

# ACR Appropriateness Criteria<sup>®</sup>

## Post-treatment Follow-up Prostate Cancer

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### Abstract

Diagnosis and management of prostate cancer post treatment is a large and complex problem, and care of these patients requires multidisciplinary involvement of imaging, medical, and surgical specialties. Imaging capabilities for evaluation of men with recurrent prostate cancer are rapidly evolving, particularly with PET and MRI. At the same time, treatment options and capabilities are expanding and improving. These recommendations separate patients into three broad categories: (1) patients status post–radical prostatectomy, (2) clinical concern for residual or recurrent disease after nonsurgical local and pelvic treatments, and (3) metastatic prostate. This article is a review of the current literature regarding imaging in these settings and the resulting recommendations for imaging.

The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision include an extensive analysis of current medical literature from peer reviewed journals and the application of well-established methodologies (RAND/UCLA Appropriateness Method and Grading of Recommendations Assessment, Development, and Evaluation or GRADE) to rate the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances where evidence is lacking or equivocal, expert opinion may supplement the available evidence to recommend imaging or treatment.

**Key Words:** Appropriateness Criteria, Appropriate Use Criteria, AUC, Choline and fluciclovine PET, Metastatic prostate cancer, MRI, Prostate cancer, Recurrent prostate cancer

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Dr. Coakley reports other from Omnicell Instruments, Inc., outside the submitted work; in addition, Dr. Coakley has a patent filed for the Omnicell device described above pending. Dr. Oto reports grants from Profound Healthcare, grants from Guerbet, grants from Philips Healthcare, personal fees from Profound Healthcare, and personal fees from Abbott, outside the submitted work.

**Disclaimer:** 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.

**Variant 1.** Prostate cancer follow-up. Status post radical prostatectomy. Clinical concern for residual or recurrent disease.

Procedure	Appropriateness Category	Relative Radiation Level
C-11 choline PET/CT skull base to mid-thigh	Usually Appropriate	⚙⚙⚙
MRI pelvis without and with IV contrast	Usually Appropriate	0
F-18 fluciclovine PET/CT skull base to mid-thigh	Usually Appropriate	⚙⚙⚙⚙
CT abdomen and pelvis with IV contrast	May Be Appropriate	⚙⚙⚙⚙
MRI-targeted biopsy prostate	May Be Appropriate	0
Tc-99m bone scan whole body	May Be Appropriate	⚙⚙⚙
TRUS guided biopsy prostate	May Be Appropriate	0
MRI abdomen and pelvis without and with IV contrast	May Be Appropriate (Disagreement)	0
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	⚙⚙⚙⚙
CT chest abdomen pelvis with IV contrast	Usually Not Appropriate	⚙⚙⚙⚙
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	⚙⚙⚙⚙
MRI abdomen and pelvis without IV contrast	Usually Not Appropriate	0
MRI pelvis without IV contrast	Usually Not Appropriate	0
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	⚙⚙⚙⚙
CT chest abdomen pelvis without and with IV contrast	Usually Not Appropriate	⚙⚙⚙⚙
CT chest abdomen pelvis without IV contrast	Usually Not Appropriate	⚙⚙⚙⚙
TRUS prostate	Usually Not Appropriate	0
X-ray skeletal survey	Usually Not Appropriate	⚙⚙⚙

FDG = fluorine-18-2-fluoro-2-deoxy-D-glucose; IV = intravenous; TRUS = transrectal ultrasound.

**Variant 2.** Prostate cancer follow-up. Clinical concern for residual or recurrent disease after nonsurgical local and pelvic treatments.

Procedure	Appropriateness Category	Relative Radiation Level
C-11 choline PET/CT skull base to mid-thigh	Usually Appropriate	⚙⚙⚙
MRI pelvis without and with IV contrast	Usually Appropriate	0
F-18 fluciclovine PET/CT skull base to mid-thigh	Usually Appropriate	⚙⚙⚙⚙
MRI-targeted biopsy prostate	Usually Appropriate	0
TRUS guided biopsy prostate	Usually Appropriate	0
CT abdomen and pelvis with IV contrast	May Be Appropriate	⚙⚙⚙⚙
MRI abdomen and pelvis without and with IV contrast	May Be Appropriate (Disagreement)	0
Tc-99m bone scan whole body	May Be Appropriate (Disagreement)	⚙⚙⚙

(continued)

Variant 2. Continued

Procedure	Appropriateness Category	Relative Radiation Level
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	⚡⚡⚡⚡
CT chest abdomen pelvis with IV contrast	Usually Not Appropriate	⚡⚡⚡⚡
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	⚡⚡⚡⚡
MRI abdomen and pelvis without IV contrast	Usually Not Appropriate	0
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	⚡⚡⚡⚡
CT chest abdomen pelvis without IV contrast	Usually Not Appropriate	⚡⚡⚡⚡
CT chest abdomen pelvis without and with IV contrast	Usually Not Appropriate	⚡⚡⚡⚡
MRI pelvis without IV contrast	Usually Not Appropriate	0
TRUS prostate	Usually Not Appropriate	0
X-ray skeletal survey	Usually Not Appropriate	⚡⚡⚡

FDG = fluorine-18-2-fluoro-2-deoxy-D-glucose; IV = intravenous; TRUS = transrectal ultrasound.

Variant 3. Metastatic prostate cancer treated by systemic therapy (androgen deprivation therapy [ADT], chemotherapy, immunotherapy). Follow-up.

Procedure	Appropriateness Category	Relative Radiation Level
CT abdomen and pelvis with IV contrast	Usually Appropriate	⚡⚡⚡⚡
Tc-99m bone scan whole body	Usually Appropriate	⚡⚡⚡
C-11 choline PET/CT skull base to mid-thigh	Usually Appropriate	⚡⚡⚡
F-18 fluciclovine PET/CT skull base to mid-thigh	Usually Appropriate	⚡⚡⚡⚡
CT chest abdomen pelvis with IV contrast	May Be Appropriate	⚡⚡⚡⚡
MRI abdomen and pelvis without and with IV contrast	May Be Appropriate	0
MRI pelvis without and with IV contrast	May Be Appropriate	0
FDG-PET/CT skull base to mid-thigh	May Be Appropriate	⚡⚡⚡⚡
MRI pelvis without IV contrast	May Be Appropriate	0
CT abdomen and pelvis without IV contrast	Usually Not Appropriate	⚡⚡⚡⚡
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	⚡⚡⚡⚡
CT chest abdomen pelvis without IV contrast	Usually Not Appropriate	⚡⚡⚡⚡
CT chest abdomen pelvis without and with IV contrast	Usually Not Appropriate	⚡⚡⚡⚡
MRI abdomen and pelvis without IV contrast	Usually Not Appropriate	0
TRUS guided biopsy prostate	Usually Not Appropriate	0
TRUS prostate	Usually Not Appropriate	0
X-ray skeletal survey	Usually Not Appropriate	⚡⚡⚡

FDG = fluorine-18-2-fluoro-2-deoxy-D-glucose; IV = intravenous; TRUS = transrectal ultrasound.

