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# Salvage Therapy for Prostate Cancer: AUA/ASTRO/SUO Guideline Part I: Introduction and Treatment Decision-Making at the Time of Suspected Biochemical Recurrence after Radical Prostatectomy

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**Purpose:** The summary presented herein covers recommendations on salvage therapy for recurrent prostate cancer intended to facilitate care decisions and aid clinicians in caring for patients who have experienced a recurrence following prior treatment with curative intent. This is Part I of a three-part series focusing on treatment decision-making at the time of suspected biochemical recurrence (BCR) after radical prostatectomy (RP). Please refer to Part II for discussion of treatment delivery for non-metastatic BCR after RP and Part III for discussion of evaluation and management of recurrence after radiotherapy (RT) and focal therapy, regional recurrence, and oligometastasis.

**Materials and Methods:** The systematic review that informs this Guideline was based on searches in Ovid MEDLINE (1946 to July 21, 2022), Cochrane Central Register of Controlled Trials (through August 2022), and Cochrane Database of Systematic Reviews (through August 2022). Update searches were conducted on July 26, 2023. Searches were supplemented by reviewing electronic database reference lists of relevant articles.

**Results:** In a collaborative effort between AUA, ASTRO, and SUO, the Salvage Therapy for Prostate Cancer Panel developed evidence- and consensus-based statements to provide guidance for the care of patients who experience BCR after initial definitive local therapy for clinically localized disease.

**ABBREVIATIONS and Acronyms**

95% CI = 95% Confidence interval
ADT = Androgen deprivation therapy
ASTRO = American Society for Radiation Oncology
AUA = American Urological Association
BCR = Biochemical recurrence
CT = Computed tomography
EORTC-QLQ = The European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire
EPIC = Expanded Prostate Cancer Index Composite
FACT-P = Functional Assessment of Cancer Therapy-Prostate
FDA = U.S. Food and Drug Administration
HR = Hazard ratio
HRQOL = Health-related quality of life
IIEF = International Index of Erectile Function
mpMRI = Multiparametric MRI
MRI = Magnetic resonance imaging
OS = Overall survival
PET = Positron emission tomography
PFS = Progression-free survival
PSA = Prostate-specific antigen
PSADT = PSA doubling time
PSMA = Prostate specific membrane antigen
QOL = Quality of life
RP = Radical Prostatectomy
RT = Radiation therapy
SDM = Shared decision-making
SHIM = Sexual Health Inventory for Men
SUO = Society of Urologic Oncology

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**Conclusions:** Advancing work in the area of diagnostic tools (particularly imaging), biomarkers, radiation delivery, and biological manipulation with the evolving armamentarium of therapeutic agents will undoubtedly present new opportunities for patients to experience long-term control of their cancer while minimizing toxicity.

**Key Words:** prostate cancer, salvage therapy, salvage, therapy, biochemical recurrence, BCR, radical prostatectomy, radiation therapy



While definitive standard of care therapies cure most patients with clinically localized prostate cancer, the risk of recurrence is over 50% in patients with the highest disease risk features.[1] Understanding the evaluation and appropriate use of salvage therapies for patients with BCR is important as a cure is still possible for many patients. Novel positron emission tomography (PET)/computed tomography (CT) and magnetic resonance imaging (MRI) are now identifying regional and distant recurrences that were previously undetectable. Balancing undertreatment with overtreatment, utilizing new therapeutic agents and imaging modalities, and optimizing patient selection through use of evidence-driven prognostic markers are all critical to improving oncologic outcomes and maintaining quality of life (QOL) for these patients.

This Guideline intends to inform the care of patients who experience BCR after initial definitive local therapy for clinically localized disease. As such, this Guideline bridges the gap between the AUA Localized Prostate Cancer Guideline and the Advanced Prostate Cancer Guideline.[2,3]

The prostate cancer field has made substantial advancements since the original AUA/ASTRO Guideline on Adjuvant and Salvage Radiotherapy published in 2013.[4] The introduction of PET/CT imaging is just one of the major developments that have begun to shape the care of patients with BCR. New data providing clinical and molecular parameters for risk stratification and decision-making, use of androgen deprivation therapy (ADT), and approaches to lymphadenectomy or nodal irradiation in the absence of regional disease have collectively transformed the management landscape in this critically important prostate cancer disease state.

