

**American College of Radiology  
ACR Appropriateness Criteria®  
Post-Treatment Follow-up of Prostate Cancer**

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

Procedure	Appropriateness Category	Relative Radiation Level
MRI pelvis without and with IV contrast	Usually Appropriate	○
Choline PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼
Fluciclovine PET/MRI skull base to mid-thigh	Usually Appropriate	☼☼☼
PSMA PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
DCFPyL PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
Fluciclovine PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
MRI-targeted biopsy prostatectomy bed	May Be Appropriate	○
TRUS-guided biopsy prostatectomy bed	May Be Appropriate	○
MRI abdomen and pelvis without and with IV contrast	May Be Appropriate	○
MRI pelvis without IV contrast	May Be Appropriate	○
Bone scan whole body	May Be Appropriate	☼☼☼
Choline PET/MRI skull base to mid-thigh	May Be Appropriate (Disagreement)	☼☼☼
CT abdomen and pelvis with IV contrast	May Be Appropriate	☼☼☼
Fluoride PET/CT skull base to mid-thigh	May Be Appropriate (Disagreement)	☼☼☼☼
TRUS prostatectomy bed	Usually Not Appropriate	○
Radiography skeletal survey	Usually Not Appropriate	☼☼☼
MRI abdomen and pelvis without IV contrast	Usually Not Appropriate	○
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 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	☼☼☼☼
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☼☼☼☼

**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
MRI pelvis without and with IV contrast	Usually Appropriate	○
Choline PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼
Fluciclovine PET/MRI skull base to mid-thigh	Usually Appropriate	☼☼☼
PSMA PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
DCFPyL PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
Fluciclovine PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
MRI-targeted biopsy prostate	May Be Appropriate	○
TRUS-guided biopsy prostate	May Be Appropriate	○
MRI abdomen and pelvis without and with IV contrast	May Be Appropriate	○
MRI pelvis without IV contrast	May Be Appropriate	○
Bone scan whole body	May Be Appropriate	☼☼☼
Choline PET/MRI skull base to mid-thigh	May Be Appropriate (Disagreement)	☼☼☼
CT abdomen and pelvis with IV contrast	May Be Appropriate	☼☼☼
Fluoride PET/CT skull base to mid-thigh	May Be Appropriate (Disagreement)	☼☼☼☼
TRUS prostate	Usually Not Appropriate	○
Radiography skeletal survey	Usually Not Appropriate	☼☼☼
MRI abdomen and pelvis without IV contrast	Usually Not Appropriate	○
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 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	☼☼☼☼
FDG-PET/CT skull base to mid-thigh	Usually Not Appropriate	☼☼☼☼

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

Procedure	Appropriateness Category	Relative Radiation Level
Bone scan whole body	Usually Appropriate	☼☼☼
Choline PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼
Choline PET/MRI skull base to mid-thigh	Usually Appropriate	☼☼☼
CT abdomen and pelvis with IV contrast	Usually Appropriate	☼☼☼
Fluciclovine PET/MRI skull base to mid-thigh	Usually Appropriate	☼☼☼
PSMA PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
CT chest abdomen pelvis with IV contrast	Usually Appropriate	☼☼☼☼
DCFPyL PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
Fluciclovine PET/CT skull base to mid-thigh	Usually Appropriate	☼☼☼☼
MRI abdomen and pelvis without and with IV contrast	May Be Appropriate	○
MRI abdomen and pelvis without IV contrast	May Be Appropriate (Disagreement)	○
MRI pelvis without and with IV contrast	May Be Appropriate	○
CT abdomen and pelvis without IV contrast	May Be Appropriate	☼☼☼
CT chest abdomen pelvis without IV contrast	May Be Appropriate	☼☼☼☼
FDG-PET/CT skull base to mid-thigh	May Be Appropriate	☼☼☼☼
Fluoride PET/CT skull base to mid-thigh	May Be Appropriate (Disagreement)	☼☼☼☼
MRI-targeted biopsy prostatectomy bed	Usually Not Appropriate	○
TRUS prostatectomy bed	Usually Not Appropriate	○
TRUS-guided biopsy prostatectomy bed	Usually Not Appropriate	○
Radiography skeletal survey	Usually Not Appropriate	☼☼☼
MRI pelvis without IV contrast	Usually Not Appropriate	○
CT abdomen and pelvis without and with IV contrast	Usually Not Appropriate	☼☼☼☼
CT chest abdomen pelvis without and with IV contrast	Usually Not Appropriate	☼☼☼☼

## POST-TREATMENT FOLLOW-UP OF PROSTATE CANCER

Expert Panel on Urologic Imaging: Baris Turkbey, MD<sup>a</sup>; Aytakin Oto, MD<sup>b</sup>; Brian C. Allen, MD<sup>c</sup>; Oguz Akin, MD<sup>d</sup>; Lauren F. Alexander, MD<sup>e</sup>; Mim Ari, MD<sup>f</sup>; Adam T. Froemming, MD<sup>g</sup>; Pat F. Fulgham, MD<sup>h</sup>; Lori Mankowski Gettle, MD, MBA<sup>i</sup>; Jodi K. Maranchie, MD<sup>j</sup>; Seth A. Rosenthal, MD<sup>k</sup>; Nicola Schieda, MD<sup>l</sup>; David M. Schuster, MD<sup>m</sup>; Aradhana M. Venkatesan, MD<sup>n</sup>; Mark E. Lockhart, MD, MPH.<sup>o</sup>

### **Summary of Literature Review**

#### **Introduction/Background**

Prostate cancer is primarily managed by 4 standard treatment methods: radical prostatectomy (RP), radiation therapy (RT), androgen deprivation therapy (ADT), and active surveillance (AS). A detailed discussion of relatively new focal therapies, such as cryotherapy, high-intensity focused ultrasound (US), and MRI-guided ablative techniques are beyond the scope of this document. 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 the 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 as PSA recurrence, PSA failure, or biochemical failure, is the most clinically used endpoint 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 disease 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 or recurrent 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 a fistula or abscess [6].

