Prostate cancer is the most common noncutaneous male malignancy in the United States. The use of serum prostate-specific antigen as a screening tool is complicated by a significant fraction of nonlethal cancers diagnosed by biopsy. Ultrasound is used predominately as a biopsy guidance tool. Combined rectal examination, prostate-specific antigen testing, and histology from ultrasound-guided biopsy provide risk stratification for locally advanced and metastatic disease. Imaging in low-risk patients is unlikely to guide management for patients electing up-front treatment. MRI, CT, and bone scans are appropriate in intermediate-risk to high-risk patients to better assess the extent of disease, guide therapy decisions, and predict outcomes. MRI (particularly with an endorectal coil and multiparametric functional imaging) provides the best imaging for cancer detection and staging. There may be a role for prostate MRI in the context of active surveillance for low-risk patients and in cancer detection for undiagnosed clinically suspected cancer after negative biopsy results.

The ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every 2 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer-reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances in which evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment.

Key Words: Appropriateness Criteria, prostate cancer, imaging, detection, staging

prostate cancer diagnosis but seems to have little impact on cancer-specific mortality [17]. The use of PSA as a screening tool leads to increased data also suggest that the correlation between normal PSA levels will have prostate cancer on one or more biopsy cores [12].

Clinical Staging Methods Not Involving Imaging

Physical Examination. The DRE is considered insensitive for detecting extracapsular tumor extension [10-12]. At least 40% of patients with cancers judged to be clinically confined (T1 or T2) by DRE are found to have extraprostatic extension at surgery [12].

PSA. Serum PSA has been used as a screening serum biomarker to determine whether prostate biopsy is needed. PSA is also incorporated into predictive models for staging, especially when combined with the results of DRE and the biopsy Gleason score [13]. PSA is also used in monitoring treatment response [13-15]. In general, the higher the PSA level, the more advanced the disease; moreover, the likelihood of having organ-confined disease is inversely proportional to the level of PSA. Despite its utility, it is clear that as many as 15% of men with normal PSA levels will have prostate cancer on one or more biopsy cores [12]. Data also suggest that the correlation with extent of disease is poor for men with relatively low PSA levels (eg, <9 ng/mL) [16]. In addition, the use of PSA as a screening tool leads to increased prostate cancer diagnosis but seems to have little impact on cancer-specific mortality [17].

Initial PSA value is correlated with the likelihood of surviving prostate cancer [18-20]. PSA measurements are evaluated alone or by comparison with a prior measurement (PSA velocity and PSA doubling time) or in the context of the patient’s gland volume (PSA density) [21,22]. There are also age-specific PSA levels available. The density and age specificity help separate the elevations in PSA due to benign prostatic hyperplasia from those due to cancer; however, these methods provide guidance only on the likelihood of cancer versus benign disease [23]. Use of PSA level alone to predict final pathologic stage has a high false-positive rate [24]. PSA as we have discussed thus far can be more accurately termed total PSA because the bound and free components of PSA can be measured. Free PSA (ie, not bound to plasma proteins) is relatively lower in patients with cancer than in those with benign prostatic hyperplasia. As an example, free PSA fraction < 15% has been associated with more aggressive tumors, whereas a free PSA fraction > 25% generally indicates the presence of low-risk tumors.

Biopsy Results. The Gleason histologic grading system correlates with the extent of disease and prognosis. It is the single best predictor of biologic activity and tumor stage. Gleason grade ranges from 2 (well differentiated, minimally aggressive) to 5 (anaplastic, highly aggressive) [25]. The Gleason score sum is based on the addition of major and minor histologic patterns. Thus, a biopsy specimen with dominant grade 4 and minor grade 3 would have a Gleason score of 7. The probability of seminal vesicle invasion (SVI) and lymph node involvement increases with Gleason score, and Gleason score combined with serum PSA level give the greatest prognostic information [13,26]. Biopsy regimens are known to be falsely negative and to undersample some significant cancers [7,27,28]. About 25% of patients with Gleason scores of 6 will be found to have more aggressive disease after radical prostatectomy [28]. MRI guidance for biopsies has shown improvement in diagnosing clinically significant cancers relative to TRUS-guided biopsies. In a recent series, 41% of men with prior negative TRUS-guided biopsy results but suspected of having prostate cancer were diagnosed with prostate cancer on MRI-guided biopsy [27].