It is important to note the resources available to those who are undergoing prostate cancer treatment to address concerns outside of direct disease management. These resources may be engaged at any time in the patient's clinical course, including at the time of diagnosis (pre-treatment) as well as following definitive local therapy. Important psychosocial support can be provided through social work services and local virtual and in-person prostate cancer support groups, as well as through national patient advocacy organizations (eg, Active Surveillance Patients International [aspatients.org], AnCan Foundation [ancan.org], Prostate Cancer Foundation [pcf.org], Prostate Cancer Research Institute [PCRI.org], Prostate Cancer Supportive Care Program [pcscprogram.ca], the Prostate Health Education Network [prostatehealthed.org], the Urology Care Foundation [urologyhealth.org], 0/UsTOO—the End of Prostate Cancer [zerocancer.org]). Additional physical and lifestyle survivorship support may be provided through referrals to dietary and nutrition services, physical therapists, pelvic floor rehabilitation specialists, and psychosexual therapists.[2]

The Panel also notes that this Guideline is intended for all patient populations with a prostate gland. For consistency purposes, this Guideline refers to these individuals as "people" or "patients" throughout this document.

## HEALTH EQUITY AND DISPARITIES

Given that novel and expensive technologies are repeatedly highlighted in this Guideline, it is imperative to first consider the ubiquitous nature of health inequities that prevent many patients from receiving guideline-concordant care.

Relevant to this Guideline, Black individuals with prostates in the United States (U.S.) are known to have the highest incidence and more than double the death rate of prostate cancer compared to all other race/ethnic groups.[5] Health inequities have been documented at every stage of prostate cancer care, from screening to work-up, treatment, and follow-up as well as clinical trial enrollment. We must be mindful of these potential inequities and disparities surrounding new technologies, particularly as novel molecular imaging is further incorporated into clinical guidelines such as this.

## GUIDELINE STATEMENTS

### Treatment Decision-making at the Time of Suspected BCR after Primary RP

1. Clinicians should inform patients that salvage radiation for a detectable prostate-specific antigen (PSA) after RP is more effective when given at lower levels of PSA. (*Strong Recommendation; Evidence Level: Grade B*)

2. For patients with a detectable PSA after RP in whom salvage radiation therapy (RT) is being considered, clinicians should provide salvage radiation when the PSA is ≤ 0.5 ng/mL. (*Moderate Recommendation; Evidence Level: Grade B*)

3. For patients with a detectable PSA after RP who are at high risk for clinical progression, clinicians may offer salvage radiation when PSA values are < 0.2 ng/mL. (*Conditional Recommendation; Evidence Level: Grade C*)

Collective data from retrospective observational studies including over 6000 patients indicate that salvage RT outcomes are superior when delivered at lower PSA levels.

In terms of secondary biochemical failure (eg, biochemical failure after salvage radiation), studies have compared outcomes based on a pre-salvage RT PSA level threshold of 0.5 ng/mL[6,7] as well as a threshold of 0.2 ng/mL.[8-10] Studies using a threshold of 0.5 ng/mL found a decreased risk of secondary BCR among patients treated with salvage RT at a PSA below 0.5 ng/mL (adjusted hazard ratios [HRs] ranged from 0.32 to 0.67).[6-8,11,12] Moreover, an analysis of 1108 patients who underwent salvage RT pooled from 10 academic centers noted that the 5-year cumulative incidence of biochemical failure was 26.6% from patients treated with a PSA ≤ 0.2 ng/mL, 32.7% with a PSA 0.21 to 0.50 ng/mL, 37.8% with PSA 0.51 to 1.0 ng/mL, and 57% for a PSA > 1.0 to 2.0 ng/mL.[10] On multivariable analysis, pre-salvage RT PSA level was statistically significantly associated with the risk of secondary biochemical failure.[10]