Although serum PSA alone does not differentiate local recurrence from distant metastatic disease, the patterns of PSA rise after failed primary therapy have been incorporated into clinical nomograms to predict whether recurrence is more likely local versus distant metastatic disease. Patients with late BCR (>24 months after local treatment), low PSA velocity (change in PSA over time), and/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 the appropriate imaging test to confirm diagnosis.

In evaluating patients with recurrent or metastatic prostate cancer, it is important to define the location, size, and extent of local and/or distant tumors. Use of more conventional imaging studies (eg, bone scan and CT) 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 <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 also be seen, bone metastases are relatively uncommon until later in the course of more advanced metastatic spread when serum PSA values correspondingly tend to also be

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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 the dependence on size criteria, which is a poor predictor of prostate cancer nodal metastasis. There are currently 4 FDA-approved prostate-specific PET agents for prostate cancer recurrence: 1) carbon-11 choline (C-11 choline), 2) F-18 fluciclovine (also known as anti-1-amino-3-[18-F]-fluorocyclobutane-1-carboxylic acid, [FACBC]), 3) Ga-68-prostate-specific membrane antigen (PSMA)-11, and 4) DCFPyL (2-(3-{1-carboxy-5-[(6-[(18F)fluoropyridine-3-carbonyl]-amino]-pentyl}-ureido)-pentanedioic acid). There is a great deal of data for all 4 radiotracers on the performance showing their usefulness for nodal and bone lesion identification. Whole body planar scintigraphic bone scans have historically been frequently performed for detecting skeletal metastases in patients with rising PSA following definitive 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 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 imaging technique at the post-treatment stage is considered ineffective 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 its combined use with PET imaging 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. There is a significant proportion of patients who 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 the disease has extensively progressed to the point that conventional CT, MRI 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 patients to palliative systemic therapy. Also, largely driven by PET, we are now discovering the existence of a surprising number of patients with solitary or oligometastatic disease in previously unexpected remote locations rather than the 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 related mortalities among Americans with prostates. The majority of these patients are not dying because of initial presentation of a high-stage incurable disease. Most of the patients who die from prostate cancer had originally presented with localized disease, 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 specifically for oligometastatic disease that will impact patient outcomes [18].

Finally, it is important to recognize that the clinical scenarios here still represent broad ranges of risk for recurrence or metastases in individuals with prostates. For example, in Variant 1, clinically appropriate imaging may be different for a patient with initially detected BCR and a PSA <1 ng/mL, versus a PSA >40 ng/mL, or for a patient 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. Finally, it should be noted that this document includes analysis of imaging techniques that are formally approved by the FDA.

### **Special Imaging Considerations**

*TRUS Prostatectomy Bed:* Drudi et al [19] showed contrast-enhanced color Doppler transrectal US (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.

### **Discussion of Procedures by Variant**

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

Following RP, serum 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 a PSA  $\geq 0.2$  ng/mL confirmed on 2 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 2 subsequent measurements should undergo a prompt search for the presence of local residual/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. Nonetheless, 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 [20] 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/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 [21]. In another study, bone scan use was very limited until PSA rose above 30 to 40 ng/mL [21]. According to the American Urological Association's (AUA) 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 [22]. Similarly, the American Society for Radiation Oncology (ASTRO)/AUA guidelines note that because most patients present with BCR with a PSA  $<1$ , the potential yield of bone scan for evaluation of BCR would be low [23]. More advanced techniques, such as single-photon emission tomography (SPECT)/CT imaging with methylene diphosphate and the newer fluoride PET, show improved performance over the conventional planar bone scan [24,25].

### **CT Abdomen and Pelvis**

CT is not effective for detecting recurrent tumors 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 a normal size [26]. CT is useful in following the 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 [27], and choline PET is much better for detection and follow-up of bone metastases. Because 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 useful when 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).

### **CT Chest, Abdomen, and Pelvis**

There is rarely any indication for consideration of extension of coverage with CT of the chest for follow-up of a patient with a clinical concern for residual or recurrent disease, status after RP. Additionally, there is limited evidence to support the use of CT chest abdomen pelvis in this setting.

### **MRI Pelvis**

Local recurrence seems to be a common site of initial disease recurrence, and MP-MRI is the most accurate imaging method for identifying sites of local recurrence after RP [6,28-32]. It is worth noting that, unlike with the Prostate Imaging Reporting and Data System (PI-RADS) applied to pretreatment imaging, there are no consensus technical standard or interpretation criteria for MRI in the BCR setting. In general, 3.0T performs better than 1.5T, and endorectal coil use can offer an improved signal-to-noise ratio and resolution to aid in detecting small early recurrences compared to 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 [32]. MP-MRI studies for detecting local recurrence after prostatectomy have reported 84% to 100% sensitivity and 89% to 97% specificity [6,10,33]. Typically, in this setting, MRI of the pelvis only is performed, at least initially. Residual, recurrent, or metastatic disease 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, similar to CT, is largely reliant on size criteria and is only minimally better than that of CT.

MRI is more sensitive and specific in the diagnosis of bone metastases, with a much better spatial and contrast resolution when compared to scintigraphic bone scan [34,35]. Gutzeit et al [36] 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 [37]. MRI has a similar performance in bone metastasis detection as choline PET [8].