Nomograms and Risk Group Stratification. Nomograms are statistical calculators used to predict the probability of extracapsular extension (ECE), SVI, and lymph node involvement [13,29]. These models have been validated and led to attempts to correlate with prognosis [30-32]. Most nomograms use combinations of PSA level, Gleason score, and physical examination T stage to stratify risk categories for locally advanced and metastatic disease [9,33]. Using such an approach, patients with similar risk for biochemical recurrence can
be divided into risk groups that have been correlated with mortality [34]:

- Low risk: AJCC clinical stage T1c or T2a and PSA \( \leq 10 \) ng/mL and biopsy Gleason score \( \leq 6 \): about 80% 10-year PSA failure-free survival rate.
- Intermediate risk: AJCC clinical stage T2b or PSA \( > 10 \) and \( \leq 20 \) ng/mL or biopsy Gleason score of 7: about 50% 10-year PSA failure-free survival rate.
- High risk: AJCC clinical stage T2c disease or PSA \( > 20 \) ng/mL or biopsy Gleason score \( \geq 8 \): about 33% 10-year PSA failure-free survival rate.

Alternative risk stratification schemes have also been described, and despite their differences, they support the notion that Gleason score, DRE T stage, and PSA level can be used to predict survival and direct therapy [19,35]. The number of positive biopsy results (eg, \( > 3 \)) and the percentage of each core that is positive at biopsy (eg, \( > 50% \)) may be associated with increased risk for recurrent disease [36]. However, the addition of the percentage of positive cores to existing models has had only minimal incremental benefit [37,38].

### Summary of Nonimaging Methods and Role of Imaging in Staging

Although DRE, PSA level, and Gleason score individually predict stage, they are more accurate when they are combined into nomograms that estimate risk for locally advanced and metastatic disease. Imaging improves risk estimates by specifically identifying lesions with anatomic features. However, imaging findings should be interpreted in the context of the nonimaging findings. In part because of the limitations of clinical staging, efforts have been made to use imaging to better assess the extent of disease and predict outcomes [39].

### Imaging Methods

A summary of imaging methods for prostate cancer detection, staging, and surveillance appears in Table 1.

**Ultrasound.** Grayscale ultrasound has not proved satisfactory for local staging of prostate cancer. The ability of TRUS to predict ECE varies from 37% to 83% and is limited by relatively low spatial resolution [40-43]. Adding color and power Doppler can improve the detection of prostate cancer by identifying increased vascularity but has not improved staging accuracy [44-46]. Contrast-enhanced and 3-D ultrasound show potential to improve staging but have not been tested in multi-institutional trials [47,48]. Similarly, 3-D ultrasound is under investigation to improve the delineation of the cancer and prostate gland margin.

**MRI.** Prostate imaging with MRI can be performed without or with an endorectal coil. Endorectal coil MRI (erMRI), whether at \( 1.5 \) T or a higher field strength, provides the highest spatial resolution among the imaging modalities currently available. In conjunction with T1-weighted and T2-weighted sequences at larger fields of view, for example, or with pelvic adenopathy and bone metastases, 4 MRI methods have been used to image and stage prostate cancer locally: high-resolution T2-weighted MRI, MR spectroscopic imaging (MRSI), diffusion-weighted MRI (DWI-MRI), and dynamic contrast-enhanced MRI (DCE-MRI). It is generally accepted for 1.5-T imaging that local staging accuracy necessitates an endorectal coil to achieve sufficient signal-to-noise ratios, a small field of view (12-16 cm), and high resolution (about 0.5 mm) [49-52]. ErMRI at 3 T further improves spatial (or temporal, in the case of DCE-MRI) resolution. Futterer et al [53,54] showed 3-T erMRI to be accurate for staging prostate cancer, with moderate to substantial interobserver agreement for the detection of minimal capsular invasion. However, the current literature is insufficient to establish the superiority of 3-T erMRI over 1.5-T erMRI. Staging using erMRI at 1.5 T was found superior to 3-T MRI without an endorectal coil in one study, but more reports on 3-T MRI without an endorectal coil are needed to properly judge efficacy [55].