Studies reported on metastatic progression-free survival (PFS) among patients (n = 5555) receiving earlier vs later salvage RT, and all found earlier salvage RT was associated with improved metastatic PFS.[6,7,9,10,13,14] In addition, several studies reported on prostate cancer-specific survival/mortality stratified by PSA at time of receipt of salvage RT.[6,7,9,14,15] Three found a positive association, with the two largest studies (n = 1106 and n = 1040) each demonstrating that a pre-salvage RT PSA level ≤ 0.5 ng/mL was associated with a lower risk of prostate cancer-specific mortality compared to pre-salvage RT PSA > 0.5 ng/mL (10-year cumulative incidence: 6% vs 13%; adjusted HR: 0.62; 95% confidence interval [CI]: 0.39 to 0.97[6] and adjusted HR: 0.31; 95% CI: 0.15 to 0.62 [incidence not reported by PSA group]).[14] Meanwhile, three studies reported the association between pre-salvage RT with overall survival (OS) and demonstrated mixed results. That is, one study (n = 1106)[6] found no statistically significant difference in OS between early and late salvage RT, while a second study (n = 657) found that patients treated with a pre-salvage RT PSA level of 0.01 to 0.2 ng/mL as well as > 0.2 to 0.5 ng/mL experienced improved 10-year OS compared with pre-salvage RT PSA levels of > 0.5 ng/mL (84% vs 82% vs 61%, respectively; $P < .001$).[9] In a third study, Tilki et al examined the association between the salvage RT PSA level and all-cause mortality: 10-year all-cause mortality was 14.5% for people who received salvage RT at a PSA of > 0.25 ng/mL vs 10.4% for PSA of ≤ 0.25 ng/mL.[15] On multivariable analysis, salvage RT below a 0.25 threshold was associated with reduced all-cause mortality (HR: 1.49; $P = .008$).[15]

Based on these data, clinicians may offer salvage RT at PSA levels less than 0.2 ng/mL to patients who are assessed as being at high risk of subsequent clinical progression. Table summarizes key high-risk factors that may be included in the decision-making process. Additional prognostic factors discussed in Statement 5 may also be incorporated into decision-making regarding timing of salvage therapy.

4. Clinicians should inform patients that salvage radiation after RP poses inherent risks to urinary control, erectile function, and bowel function. These risks must be considered in the context of the risks posed by recurrent cancer along with patient life expectancy, comorbidities, and preferences to facilitate a shared decision-making (SDM) approach to management. *(Clinical Principle)*

The decision to undertake treatment at any stage of prostate cancer should occur following a careful review of the risk-benefit balance both patient and clinician. Patient comorbidity status is particularly critical to incorporate into SDM. Cardiac comorbidity status has been associated with a nearly five-fold increased risk of all-cause mortality among people with BCR.[16] Thus, it is critical to consider competing risks of mortality and the potential adverse health-related QOL impacts of salvage therapy.[17,18]

Potential harms of salvage RT include its potential impact on both acute and late functional outcomes (urinary, sexual, and bowel function)[18-20] and

**Table.** *High-risk Features in the Setting of BCR to be Considered for Patient Counseling and Management*[a]

- Grade Group 4-5
- Stage pT3b-4
- Surgical margin status[b]
- Node-positive disease
- Short PSA doubling time (PSADT)
- Short interval from primary therapy to PSA recurrence (including persistent detectable PSA after prostatectomy)
- Higher post-prostatectomy PSA
- Genomic classifier risk
- PET imaging findings

[a] The Panel recognizes that the above does not represent an exhaustive list of relevant prognostic variables.
[b] Of note, the presence of positive surgical margins has been associated both with an increased likelihood of BCR as well as a lower risk of disease progression after salvage radiation.

the long-term risks of hemorrhagic cystitis and secondary malignancies.[21] However, different studies have reported different magnitudes of impact of salvage RT-related patient reported outcomes. In a prospective study of 120 patients treated in Norway, salvage RT (with 90% of patients also receiving hormonal therapy) was associated with worsening in all 5 EPIC-26 domains: urinary incontinence, urinary irritative function, bowel, sexual function, and hormonal function.[22] In contrast, another study from the University of Chicago of 199 patients followed for 33 months demonstrated no clinically meaningful worsening in long-term QOL in any EPIC-26 domain.[23] Differences in QOL outcomes after salvage RT are likely related to treatment technique and technology at different institutions. The only randomized data come from the SWOG 8794 trial, which compared observation after RP vs adjuvant RT.[24] RT was associated with worse short-term patient-reported bowel symptoms through two years. Long-term QOL at 5 years showed no difference between observation and RT related to bowel symptoms or sexual function; RT was associated with worse urinary symptoms but better overall QOL.

