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**American College of Radiology  
ACR Appropriateness Criteria®  
Prostate Cancer–Pretreatment Detection, Surveillance, and Staging**

**Variant 1: Clinically suspected prostate cancer, no prior biopsy (biopsy naïve). Detection.**

Radiologic Procedure	Rating	Comments	RRL*
TRUS guided biopsy prostate	9		O
MRI pelvis without and with IV contrast	7	MRI (with or without contrast) in biopsy-naïve patients may be performed before TRUS-guided biopsy so the targeted sample may be obtained using MRI or TRUS fusion technology in patients with appropriate targets. MRI is complementary to TRUS-guided biopsy in this setting.	O
MRI targeted biopsy prostate	7		O
MRI pelvis without IV contrast	6		O
CT abdomen and pelvis with IV contrast	3		☼☼☼☼
TRUS prostate	2		O
CT abdomen and pelvis without IV contrast	2		☼☼☼☼
CT abdomen and pelvis without and with IV contrast	2		☼☼☼☼
Tc-99m bone scan whole body	1		☼☼☼
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 2: Clinically suspected prostate cancer, prior negative TRUS-guided biopsy. Detection.**

Radiologic Procedure	Rating	Comments	RRL*
MRI pelvis without and with IV contrast	8		O
MRI targeted biopsy prostate	8		O
TRUS guided biopsy prostate	7	Repeat TRUS-guided systematic biopsy is a reasonable option, but MRI (with or without contrast) should be performed first so that MRI-targeted biopsies (fusion or in-bore technique) can be obtained from appropriate suspicious lesions.	O
MRI pelvis without IV contrast	6		O
TRUS prostate	2		O
CT abdomen and pelvis with IV contrast	2		☼☼☼☼
CT abdomen and pelvis without IV contrast	2		☼☼☼☼
CT abdomen and pelvis without and with IV contrast	2		☼☼☼☼
Tc-99m bone scan whole body	1		☼☼☼
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 3:****Clinically established low-risk prostate cancer. Active surveillance.**

Radiologic Procedure	Rating	Comments	RRL*
MRI pelvis without and with IV contrast	8		O
MRI targeted biopsy prostate	8		O
TRUS guided biopsy prostate	7	Serial repeat TRUS-guided systematic biopsy is standard practice for patients on active surveillance, but MRI (with or without contrast) should be performed as well so that MRI-targeted biopsies (fusion or in-bore technique) can be obtained from appropriate suspicious lesions.	O
MRI pelvis without IV contrast	7		O
TRUS prostate	2		O
CT abdomen and pelvis with IV contrast	2		☼☼☼☼
CT abdomen and pelvis without IV contrast	2		☼☼☼☼
CT abdomen and pelvis without and with IV contrast	2		☼☼☼☼
Tc-99m bone scan whole body	1		☼☼☼
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 4:****Clinically established intermediate-risk prostate cancer. Staging and/or surveillance.**

Radiologic Procedure	Rating	Comments	RRL*
MRI pelvis without and with IV contrast	8		O
MRI pelvis without IV contrast	7		O
MRI targeted biopsy prostate	6		O
CT abdomen and pelvis with IV contrast	6		☼☼☼☼
Tc-99m bone scan whole body	6		☼☼☼
TRUS guided biopsy prostate	5		O
CT abdomen and pelvis without IV contrast	5		☼☼☼☼
TRUS prostate	2		O
CT abdomen and pelvis without and with IV contrast	2		☼☼☼☼
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 5: Clinically established high-risk prostate cancer. Staging.**

<b>Radiologic Procedure</b>	<b>Rating</b>	<b>Comments</b>	<b>RRL*</b>
MRI pelvis without and with IV contrast	8		O
Tc-99m bone scan whole body	8	This procedure is complementary to MRI or CT for evaluation of possible bone metastases.	☢ ☢ ☢
CT abdomen and pelvis with IV contrast	8		☢ ☢ ☢ ☢
CT abdomen and pelvis without IV contrast	7		☢ ☢ ☢ ☢
MRI pelvis without IV contrast	6		O
MRI targeted biopsy prostate	3		O
CT abdomen and pelvis without and with IV contrast	3		☢ ☢ ☢ ☢
TRUS prostate	2		O
TRUS guided biopsy prostate	2		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

# PROSTATE CANCER–PRETREATMENT DETECTION, SURVEILLANCE, AND STAGING

Expert Panel on Urologic Imaging: Fergus V. Coakley, MD<sup>1</sup>; Aytekin Oto, MD<sup>2</sup>; Lauren F. Alexander, MD<sup>3</sup>; Brian C. Allen, MD<sup>4</sup>; Brian J. Davis, MD, PhD<sup>5</sup>; Adam T. Froemming, MD<sup>6</sup>; Pat F. Fulgham, MD<sup>7</sup>; Keyanoosh Hosseinzadeh, MD<sup>8</sup>; Christopher Porter, MD<sup>9</sup>; V. Anik Sahni, MD<sup>10</sup>; David M. Schuster, MD<sup>11</sup>; Timothy N. Showalter, MD, MPH<sup>12</sup>; Aradhana M. Venkatesan, MD<sup>13</sup>; Sadhna Verma, MD<sup>14</sup>; Carolyn L. Wang, MD<sup>15</sup>; Erick M. Remer, MD<sup>16</sup>; Steven C. Eberhardt, MD.<sup>17</sup>

## Summary of Literature Review

### Introduction/Background

Despite the frequent statement that “most men die with prostate cancer, not of it” [1], the reality is that prostate cancer is second only to lung cancer as a cause of death from malignancy in American men. Specifically, in 2015, an estimated 220,800 American men were diagnosed with prostate cancer and 27,540 died of the disease [2]. In addition to the personal toll of these deaths, the direct economic cost of prostate cancer in the United States has been estimated at approximately \$10 billion per year [3]. As with other malignancies, the primary goal during baseline evaluation of prostate cancer is disease characterization; that is, establishing disease extent, both local and distant, and aggressiveness. Determination of tumor aggressiveness is ultimately the most important factor, since this drives patient outcome.

