Transverse image shows a dominant tumor (arrow) at the right base; loss of normal contour and irregular bulging are evidence of extracapsular disease. There is direct tumor extension into both seminal vesicles (arrowheads) on (b) transverse and (c) corresponding coronal images, seen as mild enlargement of the involved seminal vesicles and low-signal-intensity tissue replacing normal thin walls and obliterating the lumen (compare to preserved vesicle architecture laterally). (d) Sagittal image shows SVI (arrow) and adjacent tumor extending into extracapsular space between urinary bladder and seminal vesicle.
findings will be correlated with a variety of molecular markers identified at high-resolution magic-angle spinning spectroscopy and immunohistochemistry, including Ki-67, p27/Kip1, PTEN, phosphorylated AKT (an activated oncogene downstream of PTEN), Bax, and Bcl-2.

To date, combined use of MR imaging and MR spectroscopic imaging has been limited to relatively few centers, but robust commercial MR spectroscopic imaging acquisition and display systems are now available. A multi-center American College of Radiology Imaging Network trial for tumor detection using MR imaging alone and MR imaging plus MR spectroscopic imaging with pathologic correlation has been completed, and the data are soon to be analyzed.

**Dynamic Contrast-enhanced MR Imaging**

Like other tumors, prostate cancers induce angiogenesis, which can be used as a diagnostic marker of disease. The normal prostate is a vascular organ, and so rapid injections with rapid scanning are needed to detect angiogenesis in a lesion. Typically, a full dose (0.1 mmol/kg) of gadolinium chelate is injected at 3 mL/sec, and serial 3D acquisitions are obtained every 2–5 seconds through the prostate. Cancers often demonstrate early nodular enhancement before the rest of the parenchyma and early washout of signal intensity. This pattern is highly predictive of prostate cancer but is not pathognomonic. Some prostate cancers are mildly or moderately hypervascular and thus are not detectable with this method. Dynamic contrast-enhanced MR imaging has been shown to have sensitivity of 73% and specificity of 81% in defining prostate cancers (86). A recent study found that dynamic contrast-enhanced MR imaging at 3 T had comparable sensitivity (73%) and specificity (77%) in prostate cancer localization (87). Combining dynamic contrast-enhanced MR imaging and 3D proton spectroscopy may prove helpful in tumor localization when T2-weighted images are inconclusive for a tumor focus (Fig 11). The analysis of dynamic contrast-enhanced MR imaging remains controversial. Relatively simple techniques such as measuring the relative peak enhancement (88) appear to work equally well with more complex methods such as two compartment models (89). For the field to move forward, however, some standardized analytic tools are required so that studies from different institutions can be directly compared.

**Future Prospects for MR Imaging**

Advances are ongoing in the development of new sequences and contrast media for MR imaging. Diffusion-weighted imaging (DWI) is a promising method of imaging prostate cancer that has recently received attention. By virtue of its larger extracellular space and interstitial fluid, prostate cancer has a higher apparent diffusion coefficient than does normal prostate; this property can be used to detect prostate cancer (90). Although DWI offers little benefit compared with T2-weighted imaging in most prostate cancers, it appears to be particularly effective in detecting recurrent disease after radiation therapy or surgery. Subtle changes in apparent diffusion coefficient detected on DWI images are indicative of recurrent disease in patients with increasing PSA levels after treatment. DWI is still not in routine clinical use but is expected to become an important adjunct to endorectal MR in the future.

Another prospect for the future is improved detection of nodal disease with the use of lymphotropic superparamagnetic nanoparticles as a contrast agent at MR imaging. The nanoparticles are taken up by circulating macrophages, which then traffic to the normal nodal tissue. The inability of malignant nodes to take up the agent provides tissue contrast within the lymph node and allows detection of metastases, even in nodes that do not meet the standard size criteria for metastasis (91). In a study in which 71.4% of nodes with histopathologically detected metastases were of normal size, sensitivity and specificity for the detection of metastasis on a node-by-node basis were 35.4% and 90.4%, respectively, for conventional MR imaging and 90.5% and 97.8%,