Meanwhile, various models have been described to predict the likelihood of disease-specific mortality among people with BCR[14,25] as well as the likelihood of disease control with salvage radiation.[26] Such data may provide additional perspective regarding the trade-off between treatment-related side effects, the risk of disease progression, and the expected benefit of RT in this setting.

Understandably, patients will approach the risk-benefit analysis of salvage radiation with different priorities, risk tolerance, and concerns. As such, it is important that clinicians engage in an SDM process.[2]

5. Clinicians should use prognostic factors (eg, PSA doubling time [PSADT], Gleason Grade Group, pathologic stage, surgical margin status, validated post-prostatectomy genomic classifier and/or PET imaging results) to counsel patients with a detectable PSA about their risk of clinical progression. *(Moderate Recommendation; Evidence Level: Grade B)*

Several clinical features are associated with disease risk among people with BCR, albeit based on studies rated with a medium risk of bias.

In particular, a more rapid PSADT has been consistently associated with higher rates of metastases and mortality.[27-30] For example, in a cohort of 2426 people with BCR after surgery (median follow-up 11.5 years from prostatectomy and 6.6 years from BCR), the HR for death from prostate cancer was 4.9, 2.4, and 1.5, respectively, for patients with a PSADT of $<$ 6 months, 6 months to 1 year, and 1 to 10 years, relative to patients with a PSADT of $\geq$ 10 years.[28] A shorter interval from primary therapy to BCR is also a clear risk factor for subsequent metastases regardless of the mode of primary treatment.[31,32] Similarly, numerous series have demonstrated an association between higher Grade Group and increased risk of metastases and death.[28-30] Interestingly, the findings regarding an association between advanced pathologic tumor stage and clinical outcomes among patients with BCR have been inconsistent. That is, while one large series demonstrated higher risks of metastases and mortality among patients with advanced stage disease,[28] this was not observed in other studies.[14,27] Similarly, evidence regarding associations between surgical margin status or time from surgery to BCR with the outcomes of metastases and mortality among patients with BCR has also been mixed.[14,27-30]

Several prognostic models have been developed to assess the risk of death from prostate cancer among patients with BCR by combining clinicopathologic variables.[14,25,33] In addition, a tissue-based genomic score from RP specimens is associated with metastasis risk.[34] However, it remains important to emphasize that while such analyses provide prognostic information that may be utilized in patient counseling regarding the risk of disease progression, these models do not provide predictive information regarding the likelihood of response to salvage therapy. As such, the Panel does not recommend reflexive use of genomic testing in all patients with BCR being considered for salvage RT. Finally, while it merits mention that a relatively small, older series of 302 patients with BCR after surgery (median PSA of 1.02 ng/mL) demonstrated worse survival outcomes in the setting of a positive ($^{11}$C-choline) PET scan,[35] the impact of prostate-specific membrane antigen (PSMA)-PET findings on the outcomes of contemporary patients with a detectable PSA $\geq$ 0.1 ng/mL remains to be determined and is the subject of ongoing randomized trials.[36,37]

6. Clinicians may obtain ultrasensitive PSA following RP in patients who are at high risk of recurrence and in whom salvage RT would be considered. (*Expert Opinion*)

The AUA definition of BCR in the post-prostatectomy setting is a rise in PSA $\geq$ 0.2 ng/mL and a confirmatory value of $>$ 0.2 ng/mL.[38] Ultrasensitive PSA assays can provide PSA levels below 0.1 ng/mL; however, these lower levels have not been prospectively evaluated to determine if this earlier detection of a detectable PSA, and subsequent treatment for such patients, results in superior oncologic outcomes compared to treatment when the PSA meets the BCR definition of

$\geq$ 0.2 ng/mL. As such, the use of ultrasensitive PSA is not routinely recommended over standard PSA for surveillance after primary local therapy. Nevertheless, given the data highlighted above regarding the association of improved outcomes for patients treated with early salvage RT for BCR after prostatectomy, ultrasensitive PSA may be helpful in patients at high risk for recurrence in whom early salvage RT (eg, at levels below 0.2 ng/mL) would be considered.