Several special circumstances make the accurate baseline evaluation of prostate cancer particularly challenging:

- The currently available standard clinical tools used to evaluate prostate cancer, such as digital rectal examination, serum prostate-specific antigen (PSA) assay, and systematic biopsy results such as fraction of cores positive for cancer and Gleason score, are all subject to varying degrees of inaccuracy. Even radical prostatectomy, often regarded as the gold standard for pathological findings, is subject to variable interpretation. The published interobserver kappa values of 0.33 to 0.63 for the detection of extracapsular extension by different pathologists analyzing radical prostatectomy specimens [4,5] are about the same as the kappa values of 0.59 to 0.67 for different radiologists looking for extracapsular extension at magnetic resonance imaging (MRI) [6]. Multiple nomograms have been described, such as the Partin Tables or the D’Amico risk stratification scheme, that aggregate data from these parameters in an attempt to better estimate tumor stage or tumor aggressiveness, [7,8]. These nomograms are a reasonable attempt to synthesize the data but ultimately are undermined by the inherent flaws and imprecisions of the input parameters [9,10]. That said, both the D’Amico and the National Comprehensive Cancer Network (NCCN) risk stratification systems are widely used and are shown below (see [Appendix 1](#) and [Appendix 2](#)). It should be noted that the number of positive biopsy cores and the clinical stage are both factors that appear to have relatively little prognostic impact when compared with the other more impactful parameters of Gleason score and PSA [11-16].

Numerous novel biomarkers have been and continue to be investigated to try and improve characterization at a patient or tumor-specific level, such as *PCA3*, tissue-gene signatures, serum-based microRNA, cell-free DNA, and circulating tumor cell analysis, but none has entered mainstream practice [17-20].

- Prostate cancer is a heterogeneous disease, ranging from small low-grade tumors that are indolent and incidental to large, aggressive, life-threatening tumors. This generates a twofold challenge. First, since we have limited ability to precisely characterize the disease in a given patient, it is difficult to match patients to optimal treatment. Ideally, those with indolent disease would be managed by active surveillance, whereas those with higher-risk disease would receive definitive management with radiation or surgery, possibly supplemented by short- or long-term androgen deprivation therapy. Those with systemic disease require systemic treatment, typically androgen deprivation therapy followed by chemotherapy after emergence of

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androgen resistance. Second, the biological heterogeneity results in a protracted natural history, so outcome studies may require 10 or 15 years of follow-up to generate meaningful data. For example, after 7 years of follow-up, analysis of the European Randomized Study of Screening for Prostate Cancer showed that 1410 patients had to be screened and 48 patients had to be treated in order to save 1 life [21]. With 6 additional years of follow-up, these numbers dropped to 781 and 27, respectively [22].

- Prostate cancer is a difficult organ and disease to image. For many years, the only imaging received by most patients was a transrectal ultrasound (TRUS) used to localize the prostate (*not* the cancer) prior to 6- to 12-core systematic biopsy. The emergence of multiparametric MRI over the last few decades as a powerful and relatively accurate tool for the local evaluation of prostate cancer has both enhanced and complicated the baseline evaluation of prostate cancer because it has added the option of MRI-targeted biopsy as a supplement or replacement for standard systematic biopsy [23,24], at least in the approximately 60% of patients who have an actionable target at MRI [25]. A recent meta-analysis demonstrated that MRI-targeted biopsy significantly increases the detection rate for both all cancers and clinically significant cancers and significantly decreases the detection of clinically insignificant cancers [26].

### Overview of Imaging Modalities

The common modalities used to evaluate prostate cancer are TRUS, MRI, computed tomography (CT), and bone scintigraphy. TRUS or MRI may be combined with biopsy. TRUS and MRI are used to evaluate local disease extent, whereas CT and bone scintigraphy are used to evaluate metastatic disease, which typically involves either nodal or bone deposits. Prostate risk stratification is central in determining the appropriateness of evaluating for locally advanced or distant disease, since both are primarily detectable in intermediate- and high-risk disease alone ([Appendix 3](#)). Although several organizations have proposed guidelines on imaging prostate cancer based on slightly differing definitions of higher-risk disease [27], it should be noted that the NCCN criteria for high-risk disease are any of the following [28]:

- PSA  $\geq 20$  ng/mL
- Gleason score  $\geq 8$
- Clinical stage  $\geq T3$
- Any 2 of: clinical stage T2b or T2c, Gleason score  $\geq 7$ , PSA of 10 to 20 ng/mL

#### *Transrectal ultrasound*

In North America, TRUS is generally performed by urologists for purposes of localizing the prostate gland (not the cancer) prior to systematic biopsy. Conventional grayscale TRUS is not widely used for tumor localization because only 11% to 35% of tumors are sonographically visible and only 17% to 57% of sonographically detected hypoechoic lesions are malignant [29]. In a study of 31,296 cores obtained from 3912 consecutive patients undergoing TRUS with biopsy, there was no statistically significant association between the presence of a hypoechoic lesion and the detection of cancer, whether on a per-patient or per-core basis [30]. Advanced ultrasound (US) techniques, such as Doppler, 3-D US, microbubble contrast-enhanced US, and elastography, have the potential to improve TRUS performance in the future [29,31,32], but none of these refinements have entered routine practice.

#### *Transrectal ultrasound with biopsy*

TRUS-guided systematic biopsy has been the standard diagnostic test for prostate cancer since a landmark study in 1989 showed that it was superior to digitally directed biopsy sampling of the prostate [33]. However, because needle positioning relative to tumor location is essentially random, TRUS biopsy has a false-negative rate of 15% to 46% [34] and a tumor undergrading rate of up to 38% when compared to final Gleason score at radical prostatectomy [35]. So-called tumor progression based on Gleason upgrading on repeat systematic biopsy during active surveillance may simply reflect inadequate initial sampling [36]. Despite this substantial sampling error, multiple risk stratification and management schemes rely heavily on systematic biopsy findings of Gleason grade and percentage of tumor-containing cores. Scientifically, it is suboptimal practice for such critical decision making to depend on inherently flawed data.

#### *Multiparametric MRI*

Over the last few decades, multiparametric MRI of the prostate has emerged as a powerful tool for the local evaluation of prostate cancer, including volumetric tumor localization within the prostate and assessment of local tumor extent and aggressiveness, as reviewed in more detail below according to clinical scenario. Pioneering studies in the 1980s established that cancer generally appears as an ovoid mass-like or crescentic subcapsular