**Table 1.** Appropriateness category names and definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

**Table 2.** Relative radiation level designations

RRL	Adult Effective Dose Estimate Range (mSv)	Pediatric Effective Dose Estimate Range (mSv)
0	0	0
⊕	<0.1	<0.03
⊕⊕	0.1-1	0.03-0.3
⊕⊕⊕	1-10	0.3-3
⊕⊕⊕⊕	10-30	3-10
⊕⊕⊕⊕⊕	30-100	10-30

Note: Relative radiation level (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."

## SUMMARY OF LITERATURE REVIEW

### Introduction/Background

Prostate cancer is primarily managed by four standard methods: radical prostatectomy (RP), radiation therapy (RT), androgen deprivation therapy (ADT), and active surveillance. A detailed discussion of newly evolving focal therapies, such as cryotherapy, high-intensity focused ultrasound (US), MRI-guided biopsy techniques for tissue sampling, are beyond the scope of this review. The treatment choice is based on the tumor stage, histology, and grade and is influenced to a certain extent by the preference of the treating physician and the patient. After treatment, patients are followed at periodic intervals with measurement of serum prostate-specific antigen (PSA) levels. RP and RT, which includes brachytherapy, are considered definitive treatment therapies.

Biochemical recurrence (BCR), also referred to variously as PSA recurrence, PSA failure, or biochemical failure, is the most clinically used end point for identification of treatment failure. A number of clinical nomograms are available to predict BCR, time to metastasis, and prostate cancer-specific mortality [1-3].

Approximately 10% to 53% of patients undergoing primary intended curative therapy will develop BCR, depending on their preoperative risk and stage of cancer [4]. For localized low-risk prostate cancer, the rate of BCR is as low as 9% after RP [2,4]. A first serum total PSA assay is recommended during the first 3 to 12 months after RP or RT. When PSA is detectable following RP, a PSA assay should be repeated 1 to 3 months later to confirm this elevation and to estimate the PSA doubling time (PSADT). In the absence of residual cancer, PSA becomes undetectable by the first month after total prostatectomy (<0.1 ng/mL) [5]. No imaging study is necessary after definitive treatment for clinically localized prostate cancer before BCR unless there are concerns for complications such as fistula or abscess [6].

Although PSA alone does not differentiate local from distant disease recurrence, the patterns of PSA rise after failed primary therapy has been incorporated into clinical nomograms to predict whether recurrence is more likely a local or distal metastatic disease. Patients with late BCR (>24 months after local treatment), low PSA velocity

(change in PSA over time), or prolonged PSADT (>6 months) most likely have recurrent local disease [7]. Conversely, patients with a rapid PSA recurrence (<24 months after local treatment), high PSA velocity, or short PSADT (<6 months) are more likely to have metastatic recurrence [7]. This can serve as a clinical guide in selecting appropriate imaging.

In evaluating patients with recurrent or metastatic prostate cancer, it is important to define the location, size, and extent of local and distant tumors. Use of more conventional imaging studies to document recurrent or metastatic disease using clinical parameters is challenging. Choueiri et al [1] demonstrated that with a PSA of <5 ng/mL and a PSADT of <10 months, both scintigraphic bone scan and CT are very unlikely to detect the recurrence.

The common sites of BCR after failure of definitive management are local recurrence and regional nodal metastasis [8,9]. Although early bone metastases can be seen, bone metastases are relatively uncommon until later in the course of more advanced metastatic spread when PSA values correspondingly tend to also be much higher. MRI can identify isolated local recurrences very early, with PSA levels < 1 ng/mL [10]. Nodal staging is still a significant diagnostic challenge, because CT and MRI have limited accuracy because of dependence on size criteria, which is a poor predictor of prostate cancer nodal metastasis. There are currently two FDA-approved prostate-specific PET agents for prostate cancer recurrence: carbon-11 choline (C-11 choline) and fluorine-18 fluciclovine (F-18 fluciclovine). There is a great deal of data from the United States, Australia, and Europe on the performance of choline PET showing its usefulness for nodal and bone lesion identification, but relatively less on F-18 fluciclovine at this time. Whole-body planar scintigraphic bone scans have historically been frequently performed for detecting skeletal metastases in patients with rising PSA following treatment but are very unlikely to be positive until relatively late in the course of advanced metastatic disease. It was previously thought that a bone scan was quite sensitive, but PET imaging with prostate-specific agents, such as those mentioned above, and more sensitive bone agents like 18-F-sodium fluoride PET have shown detectability of many lesions before a bone scan becomes positive [11]. Because planar bone scans are rarely positive without symptoms or without relatively high PSA levels, the routine use of this study post-treatment is considered unproductive by most investigators [5,12-14] and is not recommended by the

National Comprehensive Cancer Network (NCCN). MRI may be helpful in the diagnosis of bone metastasis when other examinations are conflicting, and it and PET can be used to determine response to hormonal treatment [1].

Multiparametric MRI (MP-MRI) and prostate-specific PET agents have enhanced our understanding of prostate cancer recurrence and spread. A significant proportion of men can be identified with a solitary or small number of sites of disease recurrence when imaged early in the course of BCR, rather than waiting until disease has extensively progressed to the point that conventional CT or planar bone scan become positive [15,16]. Limited sites of recurrence are often referred to as oligometastatic disease, and identification of these early, limited recurrences offers the opportunity for targeted salvage treatments rather than limiting men to palliative systemic therapy. Also, largely driven by PET, we are now discovering the existence of a surprising number of men with solitary or oligometastatic disease in previously unexpected remote locations such as a left subclavian node, rather than disease spreading in a predictable stepwise fashion in and then out of the pelvis [9,17].

It is notable that prostate cancer is the second leading cause of cancer mortality among American men. The majority of these men are not dying because of initial presentation of high-stage incurable disease. Most of the men who die from prostate cancer had originally presented with disease that was thought to be clinically localized, underwent definitive primary management with curative intent, experienced treatment failure with BCR, and then their recurrent disease progressed while on nontargeted systemic therapy to become fatal. Recent imaging advances that allow identification of limited metastatic disease early in BCR rather than once the disease has become systemically advanced may hopefully lead to targeted treatments that will impact patient outcomes.