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**Figure 9**

Graphs show receiver operating characteristic (ROC) curves in detection of ECE for base model with and without endorectal MR imaging findings in (a) patients whose MR imaging studies were evaluated by genitourinary radiologists and (b) patients whose MR imaging studies were evaluated by general body radiologists. Base model included PSA level, Gleason score, greatest percentage of cancer in all core biopsy specimens, percentage of cancer-positive core specimens in all core biopsy specimens, presence of perineural invasion, and tumor clinical stage. Base model with endorectal MR findings included MR findings with all other variables. Predicted probability was calculated with jackknife method. Diagonal line indicates area under ROC curve of 0.500. (Graphs courtesy of Michael Mullerad, MD, Department of Urology, Bnai-Zion Medical Center, Haifa, Israel.)
respectively, for MR imaging with lymphotropic superparamagnetic nanoparticles; on a patient-by-patient basis, MR imaging with lymphotropic superparamagnetic nanoparticles had a sensitivity of 100% and a specificity of 95.7% (92). Since the incidence of lymph node metastasis in patients with newly diagnosed prostate cancer appears to be only 5% or less, it has been suggested that a combination of conventional MR imaging, which offers high negative predictive value for lymph node metastasis and anatomic information useful for treatment planning, and the standard staging nomogram, which has high accuracy in predicting lymph node metastasis, might be used to select patients for MR with lymphotropic superparamagnetic nanoparticles (30,93).

**Radionuclide Bone Scanning**

Radionuclide bone scanning has no role in prostate cancer detection or local staging; however, bone metastases are a common complication of prostate cancer, and bone scanning continues to be the mainstay of diagnosis of initial spread of cancer to bone. Evidence-based guidelines on the use of imaging in assessing the risk of distant spread of prostate cancer have been available since 1993, when it was proposed that routine bone scans should not be used for patients with PSA below 10 ng/mL (94). In 1997, O’Dowd et al (39) reconfirmed the recommendation that bone scans should be obtained routinely only for patients with PSA level greater than 10 ng/mL. Use of the bone scan has been modified in recent years by the measurement of PSA level. If the PSA level is less than 10 ng/mL (95), chances of a positive bone scan are less than 1%. When the PSA level is 10–50 ng/mL, the incidence of a positive bone scan increases to about 10%, and with PSA level above 50 ng/mL, it increases to about 50%. In our practice, we generally reserve bone scanning for patients with PSA level greater than 10 ng/mL.

The radionuclide bone scan is simple to obtain and is a sensitive method for detecting osseous metastases, especially osteoblastic metastases. The most common appearance is of a focal area of...
increased tracer uptake, usually in the axial skeleton, related to host osteoblastic bone response to tumor invasion (Fig 12). Less commonly, an area of reduced uptake may be present, which reflects extensive damage to bone with little osteoblastic response. Bone scans are more reliable than symptoms alone in the evaluation of bone metastatic disease, and in one series, 34% of asymptomatic patients had abnormal scans (96). In the evaluation of 1403 patients with prostate cancer, bone scans were 28% more sensitive than conventional radiographs in detecting metastatic skeletal lesions (96).

MR imaging has been shown to be both sensitive and specific in the diagnosis of bone metastases; in fact, small metastatic deposits in the bone and bone metastasis without cortical involvement may be seen earlier on MR images than on bone scans (Fig 13) (52). However, other causes of altered marrow signal intensity (eg, infection, infarction, trauma) can mimic metastatic disease at MR imaging, and the examination typically is limited to answering a specific question raised as a result of findings of other modalities (97). Thus, the overall sensitivity of radionuclide bone scanning, combined with the ability to survey the entire skeleton, results in this modality continuing to be the initial test of choice for assessing osseous metastases.

Radionuclide bone scanning can also be used to assess the response to treatment, as uptake usually decreases after chemotherapy, hormone therapy, or radiation therapy if a response is obtained. In patients with prostate and breast cancer, a “flare” phenomenon may be observed, where uptake initially increases after chemotherapy or hormone therapy, peaking at 6 weeks after treatment as bone turnover increases as part of the healing process (98,99). Care must be taken in this situation to avoid mistaking apparent new lesions for areas of new metastatic disease, when subtle changes were in fact present in prior studies.