region of reduced T2 signal. Subsequent multicenter trials were disappointing [37-39] but did not incorporate multiparametric MRI with diffusion, perfusion, or spectroscopic sequences. In particular, diffusion imaging has been seen as a “game changer” by seasoned investigators, and more recent studies using a multiparametric approach have shown substantially improved results [40-44]. A recent meta-analysis [45] incorporating 75 studies and 9796 patients showed sensitivity and specificity of 0.57 (95% CI, 0.49–0.64) and 0.91 (95% CI, 0.88–0.93), respectively, for the diagnosis of extracapsular extension and sensitivity and specificity of 0.58 (95% CI, 0.47–0.68) and 0.96 (95% CI, 0.95–0.97), respectively, for the diagnosis of seminal vesicle invasion. The authors concluded that MRI has high specificity but poor and heterogeneous sensitivity for local prostate cancer staging, although it should be noted that any such meta-analysis inevitably includes studies that may not be considered optimal by current state-of-the-art technical and interpretative standards. Finally, the role of intravenous gadolinium-containing contrast media merits particular attention because, although it is widely recognized that diffusion imaging is a critical component of multiparametric prostate MRI, the role of perfusion imaging is more controversial [46,47]. Prostate cancer typically enhances more rapidly and washes out more quickly than benign prostatic tissue, and so detection may be aided by dynamic contrast-enhanced MRI sequences. Conversely, perfusion imaging adds time to study acquisition, poses the small risk of contrast reactions, and adds to the duration and complexity of interpretation by the radiologist tasked with reading the study. Recent work suggests the incremental benefit of perfusion imaging on tumor detection is relatively modest [48]. Accordingly, when performing a multiparametric prostate MRI, the administration of intravenous gadolinium will likely confer only slightly improved tumor evaluation over the same study performed without contrast.

#### *MRI-targeted biopsy*

MRI-targeted biopsy of the prostate, after a diagnostic multiparametric MRI has depicted a focus of possible or probable malignancy, is currently a topic of major scientific interest and promises to dramatically alter the current approach to prostate cancer diagnosis. MRI-guided biopsy may be used for baseline diagnosis in patients who are biopsy naïve, for diagnosis of cancer (often in the central gland) in patients who have had a negative TRUS-guided systematic biopsy but who continue to have an elevated PSA or other cause for clinical concern, for re-evaluation of tumor grade in patients on active surveillance, and for diagnosis of local recurrence in patients who have undergone prior therapy. After identification of a “high-value target,” MRI-targeted biopsy can be performed in 1 of 3 ways [49]:

- Direct or “in bore”: The patient is in the MRI scanner and the needle is placed in the target under MRI visualization. Generally, only the target(s) is/are sampled.
- Fusion: The patient undergoes a standard TRUS-guided biopsy, but MRI targets from a preceding MRI scan are digitally “fused” to the US images so that additional cores can also be taken from those locations under US visualization.
- Cognitive: The patient undergoes a standard TRUS-guided biopsy, but in addition the operator biopsies the MRI target based on visual anatomic coregistration. As might be expected, several studies [50-52], including a prospective comparative trial, have confirmed the inferiority of this approach.

Overall, the clinical paradigm for prostate cancer diagnosis is rapidly moving towards MRI-targeted transrectal biopsy, based on substantial evidence from several centers (notably the National Institutes of Health; New York University [NYU]; University of California, Los Angeles [UCLA]; and Nijmegen) that this approach can transform baseline cancer evaluation when compared with traditional systematic biopsy, with fewer false negatives, better tumor characterization, improved tumor localization, and better treatment stratification, especially stratification to lower-risk cohorts that may be appropriate for active surveillance or focal therapy [23,24,49,53-55].

#### *Computed tomography*

Although the primary tumor site may be seen as a focal area of mass-like enhancement in the peripheral prostate on portal venous phase contrast-enhanced CT [56], the primary role of CT in prostate cancer is the detection of nodal metastases. In a meta-analysis of 24 published studies [57], the pooled sensitivity of CT was 0.42 (95% CI, 0.26–0.56) and pooled specificity was 0.82 (95% CI, 0.8–0.83). These relatively disappointing results likely reflect the limitations of the underlying assumption that nodal size reflects nodal content—it is well known that this paradigm has limited validity. The poor performance of CT for detection of nodal metastases has been confirmed in other recent studies [58,59]. NCCN guidelines [28] recommend CT if clinical stage is T3 or T4 or nomogram probability of lymph node involvement exceeds 10%. Recent European guidelines note that patients

with stage T2 or less, PSA <10 ng/mL, Gleason score  $\leq 6$ , and <50% positive biopsy cores have a <10% likelihood of having node metastases and do not need nodal evaluation [60].

#### *Bone scan*

Bone scintigraphy remains the standard test used for detection of bone metastases in high-risk patients, although emerging techniques like positron emission tomography/CT with new tracers such as sodium fluoride or choline and whole-body MRI may replace the traditional bone scan in the years to come. In the absence of these advanced techniques, it is ideal if bone scintigraphy is performed at sites with single-photon emission CT/CT capability. That said, bone scintigraphy remains widely available, relatively cheap, and accurate. A recent meta-analysis demonstrated a sensitivity of 0.79 (95% CI, 0.73–0.83), a specificity of 0.82 (95% CI, 0.78–0.85), and an area under the curve of 0.89 for the diagnosis of bone metastases by bone scintigraphy [61]. NCCN guidelines [28] recommend bone scintigraphy if baseline PSA is  $\geq 20$ , clinical stage is T2 and PSA is  $\geq 10$ , clinical stage is T3 or T4, Gleason score is  $\geq 8$ , or any symptoms are suggestive of bone metastases.

### **Discussion of Imaging Modalities by Variant**

#### **Variant 1: Clinically suspected prostate cancer, no prior biopsy (biopsy naïve). Detection.**

##### *Transrectal ultrasound*

In isolation, TRUS is inaccurate for prostate cancer detection [29,30] and is not recommended for this purpose.

##### *Transrectal ultrasound–guided biopsy*

Despite significant concerns related to both underdiagnosis and overdiagnosis [34,35,62], TRUS-guided systematic prostate biopsy remains the standard of care for diagnosis in patients with clinically suspected prostate cancer.

##### *Magnetic resonance imaging*

Historically, given the primacy of TRUS-guided systematic biopsy for prostate cancer diagnosis, MRI has not been widely used in biopsy-naïve patients with clinically suspected prostate cancer based on an abnormal digital rectal examination or serum PSA level. However, the emerging literature on the use of MRI targeting to guide baseline prostate biopsy (whether by fusion or in-bore approaches) provides strong evidence in favor of MRI to assist in tumor localization in this population. For example, in a prospective study of 223 biopsy-naïve patients, high-value targets (ie, lesions with a Prostate Imaging Reporting and Data System [PI-RADS] score of 4 or 5) were seen in 109 patients (49%), and 94 of these patients (86%) had positive targeted in-bore biopsies [63]. Of the 94 patients with MRI-guided biopsies, the targeted cores showed intermediate- or high-risk disease in 90 (96%), and 16 of the patients (17%) had negative systematic biopsy results. Such results suggest prebiopsy MRI is a useful adjunct for tumor localization in biopsy-naïve patients.