**T2-Weighted MRI.** More than 20 years of clinical experience exists with T2-weighted erMRI. Although MRI technological advances have improved image quality over this period, staging accuracy remains limited. Low-signal intensity lesions on T2-weighted images can be cancer or can be caused by benign processes such as prostatitis. ErMRI remains limited in demonstrating microscopic or early macroscopic extraprostatic extension because of restrictions on spatial resolution and motion artifacts [56]. In one study, MRI depicted only 1 of 7 lesions with \( < 1 \) mm of ECE compared with 5 of 7 with \( > 1 \) mm of ECE [57]. Most recent reports on staging for organ-confined versus extracapsular disease show consistent accuracies of about 90% [55, 58-60]. Also, erMRI has been shown to improve the prediction of neurovascular bundle invasion before radical prostatectomy [61]. Expertise with prostate MRI can improve staging accuracy. For example, readers considered more “expert” in one case series were found to be more accurate in judging ECE compared with “nonexpert” readers and all other predictive variables [60]. In another study, one more experienced reader achieved an accuracy of 91%, while the other had an accuracy of only 56% [62]. Selzter et al [63] demonstrated that the differences between “expert” readers and less experienced readers could be reduced by incorporating other clinical data (eg, PSA level, tumor grade) and using strict imaging criteria. ErMRI has also been shown to be accurate in demonstrating SVI [64]. The combination of a tumor at the base of the prostate that extends beyond the capsule and a low signal in the seminal vesicles that have lost normal architecture is highly predictive of SVI. Several studies have documented that erMRI is most successful in men with intermediate-risk prostate cancer. In
<table>
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<th>Variant</th>
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<td>MRI Pelvis Without and With Contrast</td>
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<td>Variant 1: prostate cancer diagnosed on biopsy, patient at low risk for locally advanced disease and metastases (AJCC group I); example: PSA ≤10 ng/mL and Gleason score ≤6 and clinical stage T1 or T2a</td>
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<td>Variant 2: prostate cancer diagnosed on biopsy, patient at intermediate risk for locally advanced disease and metastases (AJCC group IIA or IIB); example: PSA 10-20 ng/mL or Gleason score 7 or clinical stage T2b</td>
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<td>Variant 3: prostate cancer diagnosed on biopsy, patient at high risk for locally advanced disease and metastases (AJCC groups III and IV); example: PSA ≥20 ng/mL or Gleason score 8-10 or clinical stage ≥T2c</td>
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<td>Variant 4: multiple negative prostate biopsy results, but there is concern for prostate cancer based on rising or persistently elevated serum markers suggestive of cancer</td>
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Note: Rating scale: 1, 2, and 3 — usually not appropriate; 4, 5, and 6 — may be appropriate; 7, 8, and 9 — usually appropriate.†May be appropriate for active surveillance. See statement regarding contrast in text under “Anticipated Exceptions.”‡May be appropriate for active surveillance.¶Should include dynamic contrast-enhanced technique. See statement regarding contrast in text under “Anticipated Exceptions.”§If contrast is contraindicated.¶Should include dynamic contrast-enhanced technique. See statement regarding contrast in text under “Anticipated Exceptions.”
these men, erMRI staging was highly predictive of PSA recurrence [65-67]. In a study involving 344 patients, Wang et al [67] demonstrated that erMRI added statistically meaningful staging data regarding ECE. ErMRI has also proven helpful in directing 3-D conformal radiotherapy and improving outcomes [68].