Single photon emission computed tomographic (SPECT) studies of the skeleton have been shown to be more sensitive in the detection of metastatic disease than planar images alone and are usually performed when symptoms or clinical suspicion for disease are present, particularly bone pain. This technique has particular utility in the evaluation of the spine in patients with low back pain who present for evaluation of possible metastatic disease. Sites of abnormal uptake may be localized to the vertebral body or posterior elements, leading to other radiologic techniques for confirmation. Uptake in facet joints, in the absence of signs of metastatic disease on radiographs, may indicate active arthritis as the cause of a patient’s back pain (100,101). Combined SPECT/CT, a recent development, adds anatomic information to SPECT, and its incremental value to SPECT is yet to be evaluated (Fig 14).

**PET Imaging**

PET uses compounds labeled with positron-emitting radioisotopes to detect pathologic processes (102). Most clinical PET studies to date have been performed with the glucose analogue fluorine 18 (¹⁸F) fluorodeoxyglucose (FDG). Cancers have increased metabolism and utilize the less-efficient glycolytic pathway, both of which lead to increased glucose analogue uptake (103,104). Increased glucose uptake and metabolism in tumors are facilitated by an elevated expression of glucose transporters, which has been shown in several cancers (105–112). The magnitude of the elevated FDG uptake and accumulation in tumors is commonly expressed by the standardized uptake value, defined as the ratio of activity per unit mass in the lesion to the ad-
ministered activity per unit mass in the patient.

In the evaluation of prostate cancer, several studies have reported a disappointingly low sensitivity of FDG PET for tumor detection. Furthermore, it has been reported that there is no difference in tracer uptake between benign prostate hyperplasia and prostate carcinoma (113–116). In support of the value of FDG PET is one study that reported an 83% sensitivity for the detection of primary prostate cancer; the study was performed in patients with advanced clinical stage and more aggressive cancers (117). In the evaluation of pelvic lymph node metastases, Shreve et al (118) found that FDG PET was not helpful owing to excreted tracer in the urinary bladder that caused obscuration of the pelvis. In another study (119), the sensitivity of PET for the detection of nodal metastases appeared to be greater than that of CT, but the difference was not statistically significant. Until recently, one of the limitations of PET for prostate cancer has been the use of filtered back-projection algorithms for image reconstruction, which causes streak artifacts arising from the FDG-filled bladder and, hence, poor image quality. Newer iterative image reconstruction techniques, with noise-reduced segmented attenuation correction, may help to eliminate this problem. New reports have shown that primary prostate cancer can be imaged with FDG PET and that the image quality is significantly improved with iterative image reconstruction (120). Use of PET/CT units results in improved attenuation correction of the PET emission data, which speeds up the acquisition of a PET scan substantially (by approximately 30%) relative to dedicated PET scanners utilizing transmission rod sources. Particularly relevant to prostate cancer is the capacity of PET/CT to demonstrate tumor location in the prostate bed (Fig 15) and to better assess pelvic lymph node disease. Furthermore, combined PET/CT allows differentiation between tumor and tortuous ureter or bowel in the midabdomen or pelvis (121). In the evaluation of bone metastasis, precise localization of metastatic disease af-

Figure 12: 

Figure 12: 

Figure 13:

Figure 13: 

Figure 13: Images in 56-year-old man after radical retropubic prostatectomy with rising PSA level at 10 ng/mL. (a) Transverse unenhanced T2-weighted fast spin-echo (5000/96 [effective]) MR image shows ovoid low-signal-intensity lesion (arrow) suspicious for bone metastasis in left inferior pubic ramus. Bone scan at that time was normal (not shown). (b) Anterior coronal image from a bone scan 3 months later shows focal increased tumor activity (arrow) as confirmatory evidence of metastasis.
fords new treatment options (bone ablation) and more precise treatment follow-up (Fig 16).

