Novel imaging techniques for prostate cancer should improve staging and better evaluate treatment results.

Introduction

Imaging for prostate carcinoma can serve several clinical goals. First, it can assist in assessing the primary or recurrent tumor within the prostate gland, as well as tumor size, multifocality, extracapsular extension, seminal vesicle extension, neurovascular bundle involvement, and bladder involvement. Second, imaging can be used to assess metastatic disease such as spread to lymph nodes and bones. Third, imaging is used to guide interventions such as prostate biopsies or computed tomography (CT)-guided biopsy of suspicious lymph nodes. Fourth, functional or metabolic imaging could potentially assess tumor aggressiveness.

Background: Imaging of prostate carcinoma is an important adjunct to clinical evaluation and prostate-specific antigen measurement for detecting metastases and tumor recurrence. In the past, the ability to assess intraprostatic tumor was limited.

Methods: Pertinent literature was reviewed to describe the capabilities and limitations of the currently available imaging techniques for assessing prostate carcinoma. Evaluation of primary tumor and metastatic disease by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and nuclear medicine techniques is discussed.

Results: Ultrasonography and MRI have limited usefulness for local staging of prostate cancer because of suboptimal sensitivity and specificity for identifying tumor extent and capsular penetration. Additional MRI techniques such as magnetic resonance-based perfusion imaging, diffusion imaging, and spectroscopy may provide incremental benefit. CT and bone scanning provide an assessment of metastatic disease but are also limited by the poor sensitivity of lymph node size as a criterion for detecting metastases. Novel imaging techniques such as hybrid imaging devices in the form of single-photon emission CT/CT gamma cameras, positron emission tomography/CT cameras, and, in the near future, positron emission tomography/MRI combined with tumor-specific imaging radiotracers may have a significant impact on tumor staging and treatment response.

Conclusions: Cross-sectional imaging and scintigraphy have an important role in assessing prostate carcinoma metastases and treatment response. Increasingly, the incremental value of primary tumor imaging through MRI is being realized.
or other parameters that correlate with outcome, although such techniques have not yet entered routine clinical practice. It is hoped that these novel imaging methods will be superior to the current standard means in assessing mortality, tumor size, and therapeutic response to targeted therapies. This review focuses on the main imaging methods and their use for these purposes.

The National Comprehensive Cancer Network clinical practice guidelines show a fairly limited role for imaging in patients with prostate carcinoma (Table 1).\(^1\) According to these guidelines, imaging is largely used to evaluate metastatic disease, with a limited role for endorectal magnetic resonance imaging (MRI) in patients who have received radiation therapy but have evidence of failure by prostate-specific antigen (PSA) level. According to these recommendations, low-risk prostate cancer requires no imaging; however, actual adherence to these guidelines by urologists is highly variable.\(^2\) Many more applications and types of imaging have been explored, with a plethora of suggested imaging applications for the management of prostate carcinoma. Many of these, such as investigational nuclear medicine agents, are exploratory, but others, such as endorectal MRI for initial staging, have been the focus of numerous studies.

Reports on the diagnostic performance of some of these techniques vary widely in the literature, particularly regarding MRI. In some respects, this resembles the decline effect\(^3\) or other statistical biases,\(^4\) but methodological aspects assess diagnostic performance in the prostate that may give rise to these varying results. To determine the accuracy of a diagnostic technique such as MRI in locating a tumor within the prostate, it is common to divide the prostate into multiple areas or segments and determine the presence or absence of the tumor in each segment. These results can be correlated with the absence or presence of tumor on MRI. If the prostate specimen is distorted during processing or if discordance exists between the orientation of the pathological specimen to MRI, then the diagnostic accuracy will be poor, not related to the actual performance of the technique.\(^5,6\) Different results can be obtained, for example, when exact correspondence is required rather than when approximate correspondence is required.\(^5\) These methodological problems may lead to varying results and introduce bias in reported results for the diagnostic performance of MRI and for other diagnostic techniques. Turkbey et al\(^7\) found a 61% sensitivity rate for the detection of tumors larger than 3 mm in size on T2-weighted images using a stringent correlation and 94% sensitivity rate for less stringent correlation. The magnitude of this discrepancy indicates that correlating imaging findings with histology is not as straightforward as one might think.

### Evaluation of the Primary Tumor

#### Transrectal Ultrasonography

Ultrasonography is the most common method used for direct visualization of the prostate, primarily because it is indispensable to imaging-guided prostate biopsies. Ultrasonography has the advantages of real-time imaging, portability, ease of use, and low cost. It can visualize intraprostatic zonal anatomy, with the peripheral zone showing slightly increased echogenicity compared with the central gland. Prostate carcinoma typically presents as a hypoechoic area within the peripheral zone (Fig 1). However, transrectal ultrasonography is not highly sensitive or specific for the detection of prostate carcinoma.\(^8\) Color Doppler and power Doppler imaging do not substantially add accuracy to the technique.\(^9\) However, vessel density as shown on color Doppler and power Doppler imaging may have prognostic importance, with high vessel densities predicting a slower rate of decline of PSA with radiation treatment.\(^10\) Similarly, transrectal ultrasonography has limited accuracy for the detection of extraprostatic extent of tumor.\(^11\)

<table>
<thead>
<tr>
<th>Clinical Group</th>
<th>Indicated Imaging</th>
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<tbody>
<tr>
<td>New diagnosis: &gt; 5-yr life expectancy</td>
<td>Bone scan if: T1 and PSA &gt; 20; T2 and PSA &gt; 10; Gleason score 8; T3, T4, or symptomatic</td>
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<tr>
<td>Pelvic CT or MRI if: T3, T4, or T1–T2 and nomogram indicate probability of lymph node involvement &gt; 10%(^*)</td>
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<tr>
<td>Rise in PSA following prostatectomy</td>
<td>± CT; ± MRI; ± Bone scan</td>
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<tr>
<td>Rise in PSA following radiation</td>
<td>± Abdomen/pelvis CT or MRI; ± Endorectal MRI; ± MR spectroscopy; Bone scan</td>
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\(\*\) Staging studies may not be cost effective until the likelihood of lymph node positivity reaches 45%.