**MRSI.** Prostate cancers have a characteristic loss of the citrate peak and gain in the choline/creatine peak on MRSI [69]. Moreover, the ratio of choline to citrate is related to the Gleason score, indicating that MRSI provides information about tumor aggressiveness [70]. Incremental improvement in the accuracy of cancer detection and staging was reported when MRSI was added to erMRI alone [69,71]. As an indicator of outcomes, MRSI has been shown to be predictive of biochemical recurrence [72]. However, a recent ACRIN® multicenter trial showed no incremental benefit of MRSI for localizing prostate cancer over 1.5-T erMRI alone [73]. MRSI cannot yet be considered to provide significant advantages in local staging before treatment.

**DCE-MRI.** Prostate cancers demonstrate angiogenesis that can be detected on DCE-MRI, with earlier and more intense enhancement in sites of tumor compared with the normal peripheral zone. Jager et al [74] found minimal improvements in diagnostic accuracy over conventional T2-weighted scans using DCE-MRI. Padhani et al [75] showed that tumors could be distinguished from noncancerous prostate with high reliability, although the study did not specifically address staging. Because stage assignment requires cancer detection, it is felt that DCE-MRI can aid in confident localization of cancer foci when used in conjunction with T2-weighted images and improve staging performance for less experienced readers when compared with more experienced readers [76]. Bloch et al [59] demonstrated that the combination of DCE-MRI and T2-weighted imaging improved assessment of ECE, with better results for prostate cancer staging compared with either technique alone. Other reports have confirmed the utility of DCE-MRI in cancer detection [77,78]. However, this method still suffers from a lack of a uniformly accepted analytic method and has not been tested in multi-institutional trials, so the value of DCE-MRI for staging is not well established.

**DWI-MRI.** The incorporation of DWI to prostate MRI provides another method to improve prostate tumor localization compared with T2-weighted images alone [79]. It has shown some utility as a biomarker predictive of histologic grade [80]. As with DCE-MRI, the incremental benefit in local staging in men with established prostate cancer has not been established.

**Multiparametric MRI of the Prostate.** Multiparametric imaging with MRI involves combining T2-weighted anatomic images with at least two other functional imaging methods (DCE-MRI, DWI, and MRSI). As outlined thus far, MRI techniques are individually limited for diagnosis and staging, but using them together yields greater accuracy. Although it is premature to make specific recommendations as guidelines for multiparametric assessments, expert international opinion is coalescing around this approach as the best available method for imaging prostate cancer [81-84].

**Nodal Staging With MRI.** MRI is roughly equivalent to CT for detecting adenopathy in men with prostate cancer [85]. Unfortunately, metastatic nodes in prostate cancer are often small, so that size criteria underestimate nodal disease and low sensitivities are observed, even in high-risk patients.

**CT.** CT of the abdomen and pelvis suffers from poor sensitivity in detecting extraprostatic disease, including SVI and nodal involvement. CT should be reserved for use in patients with a higher probability of metastases. Overall accuracy in staging was reported at 65% by Hricak et al [85] and at 67% by Platt et al [86]. For locoregional staging, such as extraprostatic extension, accuracy has been reported to be as low as 24% [87]. CT for lymph node staging has shown only 55% accuracy [88]. The positive yield of CT for PSA levels up to 20 ng/mL is <12% [89]. Thus, CT is of relatively low value in initial staging and determining the local extent of prostatic carcinoma in low-risk to intermediate-risk patients [86]. The yield for CT is about 20% for advanced and high-risk disease, characterized by high PSA levels (>50 ng/mL) or a Gleason score ≥8 with a PSA level ≥20 ng/mL [89]. For these individuals, staging with CT of the abdomen, pelvis, and sometimes chest may be used to establish disease extent and help determine fitness for localized treatment.