Overall, pelvic MRI in the setting of Variant 1 is complementary to specialized PET examinations (choline or fluciclovine), and both categories of examinations may be beneficial 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 including apparent diffusion coefficient map and high  $b$  value DWI-MRI (preferentially  $b > 1400$  sec/mm<sup>2</sup>). When these 2 are added to anatomic T2 and T2-weighted MRI, the term MP-MRI is often applied. These will be briefly discussed, but a detailed explanation of these techniques is beyond the scope of this document. In summary, all 3 have shown some evidence of incremental value when added to anatomic imaging (T2-weighted), and there is evidence that use of more than 1 functional technique can also be additive and complementary. Among the 3, DCE-MRI has the strongest evidence and has consistently shown the greatest use in the setting of BCR evaluation.

*DCE-MRI:* DCE-MRI has been shown to be the most important sequence for evaluation of BCR post-RP [38]. Wu et al [39] in a meta-analysis to assess the effectiveness of MRI in detecting local recurrent prostate cancer after RP found that DCE-MRI, compared to T2-weighted imaging, showed a higher pooled sensitivity (85%) and specificity (95%). Roy et al [38] evaluated the performance of the 3 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 [30] and Cirillo et al [6] showed that DCE-MRI had a 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 in resolution and more often adversely affected by postoperative changes and surgical clip artifacts 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 [33]. DWI is helpful for detection of nodal and bone metastases and can be performed as a whole body screening examination [40]. However, the restricted diffusion at DWI can be nonspecific and can also be observed in normal sized or hyperplastic benign lymph nodes.

### **MRI Abdomen and Pelvis**

In this setting, MRI of the pelvis only is performed, at least initially. Residual, recurrent, or metastatic disease are all most likely to be identified in the pelvis, and additional coverage of the abdomen is of little added value. Additionally, there is limited evidence to support the use of MRI abdomen and pelvis for follow-up of a patient with a clinical concern for residual or recurrent disease, status post-RP.

### **TRUS-Guided Biopsy Prostatectomy Bed**

TRUS-guided biopsy can be performed in a systematic manner, often done as a 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 [41] 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 [41]. Only about 25% of patients with prostatectomy PSA levels of  $< 1$  ng/mL have a histologic confirmation of local recurrence after systematic biopsy of the prostatic fossa, compared with 53% of patients with prostatectomy PSA levels  $> 2$  ng/mL [41].

### **MRI-Targeted Biopsy Prostatectomy Bed**

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 postprostatectomy setting (there is no gland to segment), these targeted biopsies must be done with cognitive fusion or in-bore targeting [10]. Candidacy for salvage local therapy is largely determined by identification and characterization of a treatable local recurrence by biopsy.

### **TRUS Prostatectomy Bed**

Several studies have shown the usefulness of color and power Doppler and contrast-enhanced color Doppler in detecting local recurrence after prostatectomy [19,42,43].

### **Choline PET/CT Skull Base to Mid-Thigh**

PET with newer prostate-specific radiotracers has shown excellent performance and great potential for revolutionizing the diagnosis and subsequent management of patients with BCR. Choline was the first to receive FDA approval. 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 [44,45]. For example, a meta-analysis of 19 high-quality studies comprising 1,555 patients [44] found a sensitivity of 85.6% and a 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 to not only perform very well in the setting of BCR but to have a significant impact on patient management and the selection of appropriate treatment, compared to conventional imaging modalities [46]. Choline is inferior to MRI for detection of local recurrence with low PSA levels <2 ng/mL [8], but in a meta-analysis it still showed a 75.4% sensitivity and an 82% specificity for prostatic fossa recurrence detection. Choline is one of the most useful FDA-approved tests for nodal metastases, significantly better than CT and MRI, and is capable of identifying metastatic nodes as small as 5 mm. In a multicenter study with 106 patients with BCR, patients underwent choline PET and subsequent salvage lymphadenectomy. Investigators reported an overall sensitivity, specificity, negative and positive predictive value, and accuracy for choline PET/CT as 61.6%, 79.3%, 66.3%, 75.7%, and 70.2%, respectively. Based on their regression analysis, discriminative accuracy of choline PET/CT was 70.4%, and it improved with an increased number of dissected nodes and PSADT <12 months [47]. Bone metastasis detection and treatment response evaluation is also very good [8] and is superior to bone scan [48]. The performance of choline PET is related to the PSA level and kinetics [49-53], and the yield is lower with PSA levels <1 to 2 ng/mL. An optimal PSA cutoff of 1.1 ng/mL to initiate choline PET investigation was found in 1 study [54]. Additionally, choline PET has been reported to change the clinical management in some studies in ≤55% to 66.1% of patients with BCR [55-57]. Choline requires an on-site cyclotron for generation of the agent because of its 20-minute half-life. This also makes its use challenging, with the potential to result in degraded performance both in clinical practice and investigations based on logistics.

### **Choline PET/MRI Skull base to Mid-Thigh**

PET/MRI is a relatively newer imaging modality that allows simultaneous anatomic, functional, and molecular imaging of body parts. Few studies have evaluated the use of choline in PET/MRI. In 1 study with 75 patients with BCR, choline PET/MRI had a higher cancer detection rate compared with choline PET/CT (84.7% versus 77.3%) [58].