Finally, it is important to recognize that the clinical scenarios here still represent broad ranges of risk for recurrence or metastases. For example, in [Variant 1](#), clinically appropriate imaging may be different for a man with initially detected BCR and a PSA < 1 ng/mL, versus a PSA > 40 ng/mL, or for a man with persistently detectable PSA after surgery. We chose to avoid challenging subcategorizations of many individual patient scenarios encountered in clinical practice, such as by specific PSA ranges or PSA kinetics, or other clinical parameters. It is important to note that in general the

yield of the various imaging studies can be related to these additional specific clinical risk parameters.

## DISCUSSION OF PROCEDURES BY VARIANT

### **Variant 1: Prostate cancer follow-up. Status post radical prostatectomy. Clinical concern for residual or recurrent disease**

Following RP, PSA levels are expected to be undetectable within several weeks of surgery. Waiting 6 to 8 weeks after treatment is advisable before assessing the serum PSA value, because the half-life of serum PSA is relatively long. In the presence of residual cancer, PSA either does not become undetectable or increases after an initial undetectable period. A consensus has been reached to define BCR as PSA  $\geq 0.2$  ng/mL confirmed on two successive assays. According to the Clinical Practice Guidelines in Oncology for prostate cancer developed by the NCCN [5], patients whose PSA fails to fall to undetectable levels or whose detectable PSA increases on two subsequent measurements should undergo a prompt search for the presence of local residual or recurrent disease or distant metastatic disease, each requiring different forms of therapy. If distant metastases are detected, ADT is typically initiated. However, solitary or oligometastatic disease identification offers the option of targeted therapies rather than or in addition to systemic therapies.

**Bone Scan.** A planar radionuclide bone scan has traditionally been the first examination obtained, and the assumption was that if the bone scan is positive for metastatic disease, no further imaging studies are necessary. However, if it is inconclusive, further imaging studies are performed, including MRI or CT. However, the level of post-treatment PSA that should prompt a bone scan is much higher than what is typically followed in many practices. Kane et al [18] reported that most patients with a positive bone scan had a very high PSA level (mean of 61.3 ng/mL) and a high PSA velocity ( $>0.5$  ng/mL per month). In a study of patients with biochemical failure following RP, the probability of a positive bone scan was  $<5\%$  even with high PSA levels between 40 and 45 ng/mL [19]. In another study, bone scan use was very limited until PSA rose above 30 to 40 ng/mL [19]. According to the American Urological Association's Prostate-Specific Antigen Best Practice Statement, the routine use of bone scans in the setting of a PSA rise is not justified; this is particularly true in patients with a PSADT of  $>6$  months and a PSA value of  $<10$  ng/mL [20]. Similarly, the American Society for Radiation Oncology (ASTRO)/American

Urological Association (AUA) guidelines note that because most men present with BCR with a PSA  $< 1$ , the potential yield of bone scan for evaluation of BCR would be low [21]. More advanced techniques, such as single-photon emission tomography/CT imaging with methylene diphosphate and the newer 18-F-sodium fluoride PET, show improved performance over conventional planar bone scan [22,23].

**CT.** CT is not effective for detecting recurrent tumor in the surgical bed. The mean PSA value associated with a positive CT scan after RP was 27.4 ng/mL, and this typically represents very large recurrent masses ( $>2$  cm in size) [7]. In the evaluation of nodal disease, CT relies on size to detect nodal metastases, which is a significant limitation and confers poor sensitivity for prostate cancer nodal metastases because large numbers of metastatic nodes are known to be normal size [24]. CT is useful in following response of known enlarged metastatic lymphadenopathy to treatment. CT is useful in detecting sclerotic bone and visceral metastases, although bone scan and MRI are superior in both the diagnosis and follow-up of bone metastases [25] and choline PET is much better for detection and follow-up of bone metastases. As bone metastases respond to treatment, they often become more densely sclerotic, which by CT is a common pitfall that can lead to false interpretation as disease progression. CT is most appropriately done with intravenous (IV) contrast for cancer detection and surveillance. There is no evidence to support use of CT without IV contrast or multiphasic scanning (ie, without and with IV contrast). Additionally, there is rarely any indication for consideration of extension of coverage with CT of the chest under Variant 1.

**MRI.** Local recurrence seems to be the most common site of initial disease recurrence, and MP-MRI is the most accurate imaging method for identifying sites of local recurrence after RP [6,26-30]. It is worth noting that unlike with the Prostate Imaging Reporting and Data System applied to pretreatment imaging, there are no consensus technical standard or interpretation criteria for MRI in the BCR setting. In general, 3.0 T performs better than 1.5 T, and endorectal coil use can offer an improved signal-to-noise ratio and resolution to aid detecting small early recurrences compared with surface coils. Recurrences can be accurately identified very early in BCR, at the time of initial laboratory diagnosis of BCR when the PSA is still well under 1 ng/mL [10]. Although most local recurrences are perianastomotic,



retrovesical, or in the seminal vesicle bed, 30% may be elsewhere in the pelvis at sites that can be more readily assessed by MRI than by US [30]. MP-MRI studies for detecting local recurrence after prostatectomy have reported 84% to 100% sensitivity and 89% to 97% specificity [6,10,31]. Typically in this setting, MRI of the pelvis only is performed, at least initially. Residual, recurrent, or metastatic diseases are all most likely to be identified in the pelvis, and additional coverage of the abdomen is of little added value.

The accuracy of MRI for staging pelvic lymph nodes is largely reliant on size criteria and is only minimally better than that of CT. MRI following IV administration of lymphotropic superparamagnetic iron oxide nanoparticles (sometimes referred to as MR lymphography) has been reported to greatly improve detection of positive lymph nodal metastases from prostate cancer when compared with unenhanced MRI [32] and also to F-18 choline PET in a limited comparison [24]. This MRI lymphographic contrast agent is not FDA approved, and this technique remains investigational. However, these studies demonstrate the preponderance of prostate cancer nodal metastases that are very small and falsely negative when our evaluation is limited to size criteria such as with CT and conventional MRI. For example, Fortuin et al [24] found that the mean size of prostate cancer metastatic nodes was <5 mm.

MRI is more sensitive and specific in the diagnosis of bone metastases, with much better spatial and contrast resolution when compared with scintigraphic bone scan [33,34]. Gutzeit et al [35] reported the use of whole-body diffusion-weighted imaging (DWI)-MRI in 36 patients with 45 skeletal metastases from breast cancer and prostate cancer and concluded that markedly more metastases could be discovered using the whole-body DWI technique than skeletal scintigraphy. Response of bone metastases to treatment can be more accurately monitored by serial MRI scans [36]. MRI has similar performance in bone metastasis detection as C-11 choline PET [8].