\(\text{CT} = \text{computed tomography}; \text{MR} = \text{magnetic resonance imaging}; \text{MRI} = \text{magnetic resonance imaging}; \text{NCCN} = \text{National Comprehensive Cancer Network}; \text{PSA} = \text{prostate-specific antigen}; \text{T} = \text{tumor}.\)
nography has no role in the evaluation of metastatic disease. However, ultrasonographic-guided needle biopsy of suspicious nodes found on CT or MRI is useful for confirming metastatic disease.

Ultrasonographic contrast agents can show hypervascularity, such as that caused by tumor angiogenesis, and can be used in transrectal ultrasonography of the prostate. However, the interpretation of the literature on contrast-enhanced ultrasonography for carcinoma detection is difficult for several reasons. Multiple contrast agents have been studied, and results may not be comparable across all contrast agents. The contrast effect on the ultrasonographic images is fleeting, and expertise is required. Furthermore, studies generally compare positivity rates of directed biopsies with random biopsies rather than whole mount sections after prostatectomy. However, it seems clear that contrast-enhanced ultrasonography can improve the positivity of directed biopsies vs random biopsies. Furthermore, the additional benefit of contrast-enhanced ultrasonography is fairly modest. Because contrast-enhanced ultrasonography detects hypervascularity, the detected tumors tend to have higher Gleason grades and therefore are more likely to be clinically significant. The vast majority of targeted biopsies are negative, and many tumors detected by blind biopsies are not targeted using contrast-enhanced ultrasonography.

Elastography is a relatively new technique that measures tissue stiffness using ultrasonographic waves. Cancer tissue is generally stiffer than noncancerous tissue and therefore is more resistant to mechanically induced vibration. Initial results have not shown high sensitivity and specificity.

**Magnetic Resonance Imaging**

Although generally more involved and expensive than ultrasonography, MRI has the potential to provide significantly more information. Tissue properties such as diffusion, enhancement, and specific metabolites can be imaged with high resolution. In addition, a high-resolution study of the prostate can be easily combined with an examination of the abdominal and pelvic lymph node chains for comprehensive evaluation. A glossary of selected MRI terms are provided in Table 2.

**Performing the Examination**

Clinical interest in staging prostate carcinoma with MRI arose largely after the invention of the endorectal coiler.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Diffusion-weighted imaging</td>
<td>Images or a series of images that show relative loss of signal intensity in tissues or fluid that has unrestricted diffusion. Frequently, an image map of the apparent diffusion coefficient is calculated from a set of diffusion-weighted images with increasing strengths of the diffusion encoding gradients, or b value.</td>
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<tr>
<td>Dynamic contrast-enhanced imaging</td>
<td>A set of fast images obtained during the injection of a contrast agent, showing uptake of the contrast agent in the prostate and tumor. Rapid arterial enhancement of tumors is typical because of angiogenesis.</td>
</tr>
<tr>
<td>Superparamagnetic</td>
<td>Having magnet-like properties, usually due to complexes of iron, which causes dephasing (loss of coherence) and, thus, loss of signal intensity on the images. Superparamagnetic iron oxide agents reveal loss of signal on the images due to this effect.</td>
</tr>
<tr>
<td>Endorectal coil</td>
<td>A receiver coil covered with a latex inflatable balloon and placed in the rectum to lie adjacent to the prostate to optimize the signal from the prostate, allowing higher-resolution images of the prostate.</td>
</tr>
<tr>
<td>Phased-array coils (multicoils)</td>
<td>A set of receiver coils that detects the magnetic resonance signal. These are placed in a rigid or flexible platform set directly on the patient anterior and posterior to the pelvis used in combination with the endorectal coil (or as a substitute for it).</td>
</tr>
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coil, which permitted high-resolution images of the prostate.\textsuperscript{19} Higher signal-to-noise images, high-resolution images, or both can be obtained with the use of the endorectal coil, phased-array coils, or high-field imaging with 3 Tesla magnets, or any combination of these (Fig 2). Imaging without the endorectal coil will not provide the best possible examination for staging purposes, but it may be suitable for certain clinical situations.

To perform a standard examination, the patient is placed on his side on the MRI table, and the endorectal coil is slid into place in the rectum. The coil is anteriorly oriented to receive a signal from the prostate. The patient is turned on his back, and an antiperistaltic agent such as glucagon is often intravenously administered. Phased-array coils are placed against the skin anterior and posterior to the patient, and the table is slid into the MRI magnet.

Multiple images of different types, or series, are obtained on multiple planes. These typically include T1-weighted images of the abdomen and pelvis for lymph node disease. Smaller field-of-view (higher resolution) T1-weighted images, and T2-weighted images on multiple planes (coronal, axial, and sagittal) are also obtained. Additional sequences can include diffusion-weighted imaging, dynamic contrast-enhanced (DCE) imaging, and magnetic resonance spectroscopy.

