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Authors' disclosure of potential conflicts of interest and author/staff contributions appear at the end of the article.

SALVAGE THERAPY FOR PROSTATE CANCER: AUA/ASTRO/SUO GUIDELINE (2024)

Guideline Panel

Todd M. Morgan, MD; Stephen A. Boorjian, MD; Mark K. Buyyounouski, MD, MS; Brian F. Chapin, MD; David Y.T. Chen, MD; Heather H. Cheng, MD, PhD; Heather A. Jacene, MD; Sophia C. Kamran, MD; Amy N. Luckenbaugh, MD; Ben J. Nathanson; Yaw A. Nyame, MD, MS, MBA; Edwin M. Posadas, MD; Phuoc T. Tran, MD, PhD; Ronald C. Chen, MD, MPH

Staff and Consultants

Sennett K. Kim; Erin Kirkby, MS; Roger Chou, MD

SUMMARY

Purpose

This Guideline on salvage therapy for recurrent prostate cancer is intended to facilitate care decisions and aid clinicians in caring for patients who have experienced a recurrence following prior treatment with curative intent.

Methodology

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. Criteria for inclusion and exclusion of studies were based on the Key Questions and the populations, interventions, comparators, outcomes, timing, types of studies and settings (PICOTS) of interest. The population of interest was patients with prostate cancer recurrence following primary curative treatment for prostate cancer.

GUIDELINE STATEMENTS

TREATMENT DECISION-MAKING AT THE TIME OF SUSPECTED BIOCHEMICAL RECURRENCE AFTER PRIMARY RADICAL PROSTATECTOMY (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*)
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*)
5. Clinicians should use prognostic factors (e.g., PSA doubling time [PSADT], Gleason Grade Group, pathologic stage, surgical margin status, validated post-prostatectomy genomic classifier and/or positron emission tomography (PET) imaging results) to counsel patients with a detectable PSA about their risk of clinical progression. (*Moderate Recommendation; Evidence Level: Grade B*)
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*)
7. For patients who do not meet the AUA definition of biochemical recurrence (BCR) after RP (PSA ≥0.2 ng/mL) yet have a detectable ultrasensitive PSA, clinicians should confirm a rising trend in PSA before proceeding with therapy. (*Expert Opinion*)
8. In patients with a BCR after local therapy, clinicians may obtain a prostate-specific membrane antigen (PSMA)-PET in lieu of conventional imaging or after negative conventional imaging for further evaluation of clinical recurrence. (*Conditional Recommendation; Evidence Level: Grade C*)
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*)
10. In patients with BCR following RP with PET/computed tomography (CT) positive pelvic nodal disease, the clinician should incorporate treatment of these positive findings in the radiation plan. (*Moderate Recommendation; Evidence Level: Grade C*)
11. In patients with BCR, clinicians may obtain a pelvic magnetic resonance imaging (MRI) in addition to a PET/CT for evaluation of local recurrence. (*Conditional Recommendation; Evidence Level: Grade C*)
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*)

TREATMENT DELIVERY FOR NON-METASTATIC BIOCHEMICAL RECURRENCE AFTER PRIMARY RADICAL PROSTATECTOMY

13. Clinicians should offer androgen deprivation therapy (ADT) in addition to salvage RT for patients with BCR following RP and any high-risk features (e.g., higher post-prostatectomy PSA such as PSA ≥0.7ng/mL, Gleason Grade Group 4 to 5, PSADT ≤6 months, persistently detectable post-operative PSA, seminal vesicle involvement). (*Moderate Recommendation; Evidence Level: Grade B*)
14. For patients with BCR following RP without any high-risk features, clinicians may offer radiation alone. (*Conditional Recommendation; Evidence Level: Grade C*)
15. Clinicians should discuss treatment side effects and the impact of medical comorbidities when patients are being considered for ADT (as well as duration) with salvage RT, utilizing a shared decision-making approach. (*Clinical Principle*)
16. For patients with pN1 disease being treated with post-operative RT, clinicians should include ADT rather than treating with RT alone. (*Clinical Principle*)