Despite the usefulness of FDG in PET/CT imaging, FDG has limitations with regard to distinguishing tumors from inflammation (122). Future applications of PET will therefore involve new tracers, which are currently under clinical investigation. One of these tracers is carbon 11 ($^{11}$C) methionine, which differentiates tumor from normal tissue due to elevated protein synthesis (123). $^{11}$C has an approximate half-life of 20 minutes and so must be used rapidly after production. Although the use of $^{11}$C agents requires a local cyclotron and is therefore not a widely available option, the rapid 10-minute uptake and plateau of $^{11}$C-methionine within prostate cancer allows whole-body PET/CT imaging (with decay correction). By using $^{11}$C there is also minimal interference from the bladder (124). Other $^{11}$C-labeled PET agents include $^{11}$C acetate and $^{11}$C choline, both of which have shown promise in imaging prostate cancer metastases.

Another important discovery is that the use of multiple tracer studies in the same patient frequently displays the heterogeneity of tumor biology. Patients who receive $^{11}$C-methionine and FDG scans on the same day may display metastases that are positive for both tracers, $^{11}$C-methionine only, or FDG only (125). Such features indicate changes in tumor biology as the tumor adapts to each sanctuary site.

In search of a noninvasive method to quantify androgen receptors at PET, $^{18}$F fluorodihydrotestosterone has recently been studied in patients with metastatic prostate cancer. The mismatch between FDG and $^{18}$F fluorodihydrotestosterone findings suggests the variations in androgen dependence of the different sites of disease. Histologic confirmation of this hypothesis has not yet been performed. Therefore, the optimal choice of radiotracers for tumor diagnosis and follow-up depends on the organ site. Nevertheless, the concept of using PET with multiple radiotracers that answer different questions is likely to become an important thrust in the future of metabolic prostate cancer imaging.

In the future, molecular imaging will influence prostate cancer more and more as new tracers are developed, including
antibodies that target important prostate-specific molecules such as prostate-specific membrane antigen. Gene expression imaging and imaging of cell trafficking during adoptive immunotherapy are on the near horizon.

**Use of Imaging in Treatment Planning**

Imaging plays an important role in planning treatment both for surgery and radiation. In this section, we consider the specific roles for imaging in guiding treatment selection and planning.

**Imaging prior to Surgery**

Because the size and shape of the prostate varies so greatly and the location and extent of cancer are so difficult to determine with DRE, radical prostatectomy is a particularly challenging operation (126). Removing the prostate is not in itself difficult, but complete removal of the cancer, with negative surgical margins and without damage to the surrounding structures crucial for recovery of normal urinary and sexual function after the operation, is extremely challenging (127,128). As much as with any surgical procedure, adverse results—positive surgical margins, perioperative complications, urinary incontinence, and erectile dysfunction—vary with surgical experience and technique (129–131). The information from MR imaging may help surgeons plan a safer, more effective operation that removes the cancer completely (with negative surgical margins) while preserving periprostatic tissues important for recovery of urinary and sexual function.

A study (132) of 76 patients showed that preoperative reviews of endorectal MR images significantly improved the accuracy of the surgeon’s decision to preserve or resect the neurovascular bundle(s) at radical prostatectomy ($P < .01$). Twenty-four percent of patients had a more aggressive surgical plan when MR images were reviewed together with the clinical data. For 165 neurovascular bundles, the surgeon judged that resection was definitely not necessary; MR imaging helped confirm that decision for 138 of these neurovascular bundles (84%), and the confirmation was correct in 96% (133 of 138) of the cases. In 36 high-risk patients (ie, patients with ≥75% probability of ECE), MR findings changed the surgical plan for 28 (78%) neurovascular bundles; the change was appropriate in 26 (93%) cases (132). Thus, MR imaging improved surgical planning for high-risk patients and appropriately supported the decision not to resect neurovascular bundles in other patients.