Diffusion-weighted imaging is typically performed using echoplanar fast imaging with diffusion-encoding gradients in three directions. These gradients degrade the signal intensity of water moving in the direction of the gradient, and using gradients in three directions diminishes the signal in any direction. Therefore, the tissue has a lower signal from water motion due to perfusion and diffusion. Acquiring two or more sets of images with increasing gradient strength allows a calculated apparent diffusion coefficient (ADC) map; by necessity, these images are low resolution.

DCE images are fast, fat-saturated, T1-weighted images obtained during and after the administration of an intravenous contrast agent (eg, gadopentetate). These rapid images reveal the arrival of the contrast to the vessels and tissues as increased signal intensity, which will sequentially reflect the arterial arrival of the contrast, venous perfusion, uptake in the tissue interstitium, and the subsequent washout from these compartments. Such images may be acquired at several time points for qualitative assessment and at many time points for quantitative analysis. Additional acquisitions may also include magnetic resonance spectroscopy. A complete examination usually takes 45 minutes.

**Anatomy of the Prostate**

The most important anatomical features of the prostate are shown in T2-weighted images (Fig 3). The central gland of the prostate includes the periurethral and transitional zones, generally with lower signal intensity than the peripheral zone.\textsuperscript{20} The signal intensity of the peripheral zone is generally high on T2-weighted images largely due to glandular fluid; by contrast, the signal intensity of the central gland is variable and highly dependent on the amount and characteristics of any present benign prostatic hypertrophy.\textsuperscript{20} The anterior central gland appears as low signal intensity, the anterior fibromuscular stroma. A low signal intensity line, the prostatic capsule, limits the peripheral zone. Neurovascular bundles can be identified as a group of vessels posterolateral to the prostatic capsule on either side.

Seminal vesicles appear as high-signal-intensity, grape-like clusters of tubules that reveal low-signal intensity smooth muscle walls (Fig 3).\textsuperscript{20} This appearance is due to the high-signal-intensity folded mucosa filling the lumen with pockets of fluid. The ampullae of the vas deferens can be identified as well as the
ejaculatory ducts. The low-signal intensity bladder wall can also be seen. Periprostatic structures such as veins, puborectalis and pubococcygeal muscles, and lymph nodes will also be visible.

**Prostate Cancer Imaging**

Prostate carcinoma appears on MRI as intermediate-signal intensity (gray) on T2-weighted images (Fig 2). Because the peripheral zone normally has high-signal intensity (bright), carcinomas are generally clearly visible in the peripheral zone. Conversely, because the signal intensity of the central gland is variable and generally low or intermediate, tumors are not well visualized in this area. On diffusion-weighted images, prostate carcinoma has low-signal intensity, which reflects restricted diffusion (Fig 4) that often correlates with the degree of cellularity, macromolecular density, or fibrous tissue. Diffusion imaging may also assist

![Fig 3A-D. — Prostate anatomy on endorectal coil magnetic resonance imaging. (A) Transverse image at the midprostate reveals high-signal intensity (brighter) in the peripheral zone (pz), low-signal intensity (darker) in the central gland (cg) with several scattered benign prostatic hyperplasia (BPH) nodules, and prostatic capsule (arrowhead), the neurovascular bundles (thick black arrows), urethra (thin black arrow) and the rectal wall (white arrow). (B) Coronal image of the prostate shows a high-signal intensity peripheral zone and a low-signal intensity central gland with the prostatic capsule (thick white arrows). The irregular ampulla of the vas deferens are visible (thin white arrows), as well as the prostatic urethra and verumontanum (black arrow). (C) Sagittal view of the prostate reveals the central gland (cg) with BPH producing a prominent subtrigonal nodule (stn) that protrudes into the bladder, a variant appearance of BPH. The peripheral zone (pz) has a higher signal intensity. The seminal vesicles and vas deferens lie superiorly (black arrow). White arrows denote the membranous urethra. (D) Transverse image of the seminal vesicles (black arrows) shows high-signal intensity lumens surrounded by the low-signal intensity walls. The ampullae of the vas deferens (white arrowheads) are visible as well as the low-signal intensity bladder wall (black arrowhead). The central subtrigonal nodule of the prostate is noted (stn).
in differentiating between hemorrhage and tumor in the peripheral zone.\textsuperscript{22} The enhancement of prostatic tumors is somewhat variable; however, tumors typically enhance more rapidly and to a greater degree than the peripheral zone normal tissue. Therefore, they may be best displayed on an early arterial phase image (Fig 5). Increased or more rapid contrast enhancement correlates with microvascular density in the prostate tumor.\textsuperscript{23}

Extracapsular extension, when gross, is manifested by protrusion of the intermediate-signal intensity tumors through the prostate capsule. More subtle capsular penetration may be manifested by a tumor that abuts the capsule over a wide area, capsular thickening, nodularity or bulging of the capsule, or irregularity (Fig 6).\textsuperscript{24} Seminal vesicle invasion is manifested by a low-signal intensity tumor, replacing the high-signal intensity seminal vesicle lumens, the mucosa, or both.\textsuperscript{25} Similarly, bladder wall invasion will be manifested by intermediate-signal intensity on T2-weighted images or enhancing tissue interrupting the low-signal intensity bladder wall.

**Magnetic Resonance Spectroscopy**

Spectroscopy is a magnetic resonance technique to assess the presence of metabolites in tissue. Proton spectroscopy can detect certain hydrogen-containing metabolites in the prostate such as choline, creatinine, and citrate. The normal prostate gland produces high levels of citrate and low levels of choline. Because of phospholipid metabolism and higher cell membrane turnover, prostate cancer has higher levels of choline.