##### *MRI-targeted biopsy*

Given the emerging data on the utility of prebiopsy diagnostic MRI for tumor localization, MRI-targeted biopsy is among the appropriate options for biopsy-naïve patients [63].

##### *Computed tomography*

CT is generally not recommended unless higher-risk disease has been established histologically [27,28].

##### *Bone scan*

Bone scintigraphy is generally not recommended unless or until the presence of higher-risk disease has been established histologically [27,28].

#### **Variant 2: Clinically suspected prostate cancer, prior negative TRUS-guided biopsy. Detection.**

##### *Transrectal ultrasound*

In isolation, TRUS is inaccurate for prostate cancer detection [29,30] and is not recommended for this purpose.

##### *Transrectal ultrasound–guided biopsy*

In patients with clinically suspected prostate cancer who have had 1 negative standard TRUS-guided systematic biopsy, a second TRUS-guided systematic biopsy will be positive in approximately 15% to 20% of cases [64-67], and so a second repeat biopsy in this setting is reasonable. The yield from additional systematic biopsies, particularly the yield of clinically significant cancer, falls off rapidly, with reported positive rates for the third biopsy of 8% to 17% and for the fourth biopsy of 7% to 12% [64-66,68], suggesting alternative approaches such as MRI-guided biopsy or saturation biopsy may be more appropriate in the niche setting of patients with 2 or more negative TRUS-guided systematic biopsies and persistent clinical concern for prostate cancer.

### *Magnetic resonance imaging*

Emerging data suggest using MRI to localize high-value targets for possible MRI-guided biopsy is an appropriate approach to patients with clinically suspected prostate cancer and 1 or more prior negative TRUS-guided systematic biopsies. In a series of 105 patients from UCLA with a negative TRUS biopsy and persistently elevated PSA, multiparametric MRI demonstrated intermediate- and high-value targets in 34 (32%) and 14 (13%) patients, respectively, with corresponding fusion cancer detection rates of 23% and 88% [69]. In a similar series of 172 patients from NYU, targets with suspicion scores of 3, 4, and 5 were seen in 60 (35%), 40 (23%), and 18 (10%), with overall cancer detection rates of 17%, 42%, and 89%, respectively [70]. In a Nijmegen study of 438 patients with a PSA over 4.0 ng/mL and 1 or more prior negative TRUS biopsies, 265 patients were found to have targets worthy of MRI-guided biopsy, with a cancer detection rate of 41% [53]. Such results suggest prebiopsy MRI is a useful adjunct for tumor localization in biopsy-negative patients.

### *MRI-targeted biopsy*

Given the emerging data on the utility of prebiopsy/rebiopsy diagnostic MRI for tumor localization, MRI-targeted biopsy is among the appropriate options for biopsy-negative patients [69,70].

### *Computed tomography*

CT is generally not recommended unless higher-risk disease has been established histologically [27,28].

### *Bone scan*

Bone scintigraphy is generally not recommended unless or until the presence of higher-risk disease has been established histologically [27,28].

## **Variant 3: Clinically established low-risk prostate cancer. Active surveillance.**

### *Transrectal ultrasound*

TRUS is inaccurate for prostate cancer detection [29,30] and also has limited accuracy for prostate cancer staging [71] and so is not generally recommended for the evaluation of patients on active surveillance.

### *Transrectal ultrasound-guided biopsy*

Many active surveillance programs incorporate serial PSA testing and annual repeat TRUS biopsies, and some form of serial biopsy regimen is certainly the standard practice, although compliance with recommendations for serial biopsy is low [72].

### *Magnetic resonance imaging*

The role of MRI in active surveillance has recently been the subject of a meta-analysis incorporating 7 studies and 1028 patients [73]. MRI demonstrated an unrecognized significant lesion in 33% of patients, and targeted biopsy demonstrated disease unsuitable for continued active surveillance in 15% of these cases. Conversely, only 6% of patients with a negative MRI were found to be outside criteria for active surveillance on repeat biopsy. In another study of 111 patients on active surveillance [74], multiparametric MRI showed actionable targets (PI-RADS scores of 3, 4, or 5) in 70 patients (63%). Sixty-nine of these 70 patients proceeded to targeted biopsy, which was positive in 31, including 16 patients with Gleason pattern 4 or above that was considered to preclude continuation on active surveillance. A study from Toronto showed high-value targets (Likert scores of 4 or 5) in 37 of 71 (52%) patients on active surveillance [75]. Fusion-targeted biopsy was positive for Gleason 7+ cancer in 18 of these 37 patients, including 16 in whom the higher-grade cancer was present specifically in the targeted cores. Conversely, only 1 of the 35 patients without a high-value target was found to have Gleason 7+ cancer on rebiopsy. Other similar studies have confirmed that a negative MRI is a favorable prognostic finding in patients on active surveillance [76,77], and only 9% of such patients are reclassified to higher-risk disease on repeat biopsy [78].

### *MRI-targeted biopsy*

Existing data support the use of MRI to look for visible disease as a potential biopsy target in men on active surveillance [79]. The use of serial MRI to evaluate disease progression is intuitively appealing, but as noted in a recent systematic review, “Robust data on the use of repeat MRI in active surveillance are lacking. Prospective studies with clear definitions of radiological significance and progression are needed before this approach can be adopted” [80].

### *Computed tomography*

CT is generally not recommended unless higher-risk disease has been established [27,28].

### *Bone scan*

Bone scintigraphy is generally not recommended unless higher-risk disease has been established [27,28].

### **Variant 4: Clinically established intermediate-risk prostate cancer. Staging and/or surveillance.**

#### *Transrectal ultrasound*

TRUS is unlikely to provide useful incremental information in patients with an established diagnosis of intermediate-risk prostate cancer and so is not recommended.

#### *Transrectal ultrasound–guided biopsy*

Some publications have suggested that active surveillance may be an appropriate management option for at least a subset of patients with intermediate-risk prostate cancer [81,82]. In that setting, some form of serial TRUS-guided biopsy would be appropriate as part of the monitoring regimen.

#### *Magnetic resonance imaging*

In addition to standard local and nodal staging observations, multiparametric MRI may be helpful in the management of intermediate-risk prostate cancer by revealing unfavorable disease in patients who may be considering active surveillance, demonstrating more extensive disease that may merit supplementary extended androgen deprivation therapy, localizing dominant disease for focal therapy, or guiding surgical planning [83-86].

#### *MRI-targeted biopsy*

Many patients with intermediate-risk disease choose definitive therapy, and targeted biopsy is unlikely to significantly alter management or prognostic counseling. However, MRI-targeted biopsy in patients with established intermediate-risk disease may be appropriate in selected circumstances, for example, in patients with Gleason score 3+4 cancer who might be considering active surveillance but who would opt for more aggressive therapy if targeted biopsy demonstrated Gleason score 4+3 or higher disease.