MR imaging may help predict substantial intraoperative blood loss, as the prominence of apical periprostatic veins on MR images was positively associated with blood loss in one series (133) (Figs...
In another study, a multivariable analysis of risk factors showed that the length of the membranous urethra on coronal endorectal MR images was an independent predictor for the time to recovery of urinary continence (134). Patients with longer than average (14-mm) membranous urethra lengths experienced a more rapid return to complete continence.

Most cancers treated with radical prostatectomy today are not palpable, so the surgeon has little idea of the size, location, and extent of the cancer. Systematic biopsy results have been used to “map” the location of cancer in the prostate, but this requires the physician performing the biopsy to meticulously label the location of each core (135). Many cancers can be seen at endorectal MR imaging, especially in conjunction with spectroscopy. Superior efficacy of MR imaging compared with transrectal US for the prediction of ECE has been shown (75). With accurate information about the presence and location of ECE, the surgeon can modify the operation, for example, to resect more widely in areas of possible ECE or to dissect closer to the prostate in areas of the neurovascular bundles when the risk of ECE is low. Visualization of a large, anterior transition zone cancer on preoperative MR images (Fig 7) should lead to more distal transection of the dorsal vein complex over the urethra (126). A prominent tumor in the posterior apex would warn the surgeon to dissect more widely in that difficult area. While the staging accuracy of MR imaging has not yet been firmly established in large prospective clinical trials, we believe that the information about prostate cancer provided by endorectal MR imaging has led to better patient selection, safer operations, and a lower rate of positive surgical margins (70,128).

**Imaging in Radiation Oncology**

The planning, delivery, and verification of radiation therapy are based on contemporary and evolving imaging techniques. Advances in imaging technology and the development of sophisticated radiation dose calculation algorithms have led to remarkable improvements in tumor localization and generation of dose-distribution plans that conform to the anatomic configuration of tumor targets. The development of image-based computer treatment planning systems during the 1980s allowed CT image data to be incorporated into radiation therapy treatment plans, heralding the beginning of modern 3D conformal radiation therapy (95,136). The 3D conformal radiation therapy approach is composed of a series of...
computer-based procedures to define target and nontarget tissue structures from patient-specific 3D image data sets, the design of treatment portals by using beam’s-eye-view displays, calculation and display of 3D dose distributions, and the analysis and evaluation of structure-specific dose-volume data. In the treatment of prostate cancer, the use of conventional radiation therapy dose levels of 65–70 Gy administered with traditional two-dimensional planning and delivery treatment techniques has had limited success in controlling localized disease. By improving the conformity of dose distribution, the 3D conformal radiation therapy approach has allowed significant increases in tumor dose to levels beyond those feasible with conventional two-dimensional radiation therapy, without a concomitant increase in normal tissue complications.

Intensity-modulated radiation therapy (IMRT) developed during the past decade is an advanced mode of conformal radiation therapy that improves the ability to deliver high doses to the prostate with enhanced precision (137–139). Treatment planning is based on inverse planning algorithms and iterative computer-driven optimization to generate treatment fields with varying radiation intensities within each beam. Combinations of intensity-modulated fields produce custom-tailored conformal dose distributions around the tumor, with steep dose gradients at the transition to normal tissues. In prostate cancer, IMRT has resulted in reduced rectal toxicity and has permitted tumor dose escalation to previously unattainable levels (up to 86 Gy). Both retrospective and prospective randomized trials support the concept that higher dose levels delivered with conformal approaches significantly improve disease-free survival (140–142). This approach is an example of how prostate cancer will be treated with external-beam irradiation in the years ahead.