7. For patients who do not meet the AUA definition of BCR after RP (PSA $\geq$ 0.2 ng/mL) yet have a detectable ultrasensitive PSA, clinicians should confirm a rising trend in PSA before proceeding with therapy. (*Expert Opinion*)

While a higher ultrasensitive PSA may identify patients with an increased likelihood of BCR, there does not appear to be a distinct cutoff that can clearly dichotomize groups. Moreover, some patients with residual, benign prostate tissue as well as indolent low PSA recurrence may be identified with ultrasensitive PSA. Thus, if a clinician chooses to use ultrasensitive PSA, the Panel recommends verifying a rising trend (either two consecutive rises with PSA $\geq$ 0.1 ng/mL or three consecutive rises at any PSA level) prior to instituting salvage therapies as has been done previously in a prospective trial.[20]

8. In patients with a BCR after local therapy, clinicians may obtain a PSMA PET in lieu of conventional imaging or after negative conventional imaging for further evaluation of clinical recurrence. (*Conditional Recommendation; Evidence Level: Grade C*)

Conventional imaging is typically defined as diagnostic CT, multiparametric MRI (mpMRI), and bone scan with technetium-labeled radiotracers. PET tracers can be broadly grouped into non-PSMA (eg, $^{18}$F-fluciclovine, $^{11}$C-choline), and PSMA-targeted agents. This Guideline focuses on the PET radiotracers that are currently approved and commercially available, recognizing that others are in various stages of investigation.

PSMA-targeted radiotracers are more specific for prostate cancer than $^{18}$F-fluciclovine or $^{11}$C-choline and have emerged as the most sensitive for detecting biochemically recurrent prostate cancer, especially outside the prostate bed. Several are approved, including $^{68}$Ga-PSMA-11 or gozetotide, $^{18}$F-piflufolastat (formerly $^{18}$F-DCFPyL), and $^{18}$F-flutofolastat (formerly $^{18}$F-rhPSMA 7.3). The positive predictive value (PPV) and correct localization rates for detecting BCR compared to histopathology with PSMA-PET/CT ranges from 83% to 87%.[39]

PSMA-PET/CT detection rates increase with increasing PSA levels.[40,41] In prospective cohort studies, detection rates range from 31% to 42% for PSA $<$ 0.5 ng/mL, 45% to 57% for PSA $\geq$ 0.5 to $<$ 1 ng/mL, 57% to 84% for PSA $\geq$ 1 to $<$ 2 ng/mL, and 77% to 86% for $\geq$ 2 to $<$ 5 ng/mL. For PSA $\geq$ 5 ng/mL, $^{68}$Ga-PSMA-11 or gozetotide and $^{18}$F-piflufolastat had detection rates of 90% to 97%, while $^{18}$F-flutofolastat had verified detection rates of 61% between PSA $\geq$ 5 to $<$ 10 ng/mL and 84% for PSA $\geq$ 10 ng/mL.[39,40,42] A meta-analysis of a very limited number of studies reported a PSMA-PET positive rate of 40% at PSA levels $<$ 0.2 ng/mL; however, few were with pathologic correlation.[41]

Three medium bias cohort studies consistently demonstrated that PSMA-PET/CT is a more sensitive modality to detect biochemically recurrent prostate cancer compared to conventional imaging across all the PSMA-targeted radiotracers. Using histopathology or a clinical composite of follow-up imaging and PSA, $^{68}$Ga-PSMA-11 and $^{18}$F-PSMA-1007 PET/CT detected disease in 83% to 87% of 59 patients with newly diagnosed biochemically recurrent prostate cancer (mean PSA level of 1.96 ng/mL), compared to 47% to 52% of disease detected by conventional imaging.[43] At a lower median PSA level (0.32 ng/mL, range of 0.2-2.0 ng/mL), metastatic disease was visualized in 46% of 100 patients with $^{18}$F-piflufolastat-PET/CT compared to 16% with contrast-enhanced CT chest, abdomen, and pelvis.[44] The benefit of PSMA-PET/CT appears to be detecting tumor harboring in nonenlarged lymph nodes and bone metastases[43] and disease outside the pelvis.[45]