### **Fluciclovine PET/CT Skull Base to Mid-Thigh**

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 patients with suspected prostate cancer recurrence based on elevated serum PSA levels following prior treatment. Odewole et al [59] 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 to CT, the fluciclovine PET positivity rate for recurrent disease was 77.4% versus 18.9%, although sensitivity varies with PSA level, PSADT, and original Gleason Score [59]. One-hundred patients with biochemical failure after RP underwent choline PET and fluciclovine PET in a single-center trial [60-62]. 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 a lower physiologic background, resulting in better lesion contrast, and the practical advantage of a longer half-life enabling more widespread distribution 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 choline in the United States, and the performance of both agents reported was much lower than that of many other studies, with the meta-analysis of choline showing a sensitivity of 85.6% and a specificity of 92.6% for all sites of recurrence, and a meta-analysis of fluciclovine that reported an 87% pooled



sensitivity and a 66% pooled specificity [63], which may be related to patient inclusion criteria. The lower reported pooled specificity is likely due to the amalgamation of data on local and extraprostatic recurrence. High specificity for extraprostatic disease detection has been reported in single and multisite studies [59,64]. A multicenter report [64] 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. In the subgroup of patients with serum PSA <1ng/mL, fluciclovine PET has been reported to have a recurrence detection rate of 46.4% [65]. Similar to other available PET tracers, fluciclovine PET positivity for detected lesions correlates with increasing serum PSA level. In a clinical study with 152 patients, there was a linear increase in the positivity rate with an increasing PSA level. The positivity rate for PSA levels of <1 ng/mL, 1 to <2 ng/mL, 2 to <5 ng/mL, and ≥5 ng/mL were 58% (32/55), 87% (13/15), 100% (39/39), and 92% (35/38), respectively [66]. In a trial of 79 patients who underwent both fluciclovine PET and conventional imaging (MRI or CT), the detection rate of recurrence with fluciclovine PET was 75.4% for PSA ≤1 ng/mL compared with a detection rate of 8.8% for conventional imaging. Additionally, fluciclovine PET has been reported to change clinical management in the setting of BCR in ≤35.4% to 59% of patients [67,68]. Most importantly, a recently reported prospective randomized trial in which RT decisions were based on conventional imaging alone or with the addition of fluciclovine PET, a significant improvement in failure free survival at 3 years (75.5% versus 63.0;  $P = .003$ ) and 4 years was reported (75.5% versus 51.2%;  $P < .001$ ) in the fluciclovine planning arm [69].

### **Fluciclovine PET/MRI Skull Base to Mid-Thigh**

There is limited evidence to support the use of fluciclovine PET/MRI for the follow-up of a patient with a clinical concern for residual or recurrent disease, status post-RP.

*PET Using Other Agents:* There are many additional prostate-specific tracers that are not FDA approved, including 11C-acetate [70,71], 18F-choline [72-75], Bombesin, and 18F-fluorodihydrotestosterone [76-78], 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.

### **Fluoride PET/CT Skull Base to Mid-Thigh**

Fluoride PET/CT is not routinely used in the evaluation of prostate cancer recurrence. There is limited evidence to support its use in this setting.

### **FDG-PET/CT**

Some foci of metastatic prostate cancer demonstrate increased accumulation of fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) radiotracer, although this uptake is generally low compared to the other cancers. In 1 study, FDG-PET identified local or metastatic disease in only 28 of 91 patients (31%) with BCR after RP for prostate cancer [79]. FDG-PET is relatively insensitive in detecting osseous metastases compared to standard bone scintigraphy [80]. Ghanem et al [81] 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 a higher glucose metabolism, and FDG can become useful in detection and monitoring of this subset of patients.

### **PSMA PET/CT Skull Base to Mid-Thigh**

PSMA is a transmembrane protein, which is expressed at low levels in normal prostate tissue including benign hyperplasia but is overexpressed in intermediate- to high-grade prostate cancers. PSMA is a good target for diagnostic imaging with PET because of its specific expression in tumors with a resultant high tumor to background ratio. In December 2020, FDA granted approval to the University of California, Los Angeles, and the University of California, San Francisco, for the use of PSMA in patients with suspected prostate cancer metastasis who are potentially curable with surgery or RT and in patients with BCR [82]. In a prospective study with 635 patients with BCR after surgery or RT, the positive predictive value of PSMA PET was 0.84 by histopathologic validation, whereas the positive predictive value was 0.92 by the composite reference standard, which was defined as a combination of histology, imaging, and serum PSA after salvage therapy. PSMA PET localized recurrent prostate cancer foci in 475 of 635 (75%) of patients. Cancer detection rate of PSMA PET was positively correlated with serum PSA values (38% for <0.5 ng/mL, 57% for 0.5 to <1.0 ng/mL, 84% for 1.0 to <2.0 ng/mL, 86% for 2.0 to <5.0 ng/mL, and 97% for ≥5.0 ng/mL). Additionally, PSMA PET-guided salvage therapy led to a ≥50% decrease in serum PSA in 31 of 39 (80%) study participants [83]. PSMA has been reported to outperform

choline PET in staging and restaging of prostate cancer [84]. In inpatient comparisons of PSMA and fluciclovine, a higher detection rate by PSMA for extraprostatic disease especially at lower PSA levels was reported, with superiority of fluciclovine for the prostate bed, because of significantly lower urinary excretion of fluciclovine compared with PSMA [85,86].

Ga-68 has a physical half-life of 68 minutes, and its production currently requires a generator, which can allow batch production of approximately 2 to 4 patient doses per generator elution [87]. In addition, PSMA PET radiotracers may be useful to select patients for PSMA radioligand therapy, which is recently FDA approved [88].

