# SNMMI AUC Factsheet for Imaging Evaluation of Biochemical Recurrence of Prostate Cancer After Definitive Primary Treatment

## EXECUTIVE SUMMARY

Imaging is often used to evaluate men with biochemical recurrence (BCR) of prostate cancer after definitive primary treatment (radical prostatectomy [RP] or radiotherapy [RT]). The goal of imaging is to identify the source of elevated or rising serum prostate-specific antigen (PSA) levels because subsequent management depends on disease location and extent. Salvage therapy (with surgery or radiation) may be considered for select cases with BCR to provide additional potential opportunity for cure. The salvage treatment strategy may be extended to regional adenopathy. Patients with limited distant metastases on imaging, referred to as oligometastatic disease (#5 demonstrable lesions), may be candidates for close observation, systemic hormonal therapy, or metastases-directed therapies with or without local therapy, depending on sites of recurrence. Patients with metastatic disease are typically treated with systemic therapy.

## AUC INTRODUCTION

The purpose of this document is to describe the appropriate use of imaging in the diagnostic evaluation of patients with BCR after definitive primary treatment. The imaging modalities considered included CT, bone scan, and the U.S. FDA–approved PET radiotracers that track malignancy-induced lipogenesis ($^{11}$C-choline) and amino acid metabolism ($^{18}$F-fluciclovine).

The prostate-specific membrane antigen (PSMA)–targeted monoclonal antibody, $^{111}$In-capromab pendetide, is included for historical perspective because it is neither available nor used clinically. The new class of PSMA-targeted PET radiotracers have generated considerable interest and are discussed briefly, though these agents currently are not approved for routine clinical use in the United States. Moreover, whole-body MRI (WB-MRI), with or without diffusion-weighted imaging, is excluded. Though WB-MRI may have utility in this clinical setting, particularly for the detection of bone metastases, the variability in availability, accessibility, quality, and standardization, as well as the fact that there are no currently established procedural terminology codes for reimbursement, has hindered its clinical adoption.

## BACKGROUND ON BCR OF PROSTATE CANCER AFTER PRIMARY TREATMENT

In the United States, prostate cancer is the most commonly diagnosed nonskin cancer in men and the second most common cause of cancer-related mortality. Despite local definitive therapy, up to 40 percent of patients will develop recurrent disease. Most of these patients will have BCR with no evidence of metastasis on the basis of widely used standard imaging techniques (contrast-enhanced abdomen and pelvis CT, WB 99mTc-based bone scan, or pelvis multiparametric MRI), and the disease will manifest only with elevated serum PSA levels.

The definition of BCR (also referred to as PSA relapse) depends on the type of prior definitive therapy. In patients who have undergone RP, the American Urological Association defines BCR when the serum PSA level is ≥ 0.2 ng/mL, measured 6–13 weeks after surgery, and confirmed by a second determination of a PSA level of > 0.2 ng/mL. In patients treated with RT, the American Society for Radiation Oncology Phoenix Criteria defines BCR as a rise in PSA level of 2 ng/mL or more above the nadir regardless of androgen deprivation therapy (ADT).

The significance of biochemically recurrent disease varies considerably according to individual risk factors. One clinically important prognostic variable is PSA doubling time. For instance, prostate cancer–specific survival is approximately 90 percent in patients with a PSA doubling time of ≥15 months vs. about 20 percent for patients with a PSA doubling time of 3 months. In part because of this wide variability in disease aggressiveness, coupled with competing causes of mortality and the typically long time to documented metastatic disease by standard imaging (median metastasis-free survival is 10 years in patients with BCR and no treatment), there is no defined standard management for this patient population. The development of metastasis in a patient signals that a change in treatment approach is warranted.

RT after a prostatectomy is commonly used to eradicate microscopic residual disease in the prostate bed, reducing the risk of recurrence. Defining who needs postoperative RT is most often based on surgical pathology and postoperative PSA because standard imaging does not have sufficient sensitivity to identify early recurrences in the PSA range where salvage treatment is more likely to be curative. There is growing evidence that genomic biomarkers can have utility in this clinical setting, though it remains unclear as to how this information affects imaging choice. In the adjuvant setting, pathology (pT3a/b or surgical margins positive for disease) currently drives the addition of RT. In the salvage setting, when men have persistently detectable PSA or a delayed rise in PSA level (≥ 0.2 ng/mL), conventional imaging does not have sufficient sensitivity to identify early recurrences.