#### *Computed tomography*

CT or MRI for nodal staging is generally appropriate in intermediate-risk patients, since the a priori risk of nodal disease exceeds 10% [28,60].

### *Bone scan*

NCCN guidelines and existing literature [28,87] recommend bone scintigraphy if baseline PSA is  $\geq 20$ , clinical stage is T2 and PSA is  $\geq 10$ , clinical stage is T3 or T4, Gleason score is  $\geq 8$ , or any symptoms are suggestive of bone metastases. Many intermediate-risk patients would meet these criteria.

### **Variant 5: Clinically established high-risk prostate cancer. Staging.**

#### *Transrectal ultrasound*

TRUS is unlikely to provide useful incremental information in patients with an established diagnosis of high-risk prostate cancer and so is not recommended.

#### *Transrectal ultrasound–guided biopsy*

TRUS-guided biopsy is unlikely to provide useful incremental information in patients with an established diagnosis of high-risk prostate cancer and so is not recommended.

#### *Magnetic resonance imaging*

In addition to standard local and nodal staging observations, multiparametric MRI may be helpful in the management of high-risk prostate cancer by demonstrating more extensive disease that may merit supplementary extended androgen deprivation therapy, localizing dominant disease for focal therapy, or guiding surgical planning [83-86].

#### *MRI-targeted biopsy*

Most patients with high-risk disease require definitive therapy, and targeted biopsy is unlikely to significantly alter management or prognostic counseling.

#### *Computed tomography*

CT or MRI for nodal staging is generally appropriate in high-risk patients, since the a priori risk of nodal disease exceeds 10% [28,60].

### *Bone scan*

NCCN guidelines and existing literature [28,87] recommend bone scintigraphy if baseline PSA is  $\geq 20$ , clinical stage is T2 and PSA is  $\geq 10$ , clinical stage is T3 or T4, Gleason score is  $\geq 8$ , or any symptoms are suggestive of bone metastases. Essentially all high-risk patients would meet these criteria.

### **Summary of Recommendations**

- For diagnosis of prostate cancer, TRUS-guided systematic biopsy remains the standard procedure in routine clinical practice. However, MRI-targeted biopsy of high-value lesions identified at multiparametric MRI, whether by fusion or in-bore techniques, is increasingly emerging as an important diagnostic tool that may be used to supplement (and perhaps someday supplant) TRUS-guided biopsy. MRI-targeted biopsy necessarily requires performance of a preceding multiparametric MRI. MRI-targeted biopsy is particularly appropriate for patients with an elevated PSA after 1 or more negative TRUS-guided biopsies who have a high-value target at diagnostic multiparametric MRI.
- For monitoring of lower-risk prostate cancer being managed by active surveillance, serial TRUS-guided systematic biopsy remains a standard component of active surveillance regimens. MRI-targeted biopsy of high-value lesions identified at multiparametric MRI, whether by fusion or in-bore techniques, is increasingly emerging as an important supplementary tool that often results in tumor upgrading. The role of serial multiparametric MRI as part of a surveillance regimen is undetermined.
- For staging of intermediate- or higher-risk prostate cancer, multiparametric MRI offers reasonable accuracy in the evaluation of extracapsular extension and seminal vesicle invasion. MRI or CT can be used to evaluate pelvic and retroperitoneal lymph nodes, whereas bone scintigraphy remains the standard procedure for evaluation of possible bone metastases.

### **Summary of Evidence**

Of the 93 references cited in the *ACR Appropriateness Criteria<sup>®</sup> Prostate Cancer-Pretreatment Detection Staging and Surveillance* document, 1 reference is categorized as a good-quality therapeutic reference. Additionally, 87 references are categorized as diagnostic references including 3 well-designed studies, 23 good-quality studies, and 33 quality studies that may have design limitations. There are 28 references that may not be useful as primary evidence. There are 5 references that are meta-analysis studies.

The 93 references cited in the *ACR Appropriateness Criteria<sup>®</sup> Prostate Cancer-Pretreatment Detection Staging and Surveillance* document were published from 1989 through 2016.

Although there are references that report on studies with design limitations, 27 well-designed or good-quality studies provide good evidence.

### **Relative Radiation Level Information**

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the *ACR Appropriateness Criteria<sup>®</sup> [Radiation Dose Assessment Introduction](#)* document.

Relative Radiation Level Designations		
Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
○	0 mSv	0 mSv
⊛	<0.1 mSv	<0.03 mSv
⊛ ⊛	0.1-1 mSv	0.03-0.3 mSv
⊛ ⊛ ⊛	1-10 mSv	0.3-3 mSv
⊛ ⊛ ⊛ ⊛	10-30 mSv	3-10 mSv
⊛ ⊛ ⊛ ⊛ ⊛	30-100 mSv	10-30 mSv

\*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as “Varies”.

### Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to [www.acr.org/ac](http://www.acr.org/ac).

### References

1. Uchio EM, Aslan M, Wells CK, Calderone J, Concato J. Impact of biochemical recurrence in prostate cancer among US veterans. *Arch Intern Med.* 2010;170(15):1390-1395.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66(1):7-30.
3. Roehrborn CG, Black LK. The economic burden of prostate cancer. *BJU Int.* 2011;108(6):806-813.
4. Evans AJ, Henry PC, Van der Kwast TH, et al. Interobserver variability between expert urologic pathologists for extraprostatic extension and surgical margin status in radical prostatectomy specimens. *Am J Surg Pathol.* 2008;32(10):1503-1512.
5. van der Kwast TH, Collette L, Van Poppel H, et al. Impact of pathology review of stage and margin status of radical prostatectomy specimens (EORTC trial 22911). *Virchows Arch.* 2006;449(4):428-434.
6. Graser A, Heuck A, Sommer B, et al. Per-sextant localization and staging of prostate cancer: correlation of imaging findings with whole-mount step section histopathology. *AJR Am J Roentgenol.* 2007;188(1):84-90.
7. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA.* 1998;280(11):969-974.
8. Eifler JB, Feng Z, Lin BM, et al. An updated prostate cancer staging nomogram (Partin tables) based on cases from 2006 to 2011. *BJU Int.* 2013;111(1):22-29.
9. Karakiewicz PI, Bhojani N, Capitanio U, et al. External validation of the updated Partin tables in a cohort of North American men. *J Urol.* 2008;180(3):898-902; discussion 902-893.
10. Yu JB, Makarov DV, Sharma R, Peschel RE, Partin AW, Gross CP. Validation of the partin nomogram for prostate cancer in a national sample. *J Urol.* 2010;183(1):105-111.
11. Armatys SA, Koch MO, Bihrlle R, Gardner TA, Cheng L. Is it necessary to separate clinical stage T1c from T2 prostate adenocarcinoma? *BJU Int.* 2005;96(6):777-780.
12. Klaassen Z, Singh AA, Howard LE, et al. Is clinical stage T2c prostate cancer an intermediate- or high-risk disease? *Cancer.* 2015;121(9):1414-1421.
13. Reese AC, Cooperberg MR, Carroll PR. Minimal impact of clinical stage on prostate cancer prognosis among contemporary patients with clinically localized disease. *J Urol.* 2010;184(1):114-119.
14. Reese AC, Sadetsky N, Carroll PR, Cooperberg MR. Inaccuracies in assignment of clinical stage for localized prostate cancer. *Cancer.* 2011;117(2):283-289.
15. Stephenson AJ, Scardino PT, Eastham JA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Natl Cancer Inst.* 2006;98(10):715-717.
16. Williams SG, Buyyounouski MK, Pickles T, et al. Percentage of biopsy cores positive for malignancy and biochemical failure following prostate cancer radiotherapy in 3,264 men: statistical significance without predictive performance. *Int J Radiat Oncol Biol Phys.* 2008;70(4):1169-1175.