$^{18}$F-fluciclovine PET, which images amino acid metabolism, can be utilized in patients with BCR. Cohort studies have indicated that compared to conventional imaging, $^{18}$F-fluciclovine PET/CT has improved sensitivity and specificity for detecting prostate bed recurrence, as well as extra-prostatic recurrence.[46,47] The EMPIRE-1 RCT compared the impact of $^{18}$F-fluciclovine PET/CT vs conventional imaging on oncologic outcomes.[48-50] 165 patients with detectable PSA (median 0.34 ng/mL) after prostatectomy and no extra-pelvic metastases on conventional imaging were randomized to salvage RT based on $^{18}$F-fluciclovine PET/CT plus conventional imaging or conventional imaging alone. $^{18}$F-fluciclovine PET/CT had higher detection rates compared to conventional imaging (79.7% vs 13.9%; $P < .001$), prostate bed (69.6% vs 5.1%; $P < .001$), and pelvic lymph nodes (38% vs 10.1%; $P < .001$),[48] even at low PSA levels. Median follow-up was 3.52 years, and a higher percentage of patients had 4-year failure-free survival if RT was based on the $^{18}$F-fluciclovine PET/CT and conventional imaging compared to conventional imaging alone (75.5% vs 51.2%; $P < .001$).[49,50] However, $^{18}$F-fluciclovine has been shown to have lower detection rates to detect BCR, particularly outside the prostate bed and at lower PSA levels, compared to PSMA-PET/CT. A

subset of prostate cancer may not produce PSA or express PSMA, for example poorly differentiated or neuroendocrine prostate cancer. In these instances, $^{18}$F-fluciclovine-PET/CT or FDG-PET may be useful to detect and localize recurrent disease.

No RCTs compare $^{11}$C-choline PET, which images phospholipid membrane synthesis, to conventional imaging. Cohort studies compared choline PET/CT with various other PET tracers and mpMRI[51-55]; however, methodological limitations, including high risk of bias studies, unclear blinding of outcome assessor radiolabels, and failure to report attrition, limit conclusions from these studies. Further, the short half-life of $^{11}$C limits practicality and availability for widespread use.

Overall, current evidence consistently demonstrates that PSMA-PET/CT is the most sensitive imaging modality for detecting biochemically recurrent prostate cancer and can be performed instead of or after negative conventional imaging. In the absence of PSMA-PET/CT or with known PSMA-negative disease, $^{18}$F-fluciclovine-PET/CT is an alternative and preferred over conventional imaging alone. Finally, the Panel acknowledges that although the availability of PET tracers is increasing, PET/CT is not currently available everywhere, and the availability of individual tracers varies locally.

9. For patients with BCR following RP in whom salvage radiation is being considered, the clinician should perform next generation molecular PET imaging. (*Moderate Recommendation; Evidence Level: Grade C*)

As outlined above, the EMPIRE-1 trial compared the impact of $^{18}$F-fluciclovine PET/CT vs conventional imaging on oncologic outcomes.[48-50] The 4-year event-free survival was significantly higher in the cohort who underwent salvage RT based on $^{18}$F-fluciclovine PET/CT (75.5% vs 51.2%; $P < .001$).[49,50] Patients with extra-pelvic or distant metastases detected on the $^{18}$F-fluciclovine PET/CT were excluded from salvage radiation, which may have enriched the $^{18}$F-fluciclovine arm to have seemingly better outcomes.

In addition, a medium risk of bias study compared 298 patients who underwent PSMA-PET/CT with $^{18}$F-piflufolastat or $^{18}$F-PSMA-1007 for radiation planning vs 312 historical controls without PSMA-PET/CT imaging.[56] Patients were excluded from salvage RT if lymph node or distant metastases were identified during surgery or restaging PSMA-PET/CT. Here, the risk of biochemical progression at 1 year was found to be significantly decreased in patients evaluated with PSMA-PET/CT (HR: 0.56; 95% CI: 0.49-0.92). Overall, as the detection of disease outside the prostate bed and pelvic node fields typically covered by salvage radiation has the potential to meaningfully influence salvage therapy approach, the Panel recommends obtaining a PET/CT when salvage pelvic RT is being considered.