The ability to detect residual or recurrent disease within the pelvis can affect RT dose and target. In the absence of molecular imaging, the question of whether to include pelvic lymph nodes in the RT field in patients with pathologic node-negative disease is a question that has been studied by the Radiation Therapy Oncology Group (RTOG) 0534 trial and is awaiting final results. The first report from RTOG 0534 (3-arm randomized trial) shows gains in freedom from progression with the addition of short-term (4–6 month) ADT to prostate bed radiation and further gains with the inclusion of pelvic lymph node RT and short-term ADT over a PSA level of 0.34 ng/mL. With the ability to visualize prostate cancer cells, molecular imaging can help define RT treatment fields. Similarly, it can identify patients who have early metastatic disease and could avoid RT to the prostate fossa. The use of molecular imaging to identify oligometastatic prostate cancer has allowed for additional treatment strategies in patient care. Studies show a benefit (e.g., biochemical progression-free survival, distant progression-free survival) to metastasis-directed stereotactic body RT in the setting of oligometastatic prostate cancer. Molecular imaging can enhance the postoperative treatment algorithm for prostate cancer patients by identifying targets for RT.

## TABLE 1: Clinical Categories and AUC Scores

Table 1 presents the clinical category and final AUC scores for the use of imaging in the evaluation of BCR of prostate cancer after definitive primary treatment with RP or RT – Initial Imaging Investigation.

**TABLE 1**

CATEGORY 1: Clinical Scenarios for BCR After Prior Definitive Treatment with RP or RT—Initial Imaging Investigation

| Scenario no. | Description | Appropriateness | Score |
|---|---|---|---|
| 1 | CT abdomen and pelvis with intravenous contrast | Appropriate | 8 |
| 2 | CT chest with intravenous contrast | Rarely appropriate | 2 |
| 3 | Bone scan ($^{99m}$Tc, $^{18}$F-NaF) | Appropriate | 8 |
| 4 | Pelvis MRI with and without intravenous contrast | Appropriate | 8 |
| 5 | $^{18}$F-FDG PET/CT (skull base to midthigh) | Rarely appropriate | 2 |
| 6 | $^{11}$C-choline PET/CT (skull base to midthigh) | May be appropriate | 6 |
| 7 | $^{18}$F-fluciclovine PET/CT (skull base to midthigh) | May be appropriate | 6 |
| 8 | $^{111}$In-capromab pendetide | Rarely appropriate | 1 |

## TABLE 2: Clinical Categories and AUC Scores

Table 2 presents the clinical category and final AUC scores for the use of imaging in the evaluation of BCR of prostate cancer after definitive primary treatment with RP or RT, with negative or equivocal results on standard imaging.

**TABLE 2**

CATEGORY 2: Clinical Scenarios for BCR After Prior Definitive Treatment with RP or RT—Negative Or Equivocal Results on Initial Standard Imaging

| Scenario no. | Description | Appropriateness | Score |
|---|---|---|---|
| 1 | $^{18}$F-FDG PET/CT (skull base to midthigh) | Rarely appropriate | 2 |
| 2 | $^{11}$C-choline PET/CT (skull base to midthigh) | Appropriate | 9 |
| 3 | $^{18}$F-fluciclovine PET/CT (skull base to midthigh) | Appropriate | 9 |
| 4 | $^{111}$In-capromab pendetide | Rarely appropriate | 1 |

## QUALIFYING STATEMENTS

In addition to the currently approved radiotracers for imaging of prostate cancer ($^{18}$F-fluciclovine and $^{11}$C-choline), a new class of radiotracers has been developed that targets the PSMA. PSMA PET is anticipated to have a significant role in the imaging evaluation of patients with BCR given its higher sensitivity and accuracy, although currently we are awaiting approval of these agents in the United States. Aside from regulatory approval, ongoing and future investigations will be needed to examine how PSMA-based theranostics provide added clinical value and have an impact on treatment strategy, patient outcome and relative economic outlay.

*This AUC was developed with participation from experts affiliated with the following organizations: American College of Nuclear Medicine, American College of Radiology, American Society of Clinical Oncology, American College of Physicians, American Society for Radiation Oncology, American Urological Association, European Association of Nuclear Medicine, Society of Nuclear Medicine and Molecular Imaging, and the World Molecular Imaging Society.*

For the complete manuscript and listing of references, visit https://go.aws/351uNU4.