Overall, pelvic MRI in the setting of **Variant 1** is complementary to specialized PET examinations (C-11 choline or F-18 fluciclovine), and both categories of examinations may be appropriate to perform.

**MRI Functional and Multiparametric.** Traditional T1- and T2-weighted MRI sequences can be supplemented with functional techniques: dynamic contrast-enhanced MRI (DCE-MRI) imaging, DWI-MRI, and magnetic resonance spectroscopic imaging (MRSI). When two of these are added, typically DCE-MRI and DWI-MRI, the

term MP-MRI is often applied. These will be briefly discussed, but detailed treatment is beyond the scope of this document. In summary, all three have shown some evidence of incremental value when added to anatomic imaging (T2-weighted), and there is evidence that use of more than one functional technique can also be additive and complementary. Among the three, DCE-MRI has the strongest evidence and has consistently shown the greatest use in the setting of BRC evaluation.

**DCE-MRI.** DCE-MRI has been shown to be the most important sequence for evaluation of BCR after RP [37]. Wu et al [38] in a meta-analysis to assess the effectiveness of MRI in detecting local recurrent prostate cancer after RP found that DCE-MRI, compared with T2-weighted imaging, showed higher pooled sensitivity (85%) and specificity (95%). Roy et al [37] evaluated the performance of the three types of functional MRI techniques in the detection of local prostate cancer recurrence after RP and concluded DCE-MRI to be the most efficient tool to detect prostate cancer recurrence post-RP. Similarly, Casciani et al [28] and Cirillo et al [6] showed that DCE-MRI had significantly higher sensitivity and accuracy than T2-weighted imaging alone in detecting local recurrences after RP.

**DWI-MRI.** DWI-MRI can be helpful for local recurrence depiction, but DWI is typically lower resolution and more often adversely affected by postoperative changes and surgical clip artifact than DCE, making it less reliable for local recurrence. A combination of these functional sequences can be more accurate to evaluate for recurrence in the postprostatectomy bed [31]. DWI is helpful for detection of nodal and bone metastases and can be performed as a whole-body screening examination.

**MRSI.** MRSI added to T2-weighted by endorectal coil MRI can help detect local tumor recurrence after prostatectomy [29]. Compared with DWI or DCE, MRSI is a more complex functional technique and requires additional expertise and longer acquisition times and is much less commonly used in most practices. Sciarra et al [29] reported the use of DCE-MRI and MRSI in patients with biochemical failure after prostatectomy and concluded that the combination of techniques was superior for detecting local recurrence.

**TRUS-Guided Biopsy.** Transrectal US (TRUS)-guided biopsy can be performed in a systematic manner, often done as random sampling of the areas that most likely harbor recurrence: the vesicourethral anastomosis, retrovesical region, and seminal vesicle beds. Negative results

of TRUS-guided biopsy, regardless of a palpable mass or indurations, may be inconclusive because of sampling errors. Deliveliotis et al [39] reported negative predictive values of only 67% with TRUS-guided biopsy, and 57% with digital rectal examination (DRE)-guided biopsy in patients with PSA > 2 ng/mL and negative imaging for metastases after prostatectomy. The yield for detecting local recurrent tumor with TRUS with needle biopsy rises significantly with serum PSA levels [39]. Only about 25% of men with prostatectomy PSA levels of <1 ng/mL have histologic confirmation of local recurrence after systematic biopsy of the prostatic fossa, compared with 53% of men with prostatectomy PSA levels > 2 ng/mL [39].

**MRI-Targeted Biopsy.** Similar to the greatly increased yields of targeted biopsy informed by targets identified on MRI in initial prostate cancer detection, biopsy in the setting of BCR is much more likely to identify a local recurrence when done targeting a suspicious lesion identified by MRI rather than systematic biopsy of the operative bed. In this setting, it is the prostatectomy bed rather than the prostate itself. Because there is no commercial targeting application available in the post-prostatectomy setting (there is no gland to segment), these targeted biopsies must be done with cognitive fusion or in-bore targeting, and operator skill and experience are important as reflected by the progressively higher yields with repeat biopsy and increased biopsy yield with increasing size of the target lesion identified by MRI [10]. For this document, it is assumed the procedure is performed and interpreted by an expert. Candidacy for salvage local therapy is largely determined by identification and characterization of a treatable local recurrence by biopsy.

**TRUS.** Several studies have shown the usefulness of color and power Doppler and contrast-enhanced color Doppler in detecting local recurrence after prostatectomy [40-42]. Drudi et al [40] showed contrast-enhanced color Doppler TRUS performed as well as contrast-enhanced MRI in detecting local recurrence after prostatectomy; however, intravascular microbubble contrast agents are not FDA approved for this application.

**C-11 Choline PET.** PET with newer prostate-specific radiotracers has shown excellent performance and great potential for revolutionizing the diagnosis and subsequent management of men with BCR. C-11 choline was the first to receive FDA approval and is the best studied at this point. Choline PET can also be performed as an F-18

tracer and is often used in other countries, but that tracer is not FDA approved. Choline has been extensively used and studied with several large meta-analyses now available [43,44]. For example, a meta-analysis of 19 high-quality studies comprising 1,555 patients [43] found a sensitivity of 85.6% and specificity of 92.6% for all sites of recurrence, of which there was a pooled sensitivity of 100% for lymph node metastases with a corresponding 81.8% sensitivity. It has been shown not only to perform very well in the setting of BCR, but to have a significant impact on patient management and selection of appropriate treatment compared with conventional imaging modalities [45]. Choline is inferior to MRI for detection of local recurrence with low PSA levels < 2 ng/mL [8], but in meta-analysis still showed 75.4% sensitivity and 82% specificity for prostatic fossa recurrence detection. C-11 choline is the best FDA-approved test for nodal metastases, significantly better than CT and MRI, and is capable of identifying metastatic nodes as small as 5 mm. Bone metastasis detection and treatment response evaluation is also very good [8], superior to bone scan [46]. The performance of choline PET is related to the PSA level and kinetics [47-51], and yield is lower with PSA levels under 1 to 2 ng/mL. An optimal PSA cutoff of 1.1 ng/mL to initiate choline PET investigation was found in one study [52]. C-11 choline requires an on-site cyclotron for generation of the agent because of its 20-minute half-life, which restricts widespread availability. This also makes its use challenging, with the potential to result in degraded performance both in clinical practice and investigations based on logistics.