![Fig 4A-D.](image-url)

*Fig 4A-D. — Typical appearance of prostate carcinoma on magnetic resonance imaging. Subsequent biopsy revealed a Gleason score of 4 + 4. (A) T1-weighted image shows homogeneous low signal of the prostate (p), with no discrimination of the central and peripheral gland. The tumor nodule is not seen because no tissue contrast is present between the tumor and peripheral zone. The neurovascular bundles (black arrows) are seen laterally. (B) T2-weighted image shows the lower-signal intensity tumor (n) compared to the curve from zone on either side. (C) Coronal image shows the tumor nodule (n) with the adjoining apical prostatic capsule shown (arrow). (D) Early-phase gadolinium chelate-enhanced sections from a fast 3-dimensional gradient echo sequence show rapid intense enhancement of the tumor nodule (n), manifested by brighter signal intensity in the rest of the prostate, with tumor extending laterally to greater extent than is apparent on the T2-weighted image.*
Fig 5A-C. — Prostatic carcinoma on magnetic resonance imaging with diffusion-weighted imaging of a patient with a prostate-specific antigen level of 3.1 ng/mL. Subsequent biopsy revealed a Gleason score of 3 + 4 with extracapsular extension. (A) T2-weighted and rectal coil image reveals a tumor nodule (n) contrasted with a higher-signal intensity peripheral zone. The central gland (cg) is expanded by benign prostatic hyperplasia, which has a lower signal intensity. (B) Apparent diffusion coefficient (ADC) map of the prostate reveals that the tumor nodule (n) has a lower signal intensity than the peripheral zone or the central gland (cg). Low signal intensity indicates that the ADC is lower than that of water and the water diffusion within the tumor is restricted. The ADC map is calculated from a set of three images at the same level (not shown) and performed with three different magnitudes of strength of diffusion-encoding gradients. (C) Early-phase gadolinium chelate-enhanced slice from a fast 3-dimensional gradient-echo sequence reveals rapid, intense enhancement of the tumor nodule (n). Portions of the central gland (cg) also reveal rapid enhancement. Note: Multiparametric imaging refers to the characteristics of abnormalities on all three sets of images.

Fig 6A-C. — Typical enhancement characteristics of a tumor on dynamic contrast-enhanced images in a patient with a prostate-specific antigen level of 15 ng/mL. Biopsy showed a Gleason score of 4 + 4. (A) Transverse T2-weighted image reveals a tumor nodule (n) involving both the central gland and the peripheral zone on the right side of the prostate. The arrow points to the capsular involvement on the right. (B) Early-phase gadolinium chelate-enhanced slice from a fast 3-dimensional gradient-echo sequence reveals a rapid, intense enhancement of the tumor nodule (n) on the right side of the prostate. (C) Late-phase enhanced T1-weighted image reveals the tumor nodule (n) with a lower signal intensity, indicating washout of the contrast compared with the rest of the prostate. Typically, a tumor demonstrates early enhancement and early washout (as shown in this case).
The ratio of choline to citrate is increased in patients with cancer. At 1.5 Tesla, the spectroscopic peaks of choline overlap with creatinine; however, these can be resolved at 3 Tesla.

Magnetic resonance spectroscopy of the prostate can be performed with a 3-dimensional (3D) water and lipid suppressed, double-spin-echo point-resolved spectroscopy sequence; however, 3D magnetic resonance spectroscopy is time consuming and technically challenging. Adequate water and lipids suppression is necessary to exclude contamination from tissue outside the prostate. Data sets are typically acquired with 16 × 8 × 8 phase-encoded spectral arrays. The magnetic resonance spectra can be displayed as a rectangular array from the individual voxels.

Multiple studies have suggested improved detection, localization, and staging with magnetic resonance spectroscopy. Studies commonly vary in patient population, particularly regarding the Gleason grading spectrum of patients or PSA levels, as well as in techniques or pulse sequences used (eg, diffusion imaging, dynamic-enhanced imaging), without standardization for coils (eg, endorectal or body coils), or field strength. Furthermore, the vast majority are single institutional and retrospective studies, which are prone to bias and can be insufficiently powered. Finally, methodological problems exist with mapping tumors or sites of capsular penetration to precise sites on any prostatectomy specimens to determine imaging accuracy.

Accuracy of Staging
The reported sensitivity and specificity for prostate carcinoma staging vary from high to low, and it is difficult to determine the most appropriate figures to use. Studies commonly vary in patient population, particularly regarding the Gleason grading spectrum of patients or PSA levels, as well as in techniques or pulse sequences used (eg, diffusion imaging, dynamic-enhanced imaging), without standardization for coils (eg, endorectal or body coils), or field strength. Furthermore, the vast majority are single institutional and retrospective studies, which are prone to bias and can be insufficiently powered. Finally, methodological problems exist with mapping tumors or sites of capsular penetration to precise sites on any prostatectomy specimens to determine imaging accuracy.

Results from a multicenter prospective trial demonstrated limited accuracy of MRI in locating the prostate tumor. One would expect that the accuracy for staging would be even lower. Several generalities can be stated regarding the accuracy of MR staging. First, the accuracy for extracapsular extension is probably between 70% and 80%, while the identification of seminal vesicle invasion is more accurate. Second, MRI at 3 Tesla is probably superior to MRI at 1.5 Tesla. Third, diffusion-weighted and DCE imaging may provide small incremental increases in accuracy. Fourth, MRI probably provides a small incremental increase in accuracy over clinical nomograms based on PSA, digital rectal examination, and Gleason grade, among others. Fifth, MRI is more accurate in patients at intermediate or high risk, but it is less accurate in patients with low-volume tumors and low Gleason grades. The detection rate of tumors is also dependent on size, with tumors smaller than 2 cm unlikely to be detected.