17. Falzarano SM, Ferro M, Bollito E, Klein EA, Carrieri G, Magi-Galluzzi C. Novel biomarkers and genomic tests in prostate cancer: a critical analysis. *Minerva Urol Nefrol.* 2015;67(3):211-231.
18. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol.* 2014;66(3):550-560.
19. Locke JA, Black PC. Next generation biomarkers in prostate cancer. *Front Biosci (Landmark Ed).* 2016;21:328-342.
20. Ross AE, D'Amico AV, Freedland SJ. Which, when and why? Rational use of tissue-based molecular testing in localized prostate cancer. *Prostate Cancer Prostatic Dis.* 2016;19(1):1-6.
21. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med.* 2009;360(13):1310-1319.
22. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet.* 2014;384(9959):2027-2035.
23. Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. *Eur Urol.* 2013;64(5):713-719.
24. van de Ven WJ, Barentsz JO. Prostate cancer: MRI/US-guided biopsy--a viable alternative to TRUS-guidance. *Nat Rev Urol.* 2013;10(10):559-560.
25. Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. *Eur Urol.* 2013;63(1):125-140.
26. Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MG. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. *Eur Urol.* 2015;68(3):438-450.
27. Bjurlin MA, Rosenkrantz AB, Beltran LS, Raad RA, Taneja SS. Imaging and evaluation of patients with high-risk prostate cancer. *Nat Rev Urol.* 2015;12(11):617-628.
28. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. Version 2.2016. 2016; Available at: [http://www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf).
29. Smeenge M, de la Rosette JJ, Wijkstra H. Current status of transrectal ultrasound techniques in prostate cancer. *Curr Opin Urol.* 2012;22(4):297-302.
30. Onur R, Littrup PJ, Pontes JE, Bianco FJ, Jr. Contemporary impact of transrectal ultrasound lesions for prostate cancer detection. *J Urol.* 2004;172(2):512-514.
31. Mitterberger M, Pinggera GM, Horninger W, et al. Comparison of contrast enhanced color Doppler targeted biopsy to conventional systematic biopsy: impact on Gleason score. *J Urol.* 2007;178(2):464-468; discussion 468.
32. Mitterberger M, Pinggera GM, Pallwein L, et al. The value of three-dimensional transrectal ultrasonography in staging prostate cancer. *BJU Int.* 2007;100(1):47-50.
33. Hodge KK, McNeal JE, Terris MK, Stamey TA. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. *J Urol.* 1989;142(1):71-74; discussion 74-75.
34. Dominguez-Escrig JL, McCracken SR, Greene D. Beyond diagnosis: evolving prostate biopsy in the era of focal therapy. *Prostate Cancer.* 2011;2011:386207.
35. Kvale R, Moller B, Wahlqvist R, et al. Concordance between Gleason scores of needle biopsies and radical prostatectomy specimens: a population-based study. *BJU Int.* 2009;103(12):1647-1654.
36. Porten SP, Whitson JM, Cowan JE, et al. Changes in prostate cancer grade on serial biopsy in men undergoing active surveillance. *J Clin Oncol.* 2011;29(20):2795-2800.
37. Rifkin MD, Zerhouni EA, Gatsonis CA, et al. Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer. Results of a multi-institutional cooperative trial. *N Engl J Med.* 1990;323(10):621-626.
38. Tempany CM, Zhou X, Zerhouni EA, et al. Staging of prostate cancer: results of Radiology Diagnostic Oncology Group project comparison of three MR imaging techniques. *Radiology.* 1994;192(1):47-54.
39. Weinreb JC, Blume JD, Coakley FV, et al. Prostate cancer: sextant localization at MR imaging and MR spectroscopic imaging before prostatectomy--results of ACRIN prospective multi-institutional clinicopathologic study. *Radiology.* 2009;251(1):122-133.