**F-18 Fluciclovine PET.** F-18 fluciclovine (also known as *anti*-1-amino-3-[18-F]-fluorocyclobutane-1-carboxylic acid, [FACBC]) is a synthetic amino acid PET radiotracer that was FDA approved in May 2016 for the imaging of men with suspected prostate cancer recurrence based on elevated blood PSA levels following prior treatment. Odewole et al [53] reported superiority to 111 indium-capromab pendetide and to CT with detection of nodes as small as 5 mm and upstaging 25.7% of patients. In comparison with CT, fluciclovine PET positivity rate for recurrent disease was 77.4% versus 18.9%, though sensitivity varies with PSA level, doubling times, and original Gleason score [53]. One hundred patients with biochemical failure after RP underwent C-11 choline PET and fluciclovine PET in a single-center trial [54-56]. The investigators reported choline and fluciclovine had overall sensitivities of 32% and 37%, specificities of 40%



and 67%, and positive predictive values of 90% and 97%, respectively, with fluciclovine having lower physiological background, resulting in better lesion contrast, and the practical advantage of a longer half-life enabling more widespread distribution and availability compared with a short half-life C-11 radiotracer. Notably, in this single-center comparison from Italy the C-11 choline dose used was only about one-third of that used for most patients imaged clinically with C-11 choline in the United States, and the performance of both agents reported was much lower than that of many other studies, with meta-analysis of C-11 choline showing a sensitivity of 85.6% and specificity of 92.6% for all sites of recurrence and a meta-analysis of fluciclovine that reported 87% pooled sensitivity and 66% pooled specificity [57], which may be related to patient inclusion criteria. Recently, a multicenter report [58] of 596 patients who underwent fluciclovine PET for recurrent prostate cancer demonstrated an overall patient level detection rate of 67.7%, with 41.4% detection in the lowest PSA quartile (0.79 ng/mL or less), including extraprostatic involvement in approximately 30% of patients.

**PET Using Other Agents.** There are many additional prostate-specific tracers that are not FDA approved, including prostate-specific membrane antigen [59-61], 11C-acetate [62,63], 18F-choline [64-66], bombesin, and 18F-fluorodihydrotestosterone [67-69], that are in various stages of investigation and have been reported to detect local and metastatic recurrent disease in patients with biochemical failure after local treatment. These agents remain investigational, but some have shown excellent results and hold great potential.

**FDG-PET/CT.** Some foci of metastatic prostate cancer demonstrate increased accumulation of fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) radiotracer, though this uptake is generally low compared with the other cancers. In one study, FDG-PET identified local or metastatic disease in only 28 of 91 patients (31%) with BCR after RP for prostate cancer [70]. FDG-PET is relatively insensitive in detecting osseous metastases compared with standard bone scintigraphy [71]. Ghanem et al [72] have demonstrated that FDG-PET alone, or using PET/CT image fusion, is less sensitive than MRI in the detection of bone metastases. In the routine setting, FDG-PET has little usefulness in the setting of BCR. However, as advanced metastatic prostate cancer migrates to a high Gleason grade, dedifferentiates, or transforms to other aggressive variants, such as small cell type, the tumor cells are more likely to convert to higher glucose

metabolism and FDG can become useful in detection and monitoring of this subset of patients.

**ProstaScint.** ProstaScint scan, Aytu BioScience, Inc. Englewood, Colorado (111 indium-capromab pendetide) is not routinely used in the evaluation of prostate cancer recurrence. It is a murine monoclonal antibody that targets prostate-specific membrane antigen. Early studies involving ProstaScint imaging reported sensitivity of 49% to 94% and specificity of 65% to 72% in the detection of metastases and local recurrence [73,74]. Others have demonstrated no benefit with the use of capromab pendetide in selection of patients for local salvage therapy [75,76]. The scans remain challenging to interpret. Studies have concluded that in selecting patients for salvage RT for rising PSA after RP for prostate cancer, use of ProstaScint examination provided no incremental value in appropriately selecting patients when compared with basic clinicopathologic factors alone [77,78].

**Radiography.** Radiographic survey is not routinely used in the evaluation of prostate cancer recurrence.

### Variant 2: Prostate cancer follow-up. Clinical concern for residual or recurrent disease after nonsurgical local and pelvic treatments

This variant covers evaluation of BCR in the setting of a broad range of failed treatments targeted locally or to the pelvis, other than RP that is specifically covered in [Variant 1](#). This includes primary radiation therapies, ablation therapies, and secondarily failed salvage therapies such as failed salvage RT done after RP.

Prostate cancer treated primarily with RT, whether by external beam radiation therapy (EBRT) or brachytherapy, is monitored differently because the prostate and the lymph nodes are not resected. Following RT, the serum PSA level decreases in the majority of patients during the first year but may not reach a nadir until 18 to 30 months after treatment. Surveillance for tumor recurrence in patients' post-RT should include a DRE and serial serum PSA levels. The prostate gland becomes atrophic and fibrotic after RT, making the distinction between local recurrent disease and benign irradiated prostatic gland very difficult by DRE alone [79]. ASTRO and the Radiation Therapy Oncology Group® at the 2005 Phoenix Consensus Conference defined biochemical failure following RT as a rise by 2 ng/mL or more above the nadir PSA [80]. Based on the PSA level, biopsy Gleason score, and American Joint Commission on Cancer tumor (T) category, approximately 10% to 70% of men will have evidence of disease recurrence at

10 years following RT with or without concurrent ADT for prostate cancer [81]. The greatest challenge in selecting a man with BCR post-RT for further local therapy is determining whether the rising PSA represents local disease, distant disease, or both. The rate of PSA rise can potentially predict clinical failure patterns similar to post-RP; an early and rapidly rising PSA suggests metastatic recurrence, and a late and slowly or moderately rising PSA suggests local relapse [82], but these clinical factors are not definitive [83]. Isolated local recurrences in the prostate gland can be potentially treated by salvage therapy (surgery, ablation, radiation), and ADT represents the common treatment of choice in the presence of systemic disease [84]. It is worth noting that the literature is less strong for imaging of recurrence postbrachytherapy as compared with EBRT.

Radiation is commonly performed in the setting of BCR after RP. Guidelines were published in 2013 jointly by ASTRO/AUA and largely endorsed by the American Society of Clinical Oncology [21]. There are two distinct clinical scenarios: adjuvant therapy and salvage therapy.

It is known that patients with adverse risk factors found at the time of RP (high Gleason scores or adverse pathology, extracapsular extension or T4 invasion, seminal vesicle invasion, or positive margins) are at increased risk for BCR [85-91]. In this subgroup, there is consideration for adjuvant RT intended to reduce the high likelihood of recurrence and progression of disease, which is commonly performed approximately 4 to 6 months after surgery. There is strong evidence that adjuvant RT in this setting reduces the risk of BCR and clinical progression of cancer, but the evidence is much less clear on the impact on overall survival.