Multiparametric imaging, or the integration of various sequences such as diffusion, DCE, and T2-weighted imaging, may provide higher accuracy. However, how these varying data are combined for optimal accuracy is not clear.

Evaluation of Prostate Cancer Metastases
Patients with prostate carcinoma are evaluated for possible metastatic disease if they fall into a high-risk group with a new diagnosis or after biochemical failure following prostatectomy, radiation treatment, or local therapy.

Computed Tomography
CT is an important part of the management of prostate carcinoma. CT scanning provides a quick evaluation for metastases in the chest, abdomen, or pelvis. It is efficient at identifying enlarged lymph nodes, although lymph node enlargement is not highly sensitive and not entirely specific for lymph node metastases. Since CT provides poor tissue contrast within the prostate itself, evaluation of the intraprostatic tumor is limited.

CT scanning can detect bone metastases, particularly those that are osteoblastic; therefore, it is useful in patients at high risk of metastatic spread on initial evaluation or with suspected progression after prostatectomy or radiation treatment. It is also useful in patients with identified metastases to monitor the effectiveness of therapy.

Because lymph node size is not sensitive or specific for metastasis in patients with prostate carcinoma, there is no one size criterion that is highly accurate. A commonly used criterion is a pelvic lymph node smaller than 10 mm but 8 mm or larger in size (if round in shape) or 10 mm or larger in size (if oval in shape). Using this criterion with contemporary scanners, one study found a sensitivity rate of 34% and a specificity rate of 97% for the detection of lymph node metastases. If CT is used to evaluate for lymph node metastases, suspicious nodes are generally subjected to fine-needle aspiration for confirmation, which can produce false-negative results. For these reasons, CT is recommended with a very high pretest probability of metastatic disease (Table 1).

Magnetic Resonance Imaging
MRI can survey for metastatic disease similar to CT of the lymph nodes and skeletal structures. MRI of the
abdomen and pelvis is used to evaluate for lymphadenopathy, bone metastases, and metastases elsewhere, but it is generally more time consuming and more expensive than CT scanning while providing similar diagnostic information.

Recent developments exist to provide a more specific evaluation of lymph node metastases than an assessment based solely on size. Diffusion-weighted imaging of lymph nodes may be a more specific assessment than size criteria. Metastatic lymph nodes demonstrate a lower apparent ADC than benign lymph nodes, presumably reflecting greater cell density in lymph nodes with metastatic tumor. DCE properties of lymph nodes differ between normal and metastatic lymph nodes in that lymph nodes with metastases show stronger and more rapid enhancement.

Another innovation in lymph node imaging using MRI has been the development of superparamagnetic contrast agents with preferential lymph node uptake. These agents accumulate in normal lymph nodes, causing losses of signal intensity within these lymph nodes on imaging. Conversely, lymph nodes with metastases within them do not accumulate the agents in the metastatic portion and do not lose signal intensity, or, conversely, they will lose signal intensity in the normal part of the lymph node. A large trial of men with intermediate or high risk of having nodal metastases compared this MR contrast agent with CT showed 82% sensitivity for lymph node metastases vs 34% for CT. This could obviate the need for lymph node dissection in patients with a negative MRI.

Because an MRI examination using a lymphotropic agent reveals all the lymph nodes in the pelvis, it can reveal metastatic lymph nodes outside the normal range of the pelvic lymph node dissection chains. For example, in a study of 296 men with prostate cancer, MRI with a superparamagnetic agent revealed lymph nodes outside of the pelvic lymph node dissection in 18 of the 44 patients (41%) with positive lymph node metastases. Currently, no approved superparamagnetic contrast agent exists in the United States for lymph node imaging. An off-label use of ferumoxytol, an agent indicated for iron deficiency anemia, is being investigated for lymph node imaging in prostate cancer, as it has similar properties to previously investigated contrast agents (NCT01296139).

MRI is sensitive for bone metastases (Fig 7). An MRI technique for skeletal imaging, as well as other organs to some extent, is termed whole-body MRI and most of the skeleton is revealed, comparable with bone scintigraphy or positron emission tomography (PET)/CT. Methods of evaluating for bone metastases by MRI include T1-weighted sequences, short TI inversion recovery imaging, and diffusion-weighted imaging. Large field-of-view coronal images can quickly image the chest, abdomen, and pelvis for bone metastases and lymph node metastases with short TI inversion recovery imaging or diffusion-weighted images. These survey examinations may be more sensitive than PET/CT or scintigraphy in identifying metastases. Diffusion-weighted images using weak diffusion gradient strength are similar in performance.

Nuclear Medicine

The use of scintigraphic (nuclear medicine) examinations for the evaluation of prostate cancer is usually reserved for patients with suspected osteoblastic skeletal metastatic disease or those with a rising PSA assay level without demonstrable bulky distant metastatic disease or skeletal metastatic disease following prostatectomy.
In patients with suspected osteoblastic skeletal metastatic disease, nuclear medicine currently offers the option of gamma emitters, such as technetium-99m (99mTc) linked to a radioligand — in this case, a “bone-seeking” agent, such as methylene diphosphonate or hydroxymethylene diphosphonate. Imaging of such radiotracers is performed using gamma cameras in the single detector (head), dual-head, or triple-head configuration. In the last 10 years, hybrid nuclear medicine–CT camera systems have become available that combine a diagnostic quality CT gantry with a dual-headed gamma camera system. These systems provide the option of obtaining a nuclear medicine tomographic examination (single-photon emission computed tomography [SPECT]) registered to a co-acquired low (nondiagnostic) or high radiographic dose (diagnostic) CT for localization purposes.