Traditionally, verification of treatment delivery has been based on conventional radiographs or electronic portal images obtained while the patient is positioned on the treatment couch by using bony anatomic landmarks as reference points. However, the increased precision of treatment planning and delivery has required the development of new, advanced imaging systems for verification that are applied before or even during treatment. The goal is to delineate the position of the targeted tissue and to make any necessary corrections for deviations related not only to patient positioning but also to organ motion. These imaging tools, when interfaced with modern radiation delivery systems, comprise what is now called image-guided radiation therapy. The approaches used in the localization of prostate cancer have included transabdominal US-guided tracking, as well as monitoring the location of radiopaque fiducial markers with electronic portal imaging devices. More recently, image-guided treatment technology has been developed to visualize the prostate by using CT technology. Several approaches are being implemented. They include the use of linear accelerator-mounted x-ray tubes and two-dimensional detectors (eg, electronic portal imaging devices) to produce kilovoltage cone-beam CT images. Megavoltage CT images of the irradiated region can be generated by rotation of the therapeutic beam. This approach is available with helical tomotherapy, where images can be acquired not only before and after but also during treatment. Last, CT scanners have been placed in the treatment room either as part of the treatment machine or with the capability of transferring the patient in the treatment position on a common couch top from one device to the other (143).

To appreciate and apply optimal imaging protocols, it is essential to understand radiation therapy needs and the new concept of “dose painting” with IMRT. Although the classic approach to radiation therapy applies homogeneous dose distributions within the targeted tumor to avoid underdosing tumor de-
posits, recent advances in imaging provide an approach to define anatomic subregions of the tumor according to their level of radiosensitivity or radiore- sistance. IMRT provides an approach for differential dose painting to selectively increase the dose to specific tumor-bearing regions. With IMRT techniques, radiation dose distributions can be produced that permit simultaneous delivery of different dose prescriptions to multiple target sites. To be able to dose paint, one needs to know the tumor location, volume, and extent. Furthermore, information regarding tumor biology (e.g., tumor aggressiveness, angiogenesis, hypoxia) is becoming essential (144). For example, functional imaging is already capable of identifying foci of hypoxic tumor clones that may require enhanced local doses. Recent data suggest that foci of high-Gleason-score prostate cancer may require doses of 90 Gy to achieve maximal levels of local control (145). Although it is not feasible to treat the whole prostate to this dose level without exceeding the tolerance of the urethra and the rectum, IMRT can be used to increase the dose to selected tumor-bearing regions within the prostate (146). The ability to deliver a dose of 90 Gy to the dominant intraprostatic lesions while treating the entire prostate to 81 Gy and keeping the dose to the rectum and bladder below tolerance represents a new paradigm in the management of prostate cancer with IMRT (147). With the ability of MR spectroscopic imaging to identify high-Gleason-score (>8) prostate cancer, and with improved tumor localization when using combined MR imaging and MR spectroscopic imaging data, the first IMRT dose-painting clinical trials are under way. On the basis of such anatomic and metabolic information, patient-specific parametric images have been used to dose paint during brachytherapy as well (Fig 18) (144).

Helical scanners—especially multidetector CT scanners—yield anatomic information with consistently high-quality images devoid of motion artifact. Relative to CT, MR imaging provides improved soft-tissue contrast. In the evaluation of the prostate, MR imaging demonstrates zonal anatomy and depicts tissue abnormalities. MR imaging by itself, however, may not be sufficient for treatment planning, since it does not provide anatomic information in terms of electron density as needed for dose calculations. However, with spatial registration of images from the two modalities, the combination of x-ray attenuation data from CT and tissue contrast from MR imaging provides a powerful planning tool. Combined CT and MR images are being explored in radiation treatment planning for prostate cancer. The additional information provided with MR imaging includes better definition of the border between the prostate and the bladder and seminal vesicles, the location of the apex of the prostate, and the length of the membranous urethra (easily measured from sagittal and coronal MR images) for determining the caudal margin of the planning target volume and for sparing the penile bulb. In addition, the presence of ECE and seminal vesicle involvement can be defined and appropriate margins can be added to ensure adequate coverage of the tumor target. We have found that treatment planning with MR images coregistered to CT simulator images is invaluable in patients with metallic orthopedic hip prostheses, which result in distortion due to a signal void on CT images. Dedicated MR stimulators are likely to become part of the radiation oncology treatment planning armamentarium in the near future (148).