BCR is associated with subsequent progression to metastatic disease and death. In patients that experience BCR after RP, radiation can be given in this setting as a salvage treatment and per ASTRO/AUA should be offered to patients that do not have evidence of metastatic disease.

The use of imaging before radiation treatment is not well defined by the ASTRO/AUA guidelines, and they state that a restaging evaluation in patients with BCR “may be considered.” Overall, their review of the literature in 2013 verified the conclusion of other meta-analyses [26,92], in which MRI proved the best and most uniform performance for detection of local prostate cancer recurrence, and other modalities lacked in either sensitivity, specificity, or both for this task. For nodal evaluation, they found that C-11 choline PET had a sensitivity of 100% across all of the studies

they evaluated (most of those studies analyzed per patient) but with variable specificities, and that MR lymphography with lymphotropic superparamagnetic iron oxide nanoparticles was promising but lacking in evidence. They warn that “clinicians should be aware that the yield of some modalities (eg, bone scan) is extremely low” in patients with lower PSA values and noted that C-11 choline PET was superior to bone scan [46]. Those statements mirror the current findings of [Variant 1](#). Importantly, they recognize the potential for advanced imaging with MRI and PET with newer agents to greatly change and impact the care of men with BCR, and call for further research in imaging.

Regarding imaging after failure of adjuvant or salvage therapy, the literature is less rigorous. However, there are some concepts that warrant recognition. The radiation port is designed to spare toxicity to the rectum, and, after failed whole-pelvis RT, the mesorectal and presacral regions that saw much lower radiation dose are a particular area where recurrences are often identified and warrant scrutiny [9]. Additionally, the nodal and bone metastases that are identified in this setting are often in the high pelvis near the level of the common iliac vasculature, at a level just cranial to the top of the radiation treatment port. Fortuin et al [24] noted in their study that 61% of metastatic prostate cancer nodes (in the setting of BCR, before salvage RT) were located in areas outside the conventional pelvic radiation target volume, which may explain the preponderance of nodes that later present after failure of salvage RT above the treated area. Local recurrence can also be seen after failed primary treatment and subsequent failed adjuvant or salvage RT, but is much less common than in [Variant 1](#).

Local ablative therapies are much less common than RP and primary RT options and make up <5% of primary treatments overall in the United States, but there is great variation in practice, and in some centers, cryoablation is the dominant treatment comprising >70% of patients [93]. Although less well studied, recurrence after ablative therapies seems to be most common locally if disease was localized initially.

**Bone Scan.** As with [Variant 1](#), a radionuclide bone scan has traditionally been the first examination obtained. However, the performance of bone scan post-primary RT is similar to after RP, typically failing to be useful until PSA levels are >20 ng/mL and possibly as high as 60 ng/mL [3,18]. The NCCN guidelines recommend against the routine use of bone scan and state that bone scan “can be considered for the evaluation of patients

with rising PSA or positive DRE after RT if the patient is a candidate for additional local therapy” [5]. Candidacy for salvage local therapy is largely determined by identification and characterization of a treatable local recurrence by biopsy, often targeted by MRI. Similarly, ASTRO/AUA guidelines note that because most men present with BCR with a PSA < 1, the potential yield of bone scan for evaluation of BCR would be low [21] and it is not routinely recommended, although that assessment is for presalvage RT, not specifically for imaging post-failed adjuvant or salvage RT. The use of bone scan for BCR after ablative primary therapy lacks specific data, but performance is likely similar in this setting.

**CT.** CT is not effective for detecting locally recurrent tumor in an irradiated prostate gland or after ablative therapy. As with [Variant 1](#), in the evaluation of nodal disease, CT relies on size to detect nodal metastases, which is a significant limitation and confers mediocre sensitivity for prostate cancer nodal metastases because large numbers of metastatic nodes are known to be a normal size [24]. CT is useful in following response of known enlarged metastatic lymphadenopathy to treatment. CT is useful in detecting sclerotic bone and visceral metastases, although bone scan and MRI are superior in the diagnosis and follow-up of bone metastases [25], and choline PET is much better for detection and follow-up of bone metastases. As bone metastases respond to treatment, they often become more densely sclerotic, which by CT is a common pitfall falsely interpreted as progression. CT is most appropriately done with IV contrast for cancer detection and surveillance. There is no evidence to support use of CT without IV contrast or multiphasic scanning (ie, without and with IV contrast). Additionally, there is rarely any indication for consideration of extension of coverage with CT of the chest under [Variant 2](#).

**MRI.** MP-MRI has shown to be helpful in detection of local recurrence after RT, and T2-weighted imaging by itself is very limited for detection of recurrence after RT [29]. Wu et al [38] in a meta-analysis to assess the effectiveness of a MP-MRI in detecting local recurrent prostate cancer post-RT found that DCE imaging, compared with T2-weighted imaging, showed higher pooled sensitivity (90%) and specificity (81%). DCE combined with MRSI had the highest pooled sensitivity and specificity (90%) [38]. Roy et al [37] evaluated the sensitivity of the three types of functional MRI techniques in the detection of local prostate cancer

recurrence after EBRT and found the combination of DCE-MRI and DWI to be highly accurate in detecting recurrence after RT; and although DCE showed very high accuracy for local recurrence detection similar to the post-RP setting, DWI showed greater usefulness post-RT than in the post-RP setting because of decreased distortion, given the absence of surgical clips. Other studies have also suggested that a combination of functional MR techniques [94], including MRSI [95-97], DCE-MRI [98-100], and DWI [99,101], be used to improve the detection of recurrent prostate cancer after RT. Furthermore, Pucar et al [102] found that clinically significant local recurrence after RT often occurs at the site of the primary tumor and suggested that monitoring the primary tumor with MRI prior to and after RT might lead to early detection of local recurrence amenable to salvage therapy. The propensity for local recurrence related to the primary site is likely also true for failure of ablation techniques. Local recurrence is less common after salvage RT, but does occur. Because local recurrence is where MRI is clearly the best-performing examination, its use in the failed salvage RT clinical setting is somewhat decreased from that of [Variant 1](#) and after local therapies.

As with [Variant 1](#), typically in this setting, MRI is performed of the pelvis only, at least initially. Residual, recurrent, or metastatic disease is all most likely to be identified in the pelvis, and additional coverage of the abdomen is of little added value.

MRI following IV administration of lymphotropic superparamagnetic iron oxide nanoparticles has been reported to improve detection of positive lymph nodal metastases from prostate cancer when compared with unenhanced MRI [32]. This MRI contrast agent, however, is not FDA approved.