The major drawback of the radiotracers used for skeletal scintigraphy (bone scan) is low specificity. Inflammatory processes such as degenerative joint disease and osteoarthritis can demonstrate significant uptake. Certainly other active inflammatory processes, such as autoimmune processes, can also have increased uptake. Infectious or reparative processes involving the bone can also have increased uptake.

The above-discussed radiotracers primarily deposits within the cortical bone through chemoabsorption. This radiotracer deposits in areas of bone deposition; therefore, these examinations demonstrate areas of osteoblastic response to tumoral deposits in bone, not deposition within the tumor tissue. Sensitivity for detection of osteoblastic activity related to metastatic prostate cancer can reach a rate of 95% in patients with PSA levels above 20 ng/mL.50-52 In cases where a rising PSA level is present following prostatectomy and negative skeletal scintigraphic findings, the likelihood of soft-tissue metastatic disease increases.

Skeletal scintigraphy is mainly reserved for patients with high-risk cancer, elevated serum alkaline phosphatase levels, bone pain, or equivocal osseous lesions on other imaging modalities.53,54 Prior studies have demonstrated the relationship of increased incidence of skeletal metastatic disease with elevated PSA levels.50-52 The flare phenomenon, which refers to evidence of increasing osteoblastic metastatic disease (worsening of bone scan appearance) following therapy, with decreasing symptomatology has been previously described.54-58 It is visible in patients with prostate carcinoma metastatic to the skeleton, observable in 20% to 25% of scans if obtained soon after therapy has been instituted.56-58 Because of this paradoxical worsening of scintigraphic appearance in patients with favorably responding metastatic disease, skeletal scintigraphy is not the only test for the evaluation of such patients. Bone scans are useful for the evaluation of patients with diagnosed prostate cancer with a rising or elevated PSA level, patients with normal PSA levels following hormonal therapy, or patients who have a normal PSA level but are symptomatic.

Bone scans using planar and tomographic techniques have adequate sensitivity and specificity rates and have been the main tool utilized for many years. However, tumor detection using novel radiotracers and newer imaging techniques may prove advantageous in the future. Novel radiotracers such as positron emitters (eg, 18F-fluoride [NaF], as well as PET or PET/CT and PET/MRI techniques, may prove indispensable in the evaluation of metastatic skeletal disease. In malignant bone lesions, NaF reflects the increase in regional blood flow and skeletal turnover associated with metastatic osteoblastic deposits (Fig 7). NaF PET/CT has been shown to be more sensitive for the detection of metastases than 99mTc methylene diphosphonate bone scans. The use of hybrid imaging techniques such as PET/CT reduces the risk of false-positive findings and improves specificity of abnormalities detected by virtue of the imaging capabilities for lesion-by-lesion characterization using CT (Fig 7).59

In a recent study that reviewed the use of 99mTc methylene diphosphonate and NaF, a direct comparison was made using whole-body planar images and tomographic (SPECT) bone scans as well as PET alone and PET/CT NaF for the detection and characterization of skeletal metastases in 44 patients with high-risk prostate cancer.59 In this study, whole-body planar imaging had sensitivity and specificity rates of 57%. Conversely, whole-body planar plus SPECT was 78% sensitive and 67% specific. 18F PET was 100% sensitive and 62% specific, whereas 18F PET/CT was 100% sensitive and 100% specific. Conversely, fludeoxyglucose 18F PET for the detection of prostate carcinoma skeletal metastases had a low yield with a sensitivity of less than 20% compared with skeletal scintigraphy.60

**Soft-Tissue/Lymph Node Metastatic Disease Evaluation**

Molecular imaging techniques, such as the use of 111In capromab pendetide, allow for the evaluation of suspected metastatic prostatic carcinoma outside of the prostate bed, particularly the pelvic sidewall and retroperitoneal lymph nodes. 111In capromab pendetide consists of a murine monoclonal antibody (7D11-C5.3) covalently joined to a linker-chelator molecule. It is directed against the intracellular domain of prostate-specific membrane antigen (PSMA) expressed on the surface of prostate cancer metastases as well as the normal prostatic tissue. It is also expressed in other tissue types, such as the kidney, liver, bowel, and brain. PSMA is upregulated in hormone-resistant states and in metastatic disease, which is why it is used for the detection of extraprostatic, bone-scan-negative metastatic disease.
These molecular imaging techniques involve multiday examinations, and time is allowed for the radiopharmaceutical to circulate in the blood pool and migrate to the targeted metastatic foci. Usual imaging protocols call for dosing on day 0, with imaging performed on day 4, day 5, or both (96 and/or 120 hours after injection). Imaging techniques available include the use of planar gamma camera images, evaluating the whole body from an anterior and posterior projection, as well as tomographic images obtained using SPECT or SPECT/CT camera systems. However, with all the advanced imaging systems used, the sensitivity rate ranges from 62% to 75% (Fig 7).61-63 This technique is also limited by nonspecific uptake in bowel, vasculature, bone marrow, and normal prostatic tissues, and it has a low sensitivity rate for low-tumor-burden prostate fossa disease as well as small metastases.