**Indium Capromab.** The usefulness of 111In radiolabeled capromab pendetide (a first-generation monoclonal antibody against prostate-specific membrane antigen) scanning to stage prostate cancer remains unproved. Initial studies suggested improved detection of metastatic lymph nodes [90]. Bermejo et al [91] conducted histopathologic correlation in lymph nodes after 111In scans in 31 patients (43 samples). The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 94%, 42%, 53%, 92%, and 65%, respectively. Scan limitations seem to be due to the intracellular binding site of the antibody [92] as well as nonprostatic expression of prostate-specific membrane antigen [93]. Indium-111 scanning as an initial staging procedure is not recommended on the basis of evidence at this time.

**Bone Scan.** The modern bone scan for metastatic survey is performed with 99mTc-methylene diphosphonate (99mTc-MDP). It is a routine evaluation for patients diagnosed with prostate cancer and can be performed with planar images or single-photon emission CT. Work
by Oesterling [94] and others [95] has shown that in patients with low PSA levels (<10 ng/mL) and without pain, the yield of a staging bone scan is too low to warrant routine use. No patient with a PSA level ≤10 ng/mL and only 1 patient in 300 with a PSA level ≤20 ng/mL had positive results on radionuclide bone scan. Such observations have been confirmed by more recent studies [89,96]. These studies suggest that patients without skeletal symptoms or advanced-stage disease should also be considered for bone scans.

Gleason scores and PSA levels ≥20 ng/mL (with any T stage or Gleason score), or Gleason scores ≥8 (with any PSA level or T stage) should undergo radionuclide bone scans [89,97,99]. Patients with skeletal symptoms or advanced-stage disease should also be considered for bone scans.

A growing alternative imaging test for diagnosing bone metastases is 18F-fluoride PET, as well as 18F-fluoride PET/CT. Even-Sapir et al [100] prospectively evaluated 18F-fluoride PET and 18F-fluoride PET/CT against both planar and single-photon emission CT 99mTc-MDP bone scan and found that 18F-fluoride PET/CT was most accurate, followed by 18F-fluoride PET alone, 99mTc-MDP single-photon emission CT, and planar 99mTc-MDP. A 2010 meta-analysis solidified the superiority of 18F-fluoride PET and 18F-fluoride PET/CT over 99mTc-MDP scans [101]. Clinical evidence is accumulating at research centers, but as of this writing, CMS has not granted coverage at nonresearch sites.

**PET.** The role of PET and PET/CT in the staging workup of newly diagnosed and recurrent prostate cancer is still being evaluated [102-105]. It has the potential to play an important role in detecting early metastatic spread and monitoring posttherapy response. Results for 2-[18F]fluoro-2-deoxyglucose PET have been disappointing in the initial staging of clinically localized prostate cancer [106]. For example, in a study of 24 primary prostate cancers, 23 lesions were not detected by 2-[18F]fluoro-2-deoxyglucose PET. Several additional radiotracers have been extensively studied, including 11C or 18F choline and acetate, 11C methionine, 18F-fluoride, 68Ga-labeled peptides, and fluorodihydrotestosterone [102-104, 107,108]. These radiotracers can have advantages over traditional agents but are not widely available, so PET scanning has a limited role in the staging of prostate cancer at present.

**Radiography.** There are no data in the literature documenting the yield of chest radiography. Therefore, it should be performed as part of the initial staging only with suspected metastatic disease (eg, PSA >100 ng/mL) or in patients who are heavy smokers with clinically localized disease.

In addition, radiography can be useful in the evaluation of bone pain or workup of bone scan findings. Any part of the body might be imaged on the basis of suspicion, especially those in the proximal appendicular skeleton when falling outside the coverage of a CT or MRI examination (if performed).