Overall, pelvic MRI in the setting of [Variant 2](#) is complementary to specialized PET examinations (C-11 choline or F-18 fluciclovine), and both categories of examinations may be appropriate to perform.

**TRUS.** Several studies have reported that TRUS is unreliable for the detection of cancer recurrence after EBRT, showing limited sensitivity of 49% and specificity of 57%, which is worse than DRE (sensitivity 73%, specificity 66%) [79,103].

**TRUS-Guided Biopsy.** TRUS-guided sextant biopsy, commonly proposed as the reference standard for detection of local recurrence, may require repeated biopsies to reach a final diagnosis [104,105]. In addition to false-negative results due to sampling error, false-positive

results may also occur because the presence of malignant cells in biopsy specimens may represent biologically inactive tumor remnants, especially in the first 1 to 2 years after RT [104,105].

**MRI-Targeted Biopsy.** As with [Variant 1](#), biopsy is best done when targeting suspicious lesions identified by MRI, rather than as nontargeted systematic TRUS biopsy of the region. However, because the native gland is still present, commercially available MRI-US fusion biopsy systems can be used to aid in targeting and improving biopsy accuracy. Candidacy for salvage local therapy is largely determined by identification and characterization of a treatable local recurrence by biopsy, often targeted by MRI.

**C-11 Choline PET.** As with [Variant 1](#), PET with newer prostate-specific radiotracers has shown excellent performance and great potential for revolutionizing the diagnosis and consequently management of men with BCR. C-11 choline was the first to receive FDA approval and has been extensively used and studied with several large recent meta-analysis available [43,44]. For example, a meta-analysis by Evangelista et al [43] found a sensitivity of 85.6% and specificity of 92.6% for all sites of recurrence, of which there was a pooled sensitivity of 100% for lymph node metastases with a corresponding 81.8% sensitivity. Note this study combines post-RP and post-RT patients, and there is no evidence of a significant difference in performance of C-11 choline PET between these two scenarios. It is inferior to MRI for detection of local recurrence, but in meta-analysis it still showed 75.4% sensitivity and 82% specificity for prostatic fossa recurrence detection. In a recent study of 184 primary RT patients who experienced BCR, and over half of whom had positive confirmatory biopsies of the prostate or distant sites, the median PSA level of those patients having a positive C-11 choline PET scan was 6.3 ng/mL with a sensitivity and specificity of 95% and 73%, respectively [106]. In another recent study of 41 patients who underwent salvage RT to the prostate bed only following RP and subsequent biochemical failure, C-11 choline PET scans were positive with median PSA of 3.1 ng/mL and interquartile range of 1.9 to 5.6 ng/mL. The vast majority of patients had disease that was found outside of the irradiated prostate bed with 61% having disease outside of the pelvis [106,107]. Bone metastasis detection and treatment response evaluation is also very good. C-11 choline requires an on-site cyclotron for generation of the

agent due to the short half-life, which restricts where it is feasible to perform.

**F-18 Fluciclovine PET.** F-18 fluciclovine (also referred to as a FACBC) was FDA approved in May 2016 for the imaging of men with suspected prostate cancer recurrence based on elevated blood PSA levels following prior treatment. A meta-analysis of 6 studies totaling 251 patients imaged with fluciclovine [57] included one study that partially included patients' post-nonsurgical treatment for a total of 14 patients. This small study reported no performance characteristics of the examination in this subgroup [108]. A subsequent multicenter report of 596 patients imaged with fluciclovine for BCR included 4 patients who had undergone primary radiation and 96 patients who had RT plus some additional treatment, but these subgroups were not separately analyzed [58].

**PET Using Other Agents.** There are many additional prostate-specific tracers that are not FDA approved, including 11C-acetate [62,63], 18F-choline [64-66], bombesin, 18F-fluorodihydrotestosterone [69], and a family of related PMSA tracers [67,68] that are in various stages of investigation and have been reported to detect local and metastatic recurrent disease in patients with biochemical failure after local treatment. These agents remain investigational, but some have shown excellent results and hold great potential.

**FDG-PET/CT.** As with [Variant 1](#), in the routine setting, FDG-PET has little usefulness. However, as advanced prostate cancer migrates to high grade or dedifferentiates, the tumor cells are more likely to convert to glucose metabolism, and as the tumor's metabolism transforms, FDG can become useful in the detection and monitoring of this subset of patients that often coincides with C-11 choline activity diminishing.

**ProstaScint.** As with [Variant 1](#), ProstaScint shows limited performance and is challenging to interpret. It is unlikely to provide benefit and is not routinely used in the evaluation of prostate cancer recurrence [75-78].

**Radiography.** Radiographic survey is not routinely used in the evaluation of prostate cancer recurrence.

**Variant 3: Metastatic prostate cancer treated by systemic therapy (androgen deprivation therapy [ADT], chemotherapy, immunotherapy).** Follow-up Various terms have been used to describe prostate cancer that relapses after initial hormonal ablation therapy



including castration-resistant prostate cancer (CRPC), androgen-independent cancers, and hormone-independent cancers. ADT using bilateral orchiectomy (surgical castration) or luteinizing hormone-releasing hormone agonist (medical castration) may control prostate cancer for long periods by decreasing the size of the tumor, thus relieving pain and other symptoms in patients with advanced disease. ADT may be added to definitive therapy in patients with early-stage disease as adjuvant therapy (after definitive therapy) or neoadjuvant therapy (prior to definitive therapy). ADT may have a direct suppressive effect on serum PSA levels that is independent of tumor activity. PSA production is under hormonal control, and ADT reduces the cell's ability to produce and secrete PSA. Therefore, serum PSA is not always a reliable marker of disease status in these patients. In patients with rising PSA or clinical signs of progression, serum testosterone is evaluated to confirm a castrate-resistant state.

After an initial favorable response to ADT, a significant fraction of men with advanced prostate cancer will develop CRPC with a median time to androgen independence of 14 to 30 months [109]. Patients invariably progress to a castration-resistant state where the cancer will grow despite low levels of serum testosterone [110]. More than 90% of patients with CRPC have bone metastases [111].

Morbidity and mortality from prostate cancer is typically the result of metastatic CRPC. CRPC represents the lethal form of the disease and carries a poor prognosis with a median survival of <2 years for those with metastatic disease [112]. In this setting, imaging is not done for detection or diagnosis of disease, but the role shifts to one of monitoring response to therapy.