### **DCFPyL PET/CT Skull Base To Mid-Thigh**

F-18-labelled PSMA targeting PET tracer DCFPyL was approved by the FDA in May 2021 in patients with prostate cancer with suspected recurrence based on elevated serum PSA level after surgery or RT. In a study with 106 patients with BCR after surgery, DCFPyL had a sensitivity of 88% for the serum PSA range of 0.5 to 3.5 ng/mL [89]. In 1 prospective study with 31 patients who experienced BCR after surgery, DCFPyL was positive in 59.1% of patients with a serum PSA level of <1.0 ng/mL and in 88.9% of patients with a serum PSA level of >1.0 ng/mL [90]. A meta-analysis including 9 studies reported a pooled cancer detection rate of DCFPyL PET/CT in BCR patients as 81%. The pooled cancer detection rate was 88.8% for PSA  $\geq$ 0.5 ng/mL and 47.2% for PSA <0.5 ng/mL [91]. In another prospective study, which included 63 BCR patients who underwent surgery, cancer detection rates were 47.6%, 62.5%, 87.5%, and 96.1% for serum PSA levels of 0.2 to 0.5, 0.5 to 1.0, 1.0 to 2.0, and >2.0 ng/mL, respectively. Additionally, this study concluded that DCFPyL PET/CT correlates with PSA, PSADT, and PSA velocity, suggesting that it may have prognostic value [92].

DCFPyL has a half-life of 110 minutes, and its production does not require an on-site cyclotron. Similar to PSMA PET tracer, DCFPyL may be useful to select patients for PSMA therapy, which is recently approved by FDA [88].

### **Radiography Skeletal Survey**

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 the 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 [93]. ASTRO and the RTOG<sup>®</sup> at the 2005 Phoenix Consensus Conference defined biochemical failure following RT as a rise by 2 ng/mL or more above the nadir PSA [94]. Based on the serum PSA level, biopsy Gleason score, and American Joint Commission on Cancer tumor (T) category, approximately 10% to 70% of patients will have evidence of disease recurrence at 10 years following RT with or without concurrent ADT for prostate cancer [95]. The greatest challenge in selecting a patient 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, whereas a late and slow/moderately rising PSA suggests local relapse [96], but these clinical factors are not definitive [97]. Isolated local recurrences in the prostate gland can be potentially treated by salvage therapy (surgery, ablation, radiation) whereas ADT represents the common treatment of choice in the presence of systemic disease [98]. It is worth noting that the literature is less strong for imaging of recurrence postbrachytherapy as compared to EBRT.

RT 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 [23]. There are 2 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 and/or adverse pathology, extracapsular extension or T4 invasion, seminal vesicle invasion, or positive margins) are at increased risk for BCR [99-105]. 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 who experience BCR after RP, radiation can be given in this setting as a salvage treatment and per ASTRO/AUA should be offered to patients who do not have evidence of metastatic disease.

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 [26] 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 [106]. Although less well studied, recurrence after ablative therapies seems to be most common locally if the disease was localized initially.

### **Bone Scan**

A radionuclide bone scan has traditionally been the first examination obtained. However, the performance of bone scan postprimary RT is quite similar to after RP, typically failing to be useful until PSA levels are >20 ng/mL and possibly as high as 60 ng/mL [3,20]. 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 patients present with BCR with a PSA <1, the potential yield of bone scan for evaluation of BCR would be low [23], and it is not routinely recommended, although that assessment is for presalvage RT, not specifically for imaging postfailed adjuvant or salvage RT. The use of bone scan for BCR after ablative primary therapy lacks specific data, but the performance is likely similar in this setting.

### **CT Abdomen and Pelvis**

CT is not effective for detecting locally recurrent tumor in an irradiated prostate gland or after ablative therapy because of its limited soft tissue resolution within the prostate gland. In the evaluation of nodal disease, CT heavily 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 [26]. CT is useful in following the 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 [27], and choline PET is much better for the 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 useful when 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).

### **CT Chest, Abdomen, and Pelvis**

There is rarely any indication for consideration of extension of coverage with CT of the chest for follow-up of a patient with a clinical concern for residual or recurrent disease after nonsurgical local and pelvic treatments. Additionally, there is limited evidence to support the use CT chest abdomen and pelvis in this setting.

### **MRI Pelvis**

MP-MRI has shown to be helpful in the 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 [39] in a meta-analysis to assess the effectiveness of an 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 MR spectroscopic imaging had the highest pooled sensitivity and specificity (90%) [39]. Roy et al [38] evaluated the sensitivity of the 3 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 MRI techniques [107], including MR spectroscopic imaging [108-110], DCE-MRI [111-113], and DWI [112,114], be used to improve the detection of recurrent prostate cancer after RT. Furthermore, Pucar et al [115] 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 before and after RT might lead to early detection of local recurrence amenable to salvage therapy. Use of MRI in restaging of the localized recurrent disease after RT has been rarely studied. In a study with 19 patients with BCR after RT, MRI of the prostate and subsequent salvage prostatectomy was performed. Results indicated that the sensitivity of MRI for extraprostatic extension, seminal vesicle invasion, and local nodal metastases was 50% to 71.4%, 61.5% to 76.9%, 60%, respectively, whereas the corresponding specificity values were 80% to 100%, 66.6%, 85.7% to 92.8%, respectively [116]. Additionally, MP-MRI has been reported to be useful for the detection of recurrence foci after brachytherapy with an average sensitivity of 88%, and it has a moderate interreader agreement for BCR on both patient (54.4%) and lesion (48.2%) level [117]. It should be noted that, in practice, MR detection of recurrence in the “intact” prostate setting, especially with brachytherapy seeds, may be plagued by artifact as well as other limitations such as inflammatory changes. For focal therapy applications such as ablation with laser or cryotherapy, and high intensity-focused US (HIFU), there is a growing literature of evidence on the utility of MRI during the follow-up course. In a study with 11 patients who underwent HIFU, sensitivity, specificity, and negative predictive values for early MRI (<3 weeks) were 68% to 91%, 52% to 55%, and 85% to 98%, respectively, whereas corresponding performance metrics for late MRI (6 months) were 63% to 80%, 67% to 73%, and 86% to 97%, respectively [118]. Similar sensitivity results for MRI (81.8%) were reported in a different study with 35 participants who underwent HIFU and subsequent salvage prostatectomy [119]. In another phase 1 study with 18 patients who underwent focal laser ablation for localized prostate cancer, residual clinically significant prostate cancer was identified in 11 of 18 (61%) patients. Logistic regression analysis of serial PSA measurements yielded a correct classification rate of 61.1% ( $P > .05$ ) for prediction of failure, whereas using a MP-MRI the correct classifications was 89% at 6 months and 88% at 12 months [120]. 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 a first-line imaging modality, 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 on 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.