**Active Surveillance and the Role of Imaging**

The concept of active surveillance stems from the fact that there is great variability in outcomes among men diagnosed with low-risk prostate cancer. To avoid overtreatment in cancers that would otherwise prove indolent, patients can undergo a period of active surveillance (sometimes called watchful waiting) consisting of deferred treatment along with disease monitoring, usually with PSA testing, DRE, and sometimes repeat biopsy. The rationale is to allow time to discover the natural history of disease and determine if therapies, with associated treatment risks, are worth implementing [109]. Approximately 30% (14%-41%) of patients initially selected for active surveillance will progress to active treatment (radical prostatectomy or radiation) after follow-up [110].

Imaging with MRI has been studied and advocated as an aid in surveillance, especially to detect cases that have been understaged and misclassified [111,112]. Some patients can undergo repeat biopsy directed to MRI-suspected cancer sites and be reclassified as having higher risk features and deserving therapy [7,113]. However, the absence of disease on MRI may be less helpful; a retrospective assessment found that MRI with MRSI that was negative for cancer in men undergoing active surveillance was not an accurate predictor of biochemical outcomes [114]. Active surveillance remains under evaluation to determine if men with more aggressive cancers are at higher risk for treatment failure after the delay in treatment initiation [109].

**SUMMARY**

- Pretreatment staging of prostate cancer should be individualized on the basis of consideration of the clinical parameters that are predictive of the likelihood of extraprostatic extension, SVI, and metastatic disease. These clinical parameters can include the pretreatment PSA level and the rate of change, the Gleason score, the T stage on DRE, and sometimes the number of positive biopsy results, including the percentage of the core involved.
- Imaging in low-risk patients is likely to have a low yield in providing useful information to guide management for those electing up-front treatment. There may be a role for MRI in the context of active surveillance for low-risk patients.
- In intermediate-risk and high-risk individuals, imaging has a role in staging and in selecting or tailoring therapy.
MRI seems to be the most accurate imaging test available for local staging of the prostate, providing both locoregional and nodal evaluation. The use of an endorectal coil at 1.5 T is recommended and at 3.0 T is preferred. MRI staging accuracy seems related to reader experience. MRSI, DCE-MRI, and DWI-MRI are useful adjuncts, but incremental benefits provided by these additional MRI techniques over T2-weighted imaging for staging remain unproved in multi-institutional trials. Consensus is building around multiparametric prostate MRI as the most accurate and useful approach.

- In patients with the highest risk disease (clinical T3, very high PSA levels, and Gleason scores ≥8), radionuclide bone scans and CT can be useful for detecting metastases. PET scans with 2\(^{18}\)F\textsubscript{2}-deoxyglucose are of limited value in initial staging.
- When there exists strong clinical suspicion for the presence of prostate cancer in an individual because of rising or persistently high PSA level despite (generally multiple) negative biopsy sessions, MRI may be useful in identifying cancer in the prostate that can be targeted for diagnosis.

**ANTICIPATED EXCEPTIONS**

Nephrogenic systemic fibrosis is a disorder with a scleroderma-like presentation and a spectrum of manifestations that can range from limited clinical sequelae to fatality. It seems to be related to both underlying severe renal dysfunction and the administration of gadolinium-based contrast agents. It has occurred primarily in patients on dialysis, rarely in patients with very limited glomerular filtration rates (ie, <30 mL/min/1.73 m\(^2\)), and almost never in other patients. There is growing literature regarding nephrogenic systemic fibrosis. Although some controversy and lack of clarity remain, there is a consensus that it is advisable to avoid all gadolinium-based contrast agents in dialysis-dependent patients unless the possible benefits clearly outweigh the risk and to limit the type and amount in patients with estimated glomerular filtration rates <30 mL/min/1.73 m\(^2\). For more information, please see the ACR’s *Manual on Contrast Media* [115].

This article is a revised version of the ACR Appropriateness Criteria Prostate Cancer—Pretreatment Detection, Staging, and Surveillance. Practitioners are encouraged to refer to the complete version at www.acr.org/ac.

**REFERENCES**