### Imaging in Treatment Follow-up

The role of imaging after therapy depends on the treatment used (watchful waiting, radical prostatectomy, radiation therapy, or androgen deprivation therapy) and on clinical and laboratory findings. Regardless of the type of treatment, serial measurements of PSA level and DRE findings are the standard tools used in monitoring for tumor recurrence. The earliest and most common indication of recurrent cancer is an increasing serum PSA level. There is no...
need for routine imaging studies if the PSA level is undetectable and there are no new clinical findings.

When the PSA level is elevated, three main categories of prostate cancer recurrence are considered: PSA-only relapse, local recurrence (in the postprostatectomy bed after radical prostatectomy or in the gland after radiation therapy), and distant metastases (most commonly nodal or osseous). The key clinical consideration in evaluating a patient with a possible recurrence is the differentiation between local and metastatic relapse. Clinical nomograms used to predict whether a recurrence is more likely local or metastatic have been widely studied and their clinical relevance has been determined (30,149,150). The nomograms are based on clinical parameters such as tumor stage and grade at the time of diagnosis and the PSA doubling time. Distant recurrence is suggested by a short PSA doubling time (<10 months) in a patient with a high-grade cancer (Gleason score 8–10) or a high pathologic stage (SVI or lymph node metastases). By contrast, local recurrence is typically marked by a prolonged doubling time (>10 months) in a patient with a Gleason score of 2–7, a positive surgical margin, and no involvement of the seminal vesicles or lymph nodes (149).

In a patient cured with surgery, the PSA level should decline to an undetectable level within 21–30 days after surgery and remain undetectable thereafter (151,152). PSA level decreases more slowly after definitive radiation therapy than after surgery and may not reach a nadir until 18–30 months after treatment (153,154). Although any increase in PSA level after radical prostatectomy indicates recurrence, the American Society for Therapeutic Radi-
ation Oncology defines a biochemical recurrence for a postirradiated patient as three consecutive increases in PSA level from the nadir, with the date of recurrence assigned halfway between the dates of nadir and the first increase. Recently, however, it has been shown that the definition of PSA failure as nadir plus 2 ng/mL provides a better surrogate for treatment failure in patients treated with permanent prostate brachytherapy or external-beam radiation therapy (155). The reported rate of biochemical relapse after radical prostatectomy ranges from 10% to 53% (150,151,156–161). Biochemical relapse after radiation therapy occurs at a similar rate. When local recurrence is suspected because of increasing PSA level or because a nodule or induration has been felt at DRE, a diagnostic work-up is initiated.

Imaging has not been widely used for the detection of local recurrence. Transrectal US, CT, and MR imaging, however, have been evaluated for detection of local recurrence after prostatectomy. The most commonly used imaging study is transrectal US. It has been shown that transrectal US is more sensitive than DRE (76% vs 44%), albeit less specific (67% vs 91%) (162). The overall transrectal US-guided biopsy detection rate was 41%. The constellation of findings most associated with local recurrence was a PSA level above 4 ng/mL and positive DRE and transrectal US findings (162). In a study evaluating CT detection of local recurrence after radical prostatectomy, only 36% of lesions were detected, and in all patients in whom the recurrence was detected the tumor size was larger than 2 cm (163). Endorectal MR has proved capable of detecting local recurrence in many patients with an increasing PSA level but no palpable tumor in the prostatic fossa. An initial study demonstrated the potential of endorectal MR to evaluate local recurrence after prostatectomy with excellent sensitivity (100%) and specificity (100%) (164). A study in a larger patient cohort confirmed the high sensitivity and specificity of MR imaging in this setting (165). Local recurrences can be detected at MR in the perianastomotic and retrovesical regions (Fig 19). These two sites are readily identified on transrectal US scans and subsequently confirmed at transrectal biopsy (162). However, 30% of local recurrences, as shown at MR imaging, can occur elsewhere in the pelvis, at sites of retained seminal vesicles or at the lateral or anterior surgical margins (Fig 20) (165). MR imaging has the potential to direct a transrectal biopsy to these sites and thus may lead to a better diagnostic yield than transrectal US. An additional advantage of MR over transrectal US is the capacity to use both endorectal and pelvic phased-array coils to concomitantly evaluate pelvic lymph nodes and osseous structures, thus allowing detection of all sites of pelvic relapse in a single examination.