17. When providing ADT to patients undergoing salvage RT, clinicians should provide a minimum of four to six months of hormonal therapy. (*Clinical Principle*)
18. For patients with high-risk features, clinicians may extend ADT to 18 to 24 months. (*Expert Opinion*)
19. In patients with BCR following RP undergoing salvage RT with ADT, clinicians may use expanded radiation fields that include the regional lymph nodes. (*Conditional Recommendation; Evidence Level: Grade B*)
20. Clinicians should discuss with patients that including treatment of regional lymph nodes with salvage RT may increase the risk of side effects, particularly in the short term, compared to prostate bed RT alone. (*Moderate Recommendation; Evidence Level: Grade A*)
21. Clinicians should not recommend the addition of docetaxel in patients undergoing salvage RT and ADT. (*Strong Recommendation; Evidence Level: Grade B*)
22. For pN0 patients, clinicians should recommend the use of intensified androgen receptor (AR) suppression with salvage RT only within a clinical trial setting. (*Clinical Principle*)

EVALUATION AND MANAGEMENT OF SUSPECTED NON-METASTATIC RECURRENCE AFTER RADIATION THERAPY

23. For patients with BCR following primary RT or ablative therapy who have no evidence of metastatic disease and are candidates for local salvage therapy, clinicians should perform a prostate biopsy to evaluate for local recurrence. (*Clinical Principle*)
24. In patients with a biopsy-documented prostate cancer recurrence after primary RT who are candidates for salvage local therapy, clinicians should offer RP, cryoablation, high-intensity focused ultrasound (HIFU), or reirradiation as part of an SDM approach. (*Moderate Recommendation; Evidence Level: Grade C*)

EVALUATION AND MANAGEMENT OF SUSPECTED NON-METASTATIC RECURRENCE AFTER FOCAL THERAPY

25. In patients for whom salvage local therapy is being considered following focal ablation, clinicians should offer whole gland treatment by RP or RT. (*Expert Opinion*)

EVALUATION AND MANAGEMENT OF REGIONAL RECURRENCE

26. In patients with pelvic nodal recurrence following primary RP, clinicians should offer ADT plus salvage RT to the prostate bed and pelvic lymph nodes. (*Expert Opinion*)
27. In patients with pelvic nodal recurrence following primary RT who did not receive prior pelvic nodal RT, clinicians should offer salvage pelvic nodal RT plus ADT. (*Expert Opinion*)
28. Clinicians may offer salvage pelvic lymphadenectomy for patients with evidence of pelvic lymph node recurrence after RP or RT; however, these patients should be counseled regarding the uncertain oncologic benefit from surgery in this setting. (*Conditional Recommendation; Evidence Level: Grade C*)

MANAGEMENT FOR MOLECULAR IMAGING METASTATIC RECURRENCE

29. In patients with evidence of regional or metastatic oligorecurrence following primary therapy (RP or RT), clinicians may perform stereotactic ablative radiotherapy (SABR) metastasis-directed therapy (MDT) but should consider the risk of toxicity versus benefits. (*Conditional Recommendation; Evidence Level: Grade C*)
30. In patients with BCR who have non-regional disease seen on PET/CT but no visible disease on conventional imaging, clinicians may omit salvage RT to the prostate bed and should discuss the uncertain role of systemic therapy in this setting. (*Expert Opinion*)

INTRODUCTION

METHODOLOGY

The systematic review utilized to inform this Guideline was conducted by an independent methodological consultant. Determination of the Guideline scope and assessment of the final systematic review to inform Guideline statements was conducted in conjunction with the Salvage Therapy for Prostate Cancer Guideline Panel. This Guideline was developed in collaboration with ASTRO and SUO. Primary methodology was provided by the Pacific Northwest Evidence-based Practice Center of Oregon Health & Science University (OHSU).

Panel Formation

The Panel was created in 2022 by the American Urological Association Education and Research, Inc. (AUAER). The Practice Guidelines Committee (PGC) of the AUA selected the Panel Chairs who in turn appointed the additional panel members following an open nomination process to identify members with specific expertise in this area. This is a multidisciplinary panel that includes representation from urology/urologic oncology, radiation oncology, nuclear medicine, and medical oncology in addition to patient representation. Funding for the Panel was provided by the AUA, ASTRO, and SUO; panel members received no remuneration for their work.