10. In patients with BCR following RP with PET/CT positive pelvic nodal disease, the clinician should incorporate treatment of these positive findings in the radiation plan. (*Moderate Recommendation; Evidence Level: Grade C*)

In the PET/CT arm of EMPIRE-1, RT was strictly guided by PET findings, such that patients identified with distant metastases received no salvage RT, patients found to have pelvic nodal uptake were treated with RT to the pelvis and prostate bed, and patients with prostate bed uptake alone or negative PET received RT to prostate bed only. In 14 patients for whom the radiation oncologist had planned to treat only the prostate bed, PET findings of pelvic nodal uptake changed the radiation plan to add pelvic nodal regions.[48] In addition, radiation treatment volume also incorporated PET uptake areas if these areas fell outside the original contours.[49] Thus, the improvement in oncologic outcomes observed in EMPIRE-1 is attributed to obtaining a PET/CT combined with salvage RT strictly guided by PET findings. As such, the Panel recommends that positive PET/CT findings be utilized in treatment planning.

11. In patients with BCR, clinicians may obtain a pelvic MRI in addition to a PET/CT for evaluation of local recurrence. (*Conditional Recommendation; Evidence Level: Grade C*)

A feature of many PET tracers is urinary excretion, which consequently makes prostate bed/bladder neck recurrences hard to identify in a background of normal urinary uptake. A number of cohort studies have shown complementary performance characteristics for PET/CT and MRI for locoregional recurrences, and the combination of PET and MRI resulted in superior detection of prostate bed recurrences for patients with BCR in several studies.

Older choline-based PET tracers have been compared to MRI, with the largest study comprised of 115 patients with suspected tumor recurrence who underwent both $^{11}$C-choline PET/CT and mpMRI. Among 61 patients with prostate bed recurrence, 32 patients (52.4%) were correctly diagnosed as having local recurrence by both MRI and PET/CT, 22 (36.1%) were correctly diagnosed by MRI alone, 6 (9.8%) could not be diagnosed by either modality, and 1 (1.6%) was correctly diagnosed by PET/CT alone.[52] Similar performance characteristics for MRI compared to and in combination with choline PET/CT for locoregional recurrences, in particular prostate bed recurrences, have been observed.[51,55]

Newer FDA approved PSMA-PET agents have generally supplanted older PET agents such as choline in the U.S. In evaluating one of these novel agents, patients after RP and/or primary RT with rising PSA level (median, PSA 2.27 ng/mL; range, 0.2-27.45 ng/mL) and negative conventional imaging were imaged with $^{18}$F-DCFPyL (now $^{18}$F-piflufolastat) PET/CT imaging and pelvic MRI.[45] For prostate bed recurrences, sensitivity was numerically higher with MRI (83% vs 57%), while specificity (52% vs 86%) and PPV (66% vs 81%) were numerically higher with PET/CT (only specificity was statistically significant, $P = .02$). Moreover, the combination of $^{18}$F-DCFPyL and MRI improved PPV for detecting prostate bed recurrences by 30% ($P = .09$). Similar results have also been obtained with a$^{68}$Ga-PSMA-based tracer.[55]

Based on potential enhanced detection of prostate bed recurrences, the Panel concludes that it is reasonable to additionally obtain a pelvic MRI with PET/CT in this patient population.

12. In a patient with a BCR following RP, clinicians should not withhold salvage prostate bed RT in the setting of a negative PET/CT. (*Expert Opinion*)

The detection rate of PET/CT, particularly at low PSA levels, is not high enough to determine that patients would not benefit from salvage RT in the setting of a negative PET/CT.[42] As such, withholding salvage prostate bed RT in patients without detectable lesions on PET/CT may miss a "window" of opportunity to more effectively treat a minimal amount of recurrent disease. Furthermore, the limited reported data to date have demonstrated no significant differences in biochemical progression for salvage prostate bed RT between locally PET/CT positive and PET/CT negative patients.[57] Thus, the Panel recommends that clinicians proceed with salvage prostate bed RT in patients with BCR following RP including in the setting of a negative PET/CT. Similarly, if the clinical situation warrants consideration of including elective pelvic nodal irradiation, the sensitivity of nodal involvement with PET/CT at low PSA levels is not high enough to determine patients would not benefit from this treatment in the situation of a negative PET/CT.



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