MR imaging and MR spectroscopic imaging may also have a role in the assessment of recurrence after radiation treatment (Fig 21). In a recent study, two radiologists used MR imaging to evaluate prostate cancer recurrence after radiation treatment in patients scheduled for salvage prostatectomy. They achieved sensitivities of 76% and 55% and specificities of 73% and 65% for tumor detection by quadrant, sensitivities of 86% and 64% and specificities of 84% and 76% for ECE, and sensitivities of 58% and 42% and specificities of

Figure 23: Comparison of scans in evaluation of osseous metastasis. (a) Unenhanced CT scan in a patient with known metastatic prostate cancer. Focal increased mineralization in T12 vertebral body (arrow) is consistent with prostate cancer metastasis. (b) Coronal FDG PET scan obtained at same time shows increased activity at corresponding level, consistent with active metastasis. (c) Transverse CT scan in same patient after androgen ablation therapy at same level as a shows increased mineralization; lesion (arrow) measures and appears even larger, raising question of lesion growth versus healing. (d) Coronal FDG PET scan obtained at same time as c shows marked decrease in FDG activity compared with that in b, indicating healing and favorable treatment response.
96% and 96% for SVI—values similar to those found in studies of untreated patients (166). Furthermore, a preliminary study in nine patients found that MR spectroscopy had higher sensitivity than MR imaging, DRE, and transrectal US-guided biopsy (77% vs 68%, 16%, and 48%, respectively) for the detection of recurrence after radiation therapy, although MR spectroscopic imaging also had lower specificity (78%) than the three other modalities, each of which had specificity greater than 90% (167).

Imaging plays a central role in evaluating a patient for metastatic disease when recurrence is suspected. With an increasing PSA level, the initial study ordered in a search for metastases is a bone scan. Technetium bone scanning is considered the standard for detecting osseous metastases. The bone scan, however, is rarely positive until PSA levels are high, around 30 ng/mL (168). In a recent study (169), a nomogram based on commonly available data (including results of pathologic analysis of the surgical specimen and postoperative follow-up) was developed for estimating the probability of a positive bone scan after biochemical failure and before the administration of hormonal therapy; the nomogram proved to be highly discriminating (bone scan results were predicted with a concordance index of 0.93). Although the nomogram does not apply to patients treated with androgen deprivation therapy, it may prove useful for selecting patients according to their risk of a positive scan and for reducing the total number of scans ordered (169).

If the bone scan is unequivocally positive, imaging assessment is essentially completed. Equivocal findings on a bone scan may warrant further imaging for clarification. Bone scanning is also widely used in treatment follow-up, but FDG PET is emerging as a modality of choice in treatment follow-up of bone metastasis in patients with aggressive disease. PET is better than either bone scanning or CT for differentiation between “active” bone metastasis and healing bone (121) (Fig 22). The routine use of CT in follow-up of skeletal metastasis from prostate cancer is not recommended (Fig 23). CT can play a role in the assessment of more aggressive lytic lesions with potential for pathologic fracture. CT and FDG PET scans are used in the evaluation of nodal disease. Since most patients undergo a staging lymphadenectomy during radical prostatectomy, assessment for nodal disease with cross-sectional imaging in patients who have undergone surgery is focused on common iliac and retroperitoneal nodes. In patients treated with radiation therapy, cross-sectional imaging of the entire pelvis to evaluate for lymph node metastases is standard.

**Summary**

Substantial progress has been made in the imaging of prostate cancer, particularly in MR imaging, MR spectroscopic imaging, PET/CT, and SPECT/CT; these advances are beginning to translate into better treatment selection and more accurate image-guided therapies, including surgery and radiation therapy. In addition, our increased understanding of the early detection of local and distant recurrences is leading to more accurate assessments of patients with increasing PSA levels after therapy. It is hoped that these advances in imaging, and future advances in molecular imaging, will contribute to long-term improvements in morbidity from prostate cancer and patients’ quality of life and to a decrease in mortality from prostate cancer that we are now just beginning to see.

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