40. Engelbrecht MR, Huisman HJ, Laheij RJ, et al. Discrimination of prostate cancer from normal peripheral zone and central gland tissue by using dynamic contrast-enhanced MR imaging. *Radiology*. 2003;229(1):248-254.
41. Kim CK, Park BK, Kim B. Localization of prostate cancer using 3T MRI: comparison of T2-weighted and dynamic contrast-enhanced imaging. *J Comput Assist Tomogr*. 2006;30(1):7-11.
42. Li C, Chen M, Li S, et al. Detection of prostate cancer in peripheral zone: comparison of MR diffusion tensor imaging, quantitative dynamic contrast-enhanced MRI, and the two techniques combined at 3.0 T. *Acta Radiol*. 2014;55(2):239-247.
43. Turkbey B, Merino MJ, Gallardo EC, et al. Comparison of endorectal coil and nonendorectal coil T2W and diffusion-weighted MRI at 3 Tesla for localizing prostate cancer: correlation with whole-mount histopathology. *J Magn Reson Imaging*. 2014;39(6):1443-1448.
44. Vargas HA, Akin O, Franiel T, et al. Diffusion-weighted endorectal MR imaging at 3 T for prostate cancer: tumor detection and assessment of aggressiveness. *Radiology*. 2011;259(3):775-784.
45. de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM. Accuracy of Magnetic Resonance Imaging for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis. *Eur Urol*. 2015:[E-pub ahead of print].
46. Verma S, Turkbey B, Muradyan N, et al. Overview of dynamic contrast-enhanced MRI in prostate cancer diagnosis and management. *AJR Am J Roentgenol*. 2012;198(6):1277-1288.
47. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. *Eur Urol*. 2016;69(1):16-40.
48. Romero G, Foster BR, Pettersson DR, Fung AW, Guimaraes AR, Coakley FV. Endorectal multiparametric MRI of the prostate: incremental effect of perfusion imaging on biopsy target identification. *Clin Imaging*. 2016;40(3):553-557.
49. Klein EA. Prostate cancer: MR-TRUS fusion biopsy--defining a new standard. *Nat Rev Clin Oncol*. 2015;12(5):253-254.
50. Cool DW, Zhang X, Romagnoli C, Izawa JI, Romano WM, Fenster A. Evaluation of MRI-TRUS fusion versus cognitive registration accuracy for MRI-targeted, TRUS-guided prostate biopsy. *AJR Am J Roentgenol*. 2015;204(1):83-91.
51. Valerio M, McCartan N, Freeman A, Punwani S, Emberton M, Ahmed HU. Visually directed vs. software-based targeted biopsy compared to transperineal template mapping biopsy in the detection of clinically significant prostate cancer. *Urol Oncol*. 2015;33(10):424 e429-416.
52. Wysock JS, Rosenkrantz AB, Huang WC, et al. A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. *Eur Urol*. 2014;66(2):343-351.
53. Hoeks CM, Schouten MG, Bomers JG, et al. Three-Tesla magnetic resonance-guided prostate biopsy in men with increased prostate-specific antigen and repeated, negative, random, systematic, transrectal ultrasound biopsies: detection of clinically significant prostate cancers. *Eur Urol*. 2012;62(5):902-909.
54. Mendhiratta N, Rosenkrantz AB, Meng X, et al. Magnetic Resonance Imaging-Ultrasound Fusion Targeted Prostate Biopsy in a Consecutive Cohort of Men with No Previous Biopsy: Reduction of Over Detection through Improved Risk Stratification. *J Urol*. 2015;194(6):1601-1606.
55. Nassiri N, Natarajan S, Margolis DJ, Marks LS. Targeted Prostate Biopsy: Lessons Learned Midst the Evolution of a Disruptive Technology. *Urology*. 2015;86(3):432-438.
56. Jia JB, Houshyar R, Verma S, Uchio E, Lall C. Prostate cancer on computed tomography: A direct comparison with multi-parametric magnetic resonance imaging and tissue pathology. *Eur J Radiol*. 2016;85(1):261-267.
57. Hovels AM, Heesakkers RA, Adang EM, et al. The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. *Clin Radiol*. 2008;63(4):387-395.
58. Briganti A, Abdollah F, Nini A, et al. Performance characteristics of computed tomography in detecting lymph node metastases in contemporary patients with prostate cancer treated with extended pelvic lymph node dissection. *Eur Urol*. 2012;61(6):1132-1138.
59. Gabriele D, Collura D, Oderda M, et al. Is there still a role for computed tomography and bone scintigraphy in prostate cancer staging? An analysis from the EUREKA-1 database. *World J Urol*. 2016;34(4):517-523.
60. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol*. 2014;65(1):124-137.

61. Shen G, Deng H, Hu S, Jia Z. Comparison of choline-PET/CT, MRI, SPECT, and bone scintigraphy in the diagnosis of bone metastases in patients with prostate cancer: a meta-analysis. *Skeletal Radiol*. 2014;43(11):1503-1513.
62. Sandhu GS, Andriole GL. Overdiagnosis of prostate cancer. *J Natl Cancer Inst Monogr*. 2012;2012(45):146-151.
63. Pokorny MR, de Rooij M, Duncan E, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. *Eur Urol*. 2014;66(1):22-29.
64. Keetch DW, Catalona WJ, Smith DS. Serial prostatic biopsies in men with persistently elevated serum prostate specific antigen values. *J Urol*. 1994;151(6):1571-1574.
65. Ploussard G, Nicolaiew N, Marchand C, et al. Risk of repeat biopsy and prostate cancer detection after an initial extended negative biopsy: longitudinal follow-up from a prospective trial. *BJU Int*. 2013;111(6):988-996.
66. Roehl KA, Antenor JA, Catalona WJ. Serial biopsy results in prostate cancer screening study. *J Urol*. 2002;167(6):2435-2439.
67. Vencalek O, Facevicova K, Furst T, Grepl M. When less is more: a simple predictive model for repeated prostate biopsy outcomes. *Cancer Epidemiol*. 2013;37(6):864-869.
68. Zaytoun OM, Stephenson AJ, Fareed K, et al. When serial prostate biopsy is recommended: most cancers detected are clinically insignificant. *BJU Int*. 2012;110(7):987-992.
69. Sonn GA, Chang E, Natarajan S, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. *Eur Urol*. 2014;65(4):809-815.
70. Meng X, Rosenkrantz AB, Mendhiratta N, et al. Relationship Between Prebiopsy Multiparametric Magnetic Resonance Imaging (MRI), Biopsy Indication, and MRI-ultrasound Fusion-targeted Prostate Biopsy Outcomes. *Eur Urol*. 2016;69(3):512-517.
71. Jung AJ, Coakley FV, Shinohara K, et al. Local staging of prostate cancer: comparative accuracy of T2-weighted endorectal MR imaging and transrectal ultrasound. *Clin Imaging*. 2012;36(5):547-552.
72. Bokhorst LP, Alberts AR, Rannikko A, et al. Compliance Rates with the Prostate Cancer Research International Active Surveillance (PRIAS) Protocol and Disease Reclassification in Noncompliers. *Eur Urol*. 2015;68(5):814-821.
73. Guo R, Cai L, Fan Y, Jin J, Zhou L, Zhang K. Magnetic resonance imaging on disease reclassification among active surveillance candidates with low-risk prostate cancer: a diagnostic meta-analysis. *Prostate Cancer Prostatic Dis*. 2015;18(3):221-228.
74. Abdi H, Pourmalek F, Zargar H, et al. Multiparametric magnetic resonance imaging enhances detection of significant tumor in patients on active surveillance for prostate cancer. *Urology*. 2015;85(2):423-428.
75. Da Rosa MR, Milot L, Sugar L, et al. A prospective comparison of MRI-US fused targeted biopsy versus systematic ultrasound-guided biopsy for detecting clinically significant prostate cancer in patients on active surveillance. *J Magn Reson Imaging*. 2015;41(1):220-225.
76. Fradet V, Kurhanewicz J, Cowan JE, et al. Prostate cancer managed with active surveillance: role of anatomic MR imaging and MR spectroscopic imaging. *Radiology*. 2010;256(1):176-183.
77. Park BH, Jeon HG, Choo SH, et al. Role of multiparametric 3.0-Tesla magnetic resonance imaging in patients with prostate cancer eligible for active surveillance. *BJU Int*. 2014;113(6):864-870.
78. Margel D, Yap SA, Lawrentschuk N, et al. Impact of multiparametric endorectal coil prostate magnetic resonance imaging on disease reclassification among active surveillance candidates: a prospective cohort study. *J Urol*. 2012;187(4):1247-1252.
79. Hu JC, Chang E, Natarajan S, et al. Targeted prostate biopsy in select men for active surveillance: do the Epstein criteria still apply? *J Urol*. 2014;192(2):385-390.
80. Schoots IG, Petrides N, Giganti F, et al. Magnetic resonance imaging in active surveillance of prostate cancer: a systematic review. *Eur Urol*. 2015;67(4):627-636.
81. Cooperberg MR, Cowan JE, Hilton JF, et al. Outcomes of active surveillance for men with intermediate-risk prostate cancer. *J Clin Oncol*. 2011;29(2):228-234.
82. Raldow AC, Zhang D, Chen MH, Braccioforte MH, Moran BJ, D'Amico AV. Risk Group and Death From Prostate Cancer: Implications for Active Surveillance in Men With Favorable Intermediate-Risk Prostate Cancer. *JAMA Oncol*. 2015;1(3):334-340.