Overall, pelvic MRI in the setting of Variant 2 is complementary to specialized PET examinations (choline, PSMA, or fluciclovine), and both categories of examinations may be beneficial to perform.

### **MRI Abdomen and Pelvis**

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. Additionally, there is limited evidence to support the use of MRI abdomen and pelvis for follow-up of a patient with a clinical concern for residual or recurrent disease after nonsurgical local and pelvic treatments.

### **TRUS Prostate**

Several studies have reported that TRUS is unreliable for the detection of cancer recurrence after EBRT, showing a limited sensitivity of 49% and a specificity of 57%, which is worse than DRE (sensitivity 73%, specificity 66%) [93,121].

### **TRUS-Guided Biopsy Prostate**

TRUS-guided sextant biopsy, commonly proposed as the reference standard for detection of local recurrence, may require repeated biopsies to reach a final diagnosis [122,123]. 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 [122,123].

### **MRI-Targeted Biopsy Prostate**

Biopsy is best done when targeting suspicious lesions identified by MRI rather than as a 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.

### **Choline PET/CT Skull Base to Mid-Thigh**

PET with newer prostate-specific radiotracers has shown excellent performance and great potential for revolutionizing the diagnosis and, consequently, the management of patients with BCR. Choline was the first to receive FDA approval and has been extensively used and studied with several large recent meta-analyses available [44,45]. For example, a meta-analysis by Evangelista et al [44] found a sensitivity of 85.6% and a 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 choline PET between these 2 scenarios. It is inferior to MRI for detection of local recurrence, but the meta-analysis still showed a 75.4% sensitivity and an 82% specificity for prostatic fossa recurrence detection. In a study of 184 primary RT patients who experienced BCR, and over half of whom had positive confirmatory biopsies of the prostate and/or distant sites, the median PSA level of those patients having a positive choline PET scan was 6.3 ng/mL with a sensitivity and specificity of 95% and 73%, respectively [124]. In another study of 41 patients who underwent salvage RT to the prostate bed only following RP and subsequent biochemical failure, choline PET scans were positive with a median PSA of 3.1 ng/mL and an 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 [124,125]. Bone metastasis detection and treatment response evaluation is also very good. Choline requires an on-site cyclotron for generation of the agent because of the short half-life, which restricts where it is feasible to perform.

### **Choline PET/MRI Skull Base to Mid-Thigh**

There is limited evidence to support the use of choline PET/MRI for follow-up of a patient with a clinical concern for residual or recurrent disease after nonsurgical local and pelvic treatments.

### **Fluciclovine PET/CT Skull Base to Mid-Thigh**

Fluciclovine (also referred to as a FACBC) was FDA approved in May 2016 for the imaging of patients 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 [63] included 1 study that partially included patients' postnonsurgical treatment for a total of 14 patients. This small study reported no performance characteristics of the examination in this subgroup [126]. A subsequent multicenter report of 596 patients imaged with fluciclovine for BCR included 4 patients who had undergone primary RT and 96 patients who had RT plus some additional treatment, but these subgroups were not separately analyzed [64]. In a study with 24 patients who underwent nonsurgical treatment for their primary localized disease (16 of 24 was status post brachytherapy), the recurrent cancer detection rate for fluciclovine PET/CT was 94.7% whereas it ranged from 31.6% to 36.8% for MRI [127]. Additionally, fluciclovine PET/CT has been reported to be useful in guiding targeted biopsies in patients with BCR after RT. In a study with 21 patients with 50 recurrence suspicious intraprostatic lesions, the reported cancer detection rate was 34% using the fluciclovine PET/CT guided biopsy approach [128].

### **Fluciclovine PET/MRI Skull Base to Mid-Thigh**

There is limited evidence to support the use of fluciclovine PET/MRI for follow-up of a patient with a clinical concern for residual or recurrent disease after nonsurgical local and pelvic treatments.

*PET Using Other Agents:* There are many additional prostate-specific tracers that are not FDA approved, including 11C-acetate [70,71], 18F-choline [72-74], Bombesin, 18F-fluorodihydrotestosterone [78] 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.

### **Fluoride PET/CT Skull Base to Mid-Thigh**

Fluoride PET/CT is not routinely used in the evaluation of prostate cancer recurrence.

## **FDG-PET/CT**

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 choline activity diminishing.

## **PSMA PET/CT Skull Base To Mid-Thigh**

PSMA was approved by FDA in December 2020 for patients with suspected prostate cancer metastasis who are potentially curable with previous surgery or RT in the University of California, Los Angeles, and the University of California, San Francisco [82]. In a study with 50 patients with BCR after RT who underwent PSMA PET/CT and salvage prostatectomy, the sensitivity and positive predictive value of PSMA PET/CT were both 100%. A separate analysis per lymph node revealed a sensitivity, specificity, positive predictive value, and negative predictive value as 34.78%, 100%, 100%, and 97.52%, respectively [129].