**Novel Radiotracer**

Novel radiotracers in different stages of research evaluation include positron emitters such as $^{11}$C-acetate and $^{11}$C-choline.

Malignant transformation within the prostate cells leads to a change in intracellular metabolic processes, which result in a change from citrate-producing normal cells to citrate-oxidizing neoplastic cells, thereby leading to an increased acetate turnover with increased expression of fatty acid synthase. Hence, increased anabolic metabolism is associated with cytoplasmic lipid synthesis. Imaging with acetate-linked radiotracers benefits from this process.

Early studies using dedicated PET imaging systems comparing the use of fludeoxyglucose $^{18}$F and $^{11}$C-acetate for the evaluation of recurrent prostate carcinoma showed promise when used to detect metastatic disease over the use of fludeoxyglucose $^{18}$F alone, which had limited sensitivity and specificity rates (Fig 8). However, a study by Oyama et al64 showed a statistical difference in the detection of recurrent disease in patients with elevated PSA levels above 3 ng/mL but limited results in patients with PSA levels of 3 ng/mL or below. $^{11}$C-acetate PET was shown to have a sensitivity rate of 59% compared with a sensitivity rate of 17% for fludeoxyglucose $^{18}$F PET.

![Fig 8A-B](image-url)  

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Of note, this study used stand-alone PET imaging systems. In one report, Fricke et al\textsuperscript{65} noted a higher rate of overall lesion detection with acetate (83\%) compared with fludeoxyglucose \textsuperscript{18}F (75\%).

In a recent pilot study by Yu et al\textsuperscript{66} involving 8 participants, conventional skeletal scintigraphy was compared with \textsuperscript{99m}Tc methydiphosphonate, fludeoxyglucose \textsuperscript{18}F, and \textsuperscript{11}C-acetate in the detection of skeletal metastases and follow-up after therapy. Acetate PET generally detected more metastases and had a higher ratio of tumor-to-normal uptake. These results indicate that acetate PET holds promise for response assessment of prostate cancer skeletal metastases; it was also complementary to fludeoxyglucose \textsuperscript{18}F in the detection of bone metastasis.

\textsuperscript{11}C- and \textsuperscript{18}F-labeled choline derivatives have been used to detect primary or relapsing prostate carcinoma based on increased levels of phosphorylcholine, upregulated enzymes of choline metabolism, choline kinase with increased phosphatidylcholine turnover, and the metabolic flux of radiolabeled choline through phospholipid biosynthesis and degradation in prostate carcinoma.\textsuperscript{67} This uptake is unrelated to proliferation (Ki67). Several authors\textsuperscript{68-70} have shown that \textsuperscript{11}C-choline is taken up by prostate carcinoma and its nodal and distant metastases (Fig 9).

In a recent study using hybrid imaging (PET/CT), Reske et al\textsuperscript{71} investigated the ability of \textsuperscript{11}C-choline contrast-enhanced PET/CT for the evaluation of prostatic carcinoma and differentiation of prostatic cancer tissue from normal prostate tissue, benign prostate hyperplasia, and focal chronic prostatitis. The authors concluded that \textsuperscript{11}C-choline PET/CT accurately located and detected major areas of prostate carcinoma within the prostate gland and differentiated segments with prostate cancer from those with chronic prostatitis, benign hyperplasia, or normal prostatic tissue (Fig 10).

A study that compared \textsuperscript{11}C-choline and \textsuperscript{11}C-acetate PET in 10 patients with residual or recurrent prostate cancer showed similar detection rates for local tumor, lymph node, and skeletal metastases, but only in patients with high PSA levels.\textsuperscript{70} In those with low PSA levels, studies performed thus far have shown low to moderate sensitivity in detection of local residual or

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**Fig 9.** — Anti-1-amino-3-\textsuperscript{18}F-fluorocyclobutane-1-carboxylic acid image of a patient with extensive prostate carcinoma (arrowheads) with involved bilateral obturator (open arrows) and left iliac lymph nodes (solid straight arrows). Urinary activity is minimal and not present on the image (curved arrow at bladder location). From Schuster DM, Votaw JR, Nieh PT, et al. Initial experience with the radiotracer anti-1-amino-3-\textsuperscript{18}F-fluorocyclobutane-1-carboxylic acid with PET/CT in prostate carcinoma. J Nucl Med. 2007;48(1):56-63. Reprinted by permission of the Society of Nuclear Medicine.

**Fig 10A-B.** — Focal (A) and multifocal (B) distribution of prostate carcinoma within the prostate gland (arrows). Scatter plots of the segmental \textsuperscript{11}C-choline maximal standardized uptake value reveal higher \textsuperscript{11}C-choline maximal standardized uptake values in most segments with prostate carcinoma compared with segments with benign histopathological lesions. From Reske SN, Blumstein NM, Neumaier B, et al. Imaging prostate cancer with \textsuperscript{11}C-choline PET/CT. J Nucl Med. 2006;47(8):1249-1254. Reprinted by permission of the Society of Nuclear Medicine.
recurrent tumor. Similarly, these studies have shown moderate sensitivity in the detection of distant metastatic disease.72,73 In a recent study, Vees et al74 evaluated 20 patients with early-stage prostate carcinoma staging after prostatectomy with low PSA levels (< 1 ng/mL) for the presence of local or metastatic prostate carcinoma with 18F-choline, 11C-acetate, or both. Two of the 20 patients were evaluated with both radiotracers. Both radiopharmaceuticals detected the presence of neoplastic disease in 50% of the participants.