83. Anwar M, Westphalen AC, Jung AJ, et al. Role of endorectal MR imaging and MR spectroscopic imaging in defining treatable intraprostatic tumor foci in prostate cancer: quantitative analysis of imaging contour compared to whole-mount histopathology. *Radiother Oncol*. 2014;110(2):303-308.
84. Hricak H, Wang L, Wei DC, et al. The role of preoperative endorectal magnetic resonance imaging in the decision regarding whether to preserve or resect neurovascular bundles during radical retropubic prostatectomy. *Cancer*. 2004;100(12):2655-2663.
85. Muglia VF, Westphalen AC, Wang ZJ, Kurhanewicz J, Carroll PR, Coakley FV. Endorectal MRI of prostate cancer: incremental prognostic importance of gross locally advanced disease. *AJR Am J Roentgenol*. 2011;197(6):1369-1374.
86. Roethke MC, Lichy MP, Kniess M, et al. Accuracy of preoperative endorectal MRI in predicting extracapsular extension and influence on neurovascular bundle sparing in radical prostatectomy. *World J Urol*. 2013;31(5):1111-1116.
87. Merdan S, Womble PR, Miller DC, et al. Toward better use of bone scans among men with early-stage prostate cancer. *Urology*. 2014;84(4):793-798.
88. Edge SB, American Joint Committee on Cancer. *AJCC cancer staging manual*. 7th ed. New York: Springer; 2010.
89. Gleave ME, Coupland D, Drachenberg D, et al. Ability of serum prostate-specific antigen levels to predict normal bone scans in patients with newly diagnosed prostate cancer. *Urology*. 1996;47(5):708-712.
90. Hirobe M, Takahashi A, Hisasue S, et al. Bone scanning--who needs it among patients with newly diagnosed prostate cancer? *Jpn J Clin Oncol*. 2007;37(10):788-792.
91. Lee IH, Roberts R, Shah RB, Wojno KJ, Wei JT, Sandler HM. Perineural invasion is a marker for pathologically advanced disease in localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2007;68(4):1059-1064.
92. Pettus JA, Masterson TA, Abel EJ, Middleton RG, Stephenson RA. Risk stratification for positive lymph nodes in prostate cancer. *J Endourol*. 2008;22(5):1021-1025.
93. Rhoden EL, Torres O, Ramos GZ, Lemos RR, Souto CA. Value of prostate specific antigen in predicting the existence of bone metastasis in scintigraphy. *Int Braz J Urol*. 2003;29(2):121-125; discussion 126.

The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

<b>Appendix 1. D'Amico risk stratification system.</b>	
<i>Risk group</i>	<i>Characteristics*</i>
<i>Low</i>	PSA <10 ng/mL <u>and</u> Gleason score ≤6 <u>and</u> clinical stage T1 or T2a
<i>Intermediate</i>	PSA ≥10 and <20 <u>or</u> Gleason score = 7 <u>or</u> clinical stage T2b
<i>High</i>	PSA ≥20 ng/mL <u>or</u> Gleason score ≥8 <u>or</u> clinical stage ≥T2c

\*Clinical stage based on digital rectal examination results [88]:

- T1: Clinically unapparent tumor neither palpable nor visible by imaging
- T2: Palpable or visible tumor confined to prostate
- T2a: Tumor involves one-half of one lobe or less
- T2b: Tumor involves more than one-half of one lobe but not both lobes
- T2c: Tumor involves both lobes
- T3: Tumor extends through the prostate capsule
- T3a: Unilateral or bilateral extracapsular extension
- T3b: Tumor invades seminal vesicle(s)
- T4: Tumor is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

<b>Appendix 2. NCCN risk stratification system.</b>	
<i>Risk group</i>	<i>Characteristics</i>
<i>Very low</i>	Clinical stage T1c <u>and</u> PSA <10 ng/mL <u>and</u> PSA density <0.15 ng/mL/g <u>and</u> 1–2 positive biopsy cores with ≤50% cancer in each <u>and</u> Gleason score ≤6
<i>Low</i>	Clinical stage T1-T2a <u>and</u> PSA <10 ng/mL <u>and</u> Gleason score ≤6
<i>Intermediate</i>	Clinical stage T2b-T2c <u>or</u> PSA 10–20 ng/mL <u>or</u> Gleason score 7
<i>High</i>	Clinical stage T3a <u>or</u> PSA >20 ng/mL <u>or</u> Gleason score 8+
<i>Very high</i>	Clinical stage T3b-T4 <u>or</u> primary Gleason pattern 5 <u>or</u> >4 cores with Gleason 8+

<b>Appendix 3: Likelihood of locally advanced or distant disease in prostate cancer stratified by D'Amico risk category [89-93].</b>				
<i>D'Amico risk group</i>	<i>Extracapsular extension</i>	<i>Seminal vesicle invasion</i>	<i>Nodal metastases</i>	<i>Positive bone scan</i>
<i>Low</i>	9%	1%	1.3%	0%
<i>Intermediate</i>	20%	5%	6%	1.6%–4.5%
<i>High</i>	47%	30%	20%	21%–41%