## **DCFPyL PET/CT Skull Base To Mid-Thigh**

In a study with 27 BCR patients with initial RT, DCFPyL PET/CT had a 55.5% positivity rate within the treated prostate [92]. In another study comparing PSMA PET/CT and DCFPyL PET/CT in 85 BCR patients after RT, cancer detection rates ranged from 75% to 100% at various PSA levels and were largely PSA independent for PSA levels  $\leq 25$  ng/mL [89].

## **Radiography Skeletal Survey**

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 and/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 patients with advanced prostate cancer will develop CRPC with a median time to androgen independence of 14 to 30 months [130]. Patients invariably progress to a castration-resistant state in which the cancer will grow despite low levels of serum testosterone [131]. More than 90% of patients with CRPC have bone metastases [132].

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 [133]. 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 [134]. Bone scan and CT are often performed as complimentary modalities, the pair serving as an alternative to specialized PET examinations (choline or fluciclovine).

## **CT Chest, Abdomen, and Pelvis**

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 [135]. 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 [27], 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 useful when done with IV contrast for cancer detection and surveillance. There is no evidence to support use of CT without IV contrast or multiphase scanning (ie, without and with IV contrast). In the setting of metastatic disease, chest CT becomes clinically relevant and is a first-line imaging modality for detection of pulmonary metastases. Bone scan and CT are often performed as complimentary modalities, the pair serving as an alternative to specialized PET examinations (choline or fluciclovine or PSMA).

### **CT Abdomen and Pelvis**

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 [135]. 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 [27], and choline PET is much better for the 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 useful when done with IV contrast for cancer detection and surveillance. There is no evidence to support use of CT without IV contrast or multiphase 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 a first-line imaging modality for detection of pulmonary metastases.

### **MRI Abdomen and Pelvis**

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 apparent diffusion coefficient 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. It is probable that coverage of the abdomen in addition to the pelvis would provide more benefit in this setting, but evidence is lacking.

### **MRI Pelvis**

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. It is probable that coverage of the abdomen in addition to the pelvis would provide more benefit, but evidence is lacking. 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-Targeted Biopsy Prostatectomy Bed**

Because local recurrence is of lesser clinical importance in the setting of metastatic prostate cancer, MRI-targeted biopsy of the prostate is not routinely used for evaluation.

### **Choline PET/CT Skull Base to Mid-Thigh**

Although choline PET has been extensively used and studied, with several large meta-analyses available [44,45], the literature is less rigorous for this specific application. There are multiple studies showing its utility in this application [136-139], with no evidence that choline PET has any detriment in performance, 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 is 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. 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.

### **Choline PET/MRI Skull Base to Mid-Thigh**

There is limited evidence to support the use of choline PET/MRI for follow-up of a patient treated by systemic therapy.

### **Fluoride PET/CT Skull Base to Mid-Thigh**

Fluoride is a tracer that has been available for clinical use for several decades, and it aims to demonstrate the increased uptake within foci in the bone with increased bone turnover in biologic processes such as metastatic involvement, fracture, or degenerative changes. Fluoride PET has a similar mechanism with bone scan; however, it is a much more sensitive imaging agent, and it offers tomographic evaluation. A recent meta-analysis revealed fluoride PET has a much higher sensitivity compared to bone scan (96% versus 86%) [140]. Another meta-analysis compared fluoride with bone scan and whole body MRI. The results indicated that fluoride has a higher diagnostic accuracy compared to bone scan (0.97 versus 0.842), whereas the diagnostic accuracy of fluoride was similar to that of whole body MRI for detecting bone lesions (0.97 versus 0.947) [141]. In addition to its use for detecting bone lesions in the setting of metastatic prostate cancer, quantitative features extracted from fluoride PET have been reported to be promising in treatment response evaluation and prognosis [141]. Although its higher sensitivity for detecting bone metastases, the actual clinical benefit of fluoride PET on patient outcomes is yet to be reported.

### **Fluciclovine PET/CT Skull Base to Mid-Thigh**

Fluciclovine is FDA approved (May 2016) for imaging of prostate cancer patients with BCR, and its use in metastatic prostate cancer is not as commonly reported as in BCR naturally. There are in vitro studies and anecdotal experience suggesting the potential utility with CRPC [142-144]. In a recent study with 106 patients, fluciclovine PET/CT was compared with bone scan for detecting bone metastases. The sensitivity, specificity, positive predictive value, and negative predictive value for bone scan were 79%, 86%, 45%, and 96%, respectively, whereas corresponding performance metrics for fluciclovine PET/CT were 100%, 98%, 89%, and 100%, respectively [145].

### **Fluciclovine PET/MRI Skull Base to Mid-Thigh**

There is limited evidence to support the use of fluciclovine PET/MRI for follow-up of a patient treated by systemic therapy. A small study of patients with primary prostate cancer treated with ADT reported a decrease in radiotracer uptake in local and metastatic lesions on PET/MRI [146].

*PET Using Other Agents:* There are many additional prostate-specific tracers that are not FDA approved, including 11C-acetate [70,71], 18F-choline [72-74], Bombesin, 18F-fluorodihydrotestosterone [78], and a family of related PSMA tracers [76,77,140], 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**

FDG is an inferior tracer to choline and other prostate-specific agents [79,80,147-149] 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 a higher glucose metabolism, and FDG can become useful in the detection and monitoring of this subset of patients, although the literature data are limited [150-152].