**Bone Scan.** Bone metastases are common in late-stage metastatic prostate cancer, particularly CRPC. Bone scan in this setting with PSA >60 ng/mL is greatly increased in yield compared to Variants 1 and 2. Bone scan can reflect changes in disease status post-treatment, and successfully treated metastases can become negative, which usually is accompanied by a corresponding marked decrease in serum PSA level. Bone scan can show a flare phenomenon after treatment initiation that could lead to false interpretation as progression [113]. Bone scan and CT are often performed as complementary modalities, with the pair serving as an alternative to specialized PET examinations (C-11 choline or F-18 fluciclovine).

**CT.** With advanced disease, nodal metastases progress in size and become diagnosable by CT. In this setting, CT is

useful in following response of known enlarged metastatic lymphadenopathy to treatment. CT is useful in detecting visceral metastases; liver metastases in particular are the most common visceral metastasis, and CT is very accurate for that evaluation [114]. CT is also useful in detecting sclerotic bone metastases, although bone scan and MRI are superior in the diagnosis and follow-up of bone metastases [25], and choline PET is much better for detection and follow-up of bone metastases. As bone metastases respond to treatment, they often become more densely sclerotic, which by CT is a common pitfall falsely interpreted as progression. CT is most appropriately done with IV contrast for cancer detection and surveillance. There is no evidence to support use of CT without IV contrast or multiphasic scanning (ie, without and with IV contrast). As opposed to Variants 1 and 2 in the setting of metastatic disease, chest CT becomes clinically relevant and is the best modality for detection of pulmonary metastases. Bone scan and CT are often performed as complementary modalities, with the pair serving as an alternative to specialized PET examinations (C-11 choline or F-18 fluciclovine).

**MRI.** Local recurrence, even if present, becomes of lesser clinical importance in this setting, unless it is locally advanced and is causing urinary or bowel complications. MRI is capable of assessing response to metastatic nodal disease similar to CT based on size, with the addition of also being able to show functional changes. Post-ADT perfusion should greatly decrease with a positive response, and ADC values typically increase. Bone metastases can be followed for response by MRI as well in a similar way.

In this clinical setting, the likelihood of metastatic disease outside the pelvis is increased. For example, liver metastases and nodal metastases in higher stations are most often seen in the setting of Variant 3, whereas they are rare in Variants 1 and 2. It is probable that coverage of the abdomen in addition to the pelvis would provide more benefit in Variant 3, but evidence is lacking.

**C-11 Choline PET.** Although choline PET has been extensively used and studied, with several large meta-analyses available [43,44], the literature is less rigorous for this specific application. There are multiple studies showing its utility in this application [115-118], with no evidence that choline PET has any detriment in performance compared to Variants 1 and 2, and given that metastatic disease outside the pelvis is increased in frequency in this setting and that choline PET activity



correlates well with disease activity, it likely is of increased utility for monitoring response to treatment, although there are insufficient data. There is some evidence that ADT decreases choline uptake in lesions that are not CRPC, and that it is able to predict treatment response to various agents in the setting of CRPC. C-11 choline requires an on-site cyclotron for generation of the agent because of its short half-life, which restricts where it is feasible to perform.

**PET Using Other Agents.** 18-F fluciclovine is newly FDA approved (May 2016), but no formal human trials have been reported and there are only in vitro studies and anecdotal experience suggesting potential utility with CRPC [119,120]. There are many additional prostate-specific tracers that are not FDA approved, including 11C-acetate [62,63], 18F-choline [64-66], bombesin, 18F-fluorodihydrotestosterone [69], and a family of related PMSA tracers [67,68] that are in various stages of investigation and have been reported to detect local and metastatic recurrent disease in patients with biochemical failure after local treatment. These agents remain investigational, but some have shown excellent results and hold great potential.

**FDG-PET/CT.** As with [Variant 1](#), FDG is an inferior tracer to choline and other prostate-specific agents [70,71,121-123] and has limited use in standard practice. However, as advanced metastatic prostate cancer migrates to a high Gleason grade, dedifferentiates, or transforms to other aggressive variants, such as small cell type, the tumor cells are more likely to convert to higher glucose metabolism, and FDG can become useful in the detection and monitoring of this subset of patients, although the literature data are limited [124-126].

**ProstaScint.** As with [Variant 1](#), ProstaScint shows very limited performance and is challenging to interpret. It is unlikely to provide benefit and is not routinely used in the evaluation of prostate cancer recurrence [75-78].

**Radiography.** Radiographic survey is not routinely used in the evaluation of prostate cancer recurrence.

**TRUS.** TRUS is unreliable for the detection of cancer recurrence or progression and is not routinely used for this clinical setting.

**TRUS-Guided Biopsy.** TRUS-guided biopsy is not routinely used in this clinical setting. It is rarely used for detection of recurrence or for evidence of grade migration; however, targeted biopsy is much better for the task.

## SUMMARY OF RECOMMENDATIONS

- For follow-up of a patient with a clinical concern for residual or recurrent disease, status post RP, imaging with MRI of the pelvis without and with IV contrast and PET with specialized agents (C-11 choline PET/CT skull base to mid thigh or F-18 fluciclovine PET/CT skull base to mid thigh) are usually appropriate and are complementary modalities.
- For follow-up of a patient with a clinical concern for residual or recurrent disease after nonsurgical local and pelvic treatments, imaging with MRI of the pelvis without and with IV contrast and PET with specialized agents (C-11 choline PET/CT skull base to mid thigh or F-18 fluciclovine PET/CT skull base to mid thigh) are usually appropriate and are complementary modalities. Biopsy proof of recurrence is standard practice and can be performed as TRUS-guided biopsy or MRI-targeted biopsy of a lesion identified by a diagnostic MRI.
- For follow-up of a patient treated by systemic therapy, imaging with CT abdomen and pelvis with IV contrast and Tc-99m bone scan whole body are usually appropriate and are complementary. Alternatively, PET with specialized agents (C-11 choline PET/CT skull base to mid thigh or F-18 fluciclovine PET/CT skull base to mid thigh) are usually appropriate and can be performed in place of CT and bone scan.

## SUMMARY OF EVIDENCE

Of the 127 references cited in the *ACR Appropriateness Criteria® Post-treatment Follow-up of Prostate Cancer* document, 17 are categorized as therapeutic references including 2 well-designed studies and 8 good-quality studies. Additionally, 103 references are categorized as diagnostic references including 5 well-designed studies, 17 good-quality studies, and 55 quality studies that may have design limitations. There are 33 references that may not be useful as primary evidence. There are 7 references that are meta-analysis studies.

The 127 references cited in the *ACR Appropriateness Criteria® Post-treatment Follow-up of Prostate Cancer* document were published from 1991 to 2017.

Although there are references that report on studies with design limitations, 32 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 2). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document [127].

## 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).

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