Other radiopharmaceuticals being evaluated include 11C-methionine, 18F-fluoro-5-dihydrotestosterone, and anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid (Fig 9).75

Evaluation of the Prostate or Surgical Site Following Therapy

MRI and sonography are two methods used to evaluate for local recurrence following local therapy or prostatectomy. PET and CT scanning are not accurate methods for identifying recurrent tumor.76,77

Ultrasonography

Following prostatectomy in the surgical bed, transrectal ultrasonography may detect recurrence of prostate carcinoma.78 Recurrences appear as ill-defined hypoechoic lesions in the bladder neck or at the anastomosis.79 Power Doppler imaging and contrast enhancement may improve the sensitivity of ultrasonography.

Fig 11A-D. — Recurrent tumor following radical prostatectomy (prostate-specific antigen level = 4.8 ng/mL). (A) Sagittal T2-weighted image reveals low-signal intensity soft tissue (thick arrow) posterior to the urethrovesical anastomosis (thin arrow). b = bladder. (B) Transverse T2-weighted image of the bladder lumen reveals the low-signal intensity soft tissue (thick arrow) involving the rectum muscularis posterior kidney urethrovesical anastomosis (thin arrow). (C) Early-phase gadolinium chelate-enhanced image shows a rapidly enhancing tumor nodule (arrow) that appears as a higher signal intensity plaquelike lesion involving the rectum muscularis propria. The other structures, which are low in signal intensity, including the urethrovesical anastomosis, on the T2-weighted image are not rapidly enhancing. (D) Early-phase gadolinium chelate-enhanced image at a higher level through the retained seminal vesicles reveals the right-retained seminal vesicle with diffuse enhancement (arrow), which was subsequently proven to be a recurrent tumor. By contrast, the left seminal vesicle (sv) does not contain a recurrent tumor.
nography in identifying recurrent tumor. However, biopsies of the surgical site are still more sensitive than ultrasonographic imaging.

Ultrasonography and Doppler imaging of the prostate following local therapy (eg, cryosurgery, brachytherapy) may have little role in identifying residual tumor. Contrast-enhanced ultrasonography may have increased sensitivity and specificity and may help in evaluating the degree of ablation in local therapies by distinguishing between vascularized and nonvascularized (ie, ablated) tissue.

**Magnetic Resonance Imaging**

Following total prostatectomy, MRI can detect recurrence in the prostatic bed. The usual appearance after radical prostatectomy includes a descended bladder neck in the prostatectomy space with a small amount of fibrotic tissue around the urethroversical anastomosis. Linear scarring may be present at the expected former site of the seminal vesicles. T2-weighted images can detect recurrence as a higher signal intensity nodule compared with the surrounding fibrosis and smooth muscle of the bladder neck, urethra, and urethroversical anastomosis. Sensitivity rates of 95% and specificity rates of 100% have been reported for MRI. DCE images may increase sensitivity and identify enhancing nodules of recurrent tumor (Fig 11).

Following hormonal deprivation therapy, the prostate becomes smaller in size with diminished signal intensity of the peripheral zone, so tumors are more difficult to localize on T2-weighted images. As a result of apoptosis, androgen-deprivation therapies may cause atrophy of the prostatic epithelium.

The histologic changes in the prostate caused by external beam irradiation include glandular atrophy, inflammation, prostate shrinkage, and fibrosis. After external beam radiation therapy, the peripheral zone generally loses signal intensity on T2-weighted imaging, which can effectively render most carcinomas difficult or impossible to identify on standard MRI following radiation therapy. Similar effects are visible using brachytherapy with radiation seeds. Diffusion-weighted imaging or DCE imaging may increase sensitivity in the irradiated prostate for the presence of cancer. On diffusion-weighted or ADC imaging, carcinoma generally appears as a more restricted diffusion than the remainder of the prostate gland. MRI may detect residual or recurrent tumor in patients treated with high-intensity focused ultrasonography. DCE images are more sensitive than T2-weighted images to tumor recurrence (Fig 12).

Similar to the effects on T2-weighted images with external beam therapy, spectroscopic results also change with radiation. The citrate levels tend to decrease after radiation in nontumorous prostate and choline levels increase, causing confusion with a tumor. Nonetheless, spectroscopy can identify some patients with residual tumor after radiation, although reported accuracies are not as high as those seen in patients with untreated prostate cancer.
Conclusions

Local staging of the prostate tumor is limited in ultrasonography and magnetic resonance imaging; both techniques provide suboptimal sensitivity and specificity for tumor identification and capsular penetration. Additional magnetic resonance imaging techniques such as dynamic contrast-enhanced imaging, diffusion imaging, and spectroscopy may provide incremental benefit; however, none of these are highly sensitive. Computed tomography and bone scans are used to assess metastatic disease, but both techniques are limited by the poor sensitivity of lymph node size as a criterion for detecting metastases.

Accepted methodologies for evaluating metastatic prostate carcinoma to the skeletal system and soft tissues include skeletal scintigraphy (bone scan) and monoclonal antibody imaging that targets prostate-specific membrane antigen. However, novel imaging techniques such as hybrid imaging devices in the form of single-photon emission computed tomography/computed tomographic gamma cameras, positron emission/computed tomographic cameras, and, in the near future, positron emission tomography/magnetic resonance imaging combined with tumor-specific imaging radiotracers may significantly and favorably affect tumor staging, the accuracy of therapy response, and patient care.

References


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