### **PSMA PET/CT Skull Base To Mid-Thigh**

PSMA was FDA approved in December 2020 for imaging of prostate cancer patients with BCR, and its use in metastatic prostate cancer is not as commonly reported as in BCR, and it is mostly limited to research use. In 1 study that compared visual and semiautomatic bone scan evaluations with PSMA PET/CT in 30 patients, visual and semiautomatic bone scan evaluation showed similar results with an average of 19.4 and 17.8 detected bone lesion per patient, whereas PSMA PET/CT revealed 40 lesions per patient [153]. In a study with 51 patients who had inconclusive F-18-NaF PET/CT findings for bone metastases, additional PSMA PET/CT ultimately diagnosed bone metastases in 13 patients (25% of the entire cohort). Patient-based sensitivity, specificity, and accuracy of additional PSMA PET/CT were 100%, 95%, and 96%, respectively [154].

PSMA PET/CT has the potential to estimate tumor burden in metastatic prostate cancer for selecting patients who may benefit from PSMA radioligand therapies. For this purpose, the actual relationship between alterations in PSMA expression and PSMA uptake at PET/CT imaging versus ADT treatment status is yet to be reported.



### **DCFPyL PET/CT Skull Base To Mid-Thigh**

DCFPyL PET/CT was FDA approved in May 2021 for imaging of prostate cancer patients with BCR, and its use in metastatic prostate cancer is not routine clinically and is confined to research. In 1 prospective study with 15 patients with metastatic prostate cancer, DCFPyL PET/CT was compared with F-18-NaF PET/CT for detection of bone lesions. Results of this study revealed 405 bone lesions suggestive of sites of prostate cancer were identified on at least one scan. On DCFPyL PET/CT, 391 (96.5%) were definitively positive, 4 (1.0%) were equivocally positive, and 10 (2.5%) were negative. Whereas on F-18-NaF PET/CT, the corresponding values were 388 (95.8%), 4 (1.0%), and 13 (3.2%), respectively. Of the definitively negative lesions on DCFPyL PET/CT, 8 of 10 (80.0%) were sclerotic, and 2 of 10 (20.0%) were infiltrative or marrow-based. Additionally, 12 of 13 (92.3%) of the definitively negative lesions on F-18-NaF PET/CT were infiltrative or marrow-based, and 1 of 13 (7.7%) was lytic. Both tracers had similar sensitivities for detecting bone lesions in metastatic prostate cancer patients [155].

In a limited number of studies, utility of DCFPyL PET/CT is evaluated for therapeutic response to ADT in metastatic prostate cancer patients. In a prospective study with 6 patients with metastatic castration resistant prostate cancer, DCFPyL PET/CT was used at baseline and 3 months after treatment to monitor the therapy response to bipolar ADT. Results revealed that 3 of 6 (50%) patients had progression on DCFPyL PET/CT. All 3 had stable disease or better on contemporaneous conventional imaging, and radiographic progression on CT and/or bone scan was observed within 3 months of progression on DCFPyL PET/CT. For the 3 patients who did not have progression on DCFPyL PET/CT, radiographic progression was not observed for >6 months [156]. Impacts of the ADT treatment status on PSMA expression and lesion visibility at F-18-DCFPyL PET/CT needs further research. Additionally, similar to PSMA PET/CT, DCFPyL PET/CT has the potential to estimate tumor burden in metastatic prostate cancer for selecting patients who may benefit from PSMA radioligand therapies.

### **Radiography Skeletal Survey**

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

### **TRUS Prostatectomy Bed**

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

### **TRUS-Guided Biopsy Prostatectomy Bed**

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**

- **Variation 1:** MRI pelvis without and with IV contrast or choline PET/CT skull base to mid-thigh or fluciclovine PET/MRI skull base to mid-thigh or PSMA PET/CT skull base to mid-thigh or DCFPyL PET/CT skull base to mid-thigh or fluciclovine PET/CT skull base to mid-thigh is usually appropriate for follow-up imaging of prostate cancer when there is clinical concern for residual or recurrent disease, status post-RP. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). Although the panel did not agree on recommending choline PET/MRI skull base to mid-thigh or fluoride PET/CT skull base to mid-thigh because there is insufficient medical literature to conclude whether these patients would benefit from the procedure, its use may be appropriate.
- **Variation 2:** MRI pelvis without and with IV contrast or choline PET/CT skull base to mid-thigh or fluciclovine PET/MRI skull base to mid-thigh or PSMA PET/CT skull base to mid-thigh or DCFPyL PET/CT skull base to mid-thigh or fluciclovine PET/CT skull base to mid-thigh is usually appropriate for follow-up imaging of prostate cancer when there is clinical concern for residual or recurrent disease after nonsurgical local and pelvic treatments. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care). Although the panel did not agree on recommending choline PET/MRI skull base to mid-thigh or fluoride PET/CT skull base to mid-thigh because there is insufficient medical literature to conclude whether these patients would benefit from the procedure, its use may be appropriate.
- **Variation 3:** Bone scan whole body or choline PET/CT skull base to mid-thigh or choline PET/MRI skull base to mid-thigh or CT abdomen and pelvis with IV contrast or fluciclovine PET/MRI skull base to mid-thigh or PSMA PET/CT skull base to mid-thigh or CT chest abdomen pelvis with IV contrast or DCFPyL PET/CT

skull base to mid-thigh or fluciclovine PET/CT skull base to mid-thigh is usually appropriate for follow-up imaging of metastatic prostate cancer treated by systemic therapy (ADT, chemotherapy, immunotherapy). These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient’s care). Although the panel did not agree on recommending MRI abdomen and pelvis without IV contrast or fluoride PET/CT skull base to mid-thigh because there is insufficient medical literature to conclude whether these patients would benefit from the procedure, its use may be appropriate.

### Supporting Documents

The evidence table, literature search, and appendix for this topic are available at <https://acsearch.acr.org/list>. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

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

### 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.

### 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, because of both 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 with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#) document [157].

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.”

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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.