Searches and Article Selection

The systematic review that informs the Guideline statements 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 databases reference lists of relevant articles. Criteria for inclusion and exclusion of studies were based on the Key Questions and the PICOTS of interest. The population of interest was patients with prostate cancer recurrence following primary curative treatment for prostate cancer.

Several Key Questions were developed to focus on patients with BCR. BCR is defined as a detectable or rising PSA level ≥0.2 ng/mL on 2 separate determinations after undergoing RP with curative intent for prostate cancer (nadir PSA <0.2 ng/mL),[1] or meeting the Phoenix criteria (≥2 ng/mL rise in PSA over nadir)[2] for BCR following RT[3] and no evidence of metastatic disease on conventional imaging. However, salvage treatment before these conventional thresholds for BCR was also carefully evaluated in this Guideline. Patients with a persistent detectable PSA after RP were included as well. The Key Questions included the timing of salvage RT, salvage ADT, duration of ADT, risk markers, next generation imaging, and use of prophylactic pelvic nodal RT versus omission of pelvic lymph node RT. There were additional Key Questions developed to focus on intensified systemic therapy which addressed all patients undergoing salvage RT plus ADT (including patients with nodal metastases), metastasis-directed stereotactic body RT (SBRT), salvage lymphadenectomy, recurrence after focal therapy, and pelvic lymph node RT which addressed patients with regional (nodal) recurrence. Salvage brachytherapy, cryotherapy, HIFU, RP, or systematic therapy and RP, repeat ablation, and prostate RT were covered as well to focus on patients with local recurrences. For patients at high risk of recurrence following RP (based on Gleason Grade Group 4 to 5, tumor stages pT3 and pT4, presence of positive surgical margins, and/or node-positive disease), a Key Question was developed for ultrasensitive PSA. OHSU did not exclude randomized controlled trials (RCTs) that included mixed populations of patients with BCR or PSA persistence after primary treatment given the limited numbers of RCTs. However, observational studies were restricted to patients with recurrence. Primary treatments (RP, RT, and either RP or RT) were identified based on the Key Questions. The outcomes included various oncologic outcomes (e.g., overall mortality, prostate cancer specific mortality, biochemical progression, local progression, and metastasis), quality of life (QOL), and harms.

For assessment of treatments, imaging, and risk stratification tools, inclusion was restricted to randomized trials and cohort studies. OHSU excluded studies published only as conference abstracts, case reports, narrative reviews, and non-English language articles. *In vitro* and animal studies were excluded as well.

Using the pre-specified criteria, two investigators independently reviewed the titles and abstracts of all citations. Two investigators independently screened full-text articles identified during the review of titles and abstracts. OHSU identified relevant, high-quality systematic reviews, primary studies for Key Questions not

sufficiently answered by previously published systematic reviews, and new studies published after the systematic reviews.

Data Abstraction

For primary studies that met inclusion criteria, a single investigator abstracted information on study design, year, setting, country, sample size, eligibility criteria, dose and duration of the intervention, population characteristics (e.g., age, race, tumor stage), results, and source of funding. Data abstractions were reviewed by a second investigator for accuracy, and discrepancies were resolved through discussion and consensus.

Risk of Bias Assessment

Two investigators independently assessed risk of bias using predefined criteria. Disagreements were resolved by consensus. For randomized trials and cohort studies, OHSU adapted criteria for assessing risk of bias from the U.S. Preventive Services Task Force (USPSTF).[4] Criteria for randomized trials included the use of appropriate randomization and allocation concealment methods, baseline comparability of groups, blinding, attrition, and use of intention-to-treat analysis. For cohort studies on prognostic factors, criteria included methods for assembling cohorts, attrition, blinding assessment of outcomes, and adjustment for potential confounding factors. OHSU assessed systematic reviews using Assessing the Methodological Quality of Systematic Reviews (AMSTAR 2) criteria.[5] Criteria included the use of pre-specified systematic review methods, appropriate search methods, assessment of risk of bias, and appropriate synthesis methods. Studies were rated as "low risk of bias," "medium risk of bias," or "high risk of bias" based on the presence and seriousness of methodological shortcomings.

Studies rated "low risk of bias" were generally considered valid. "Low risk of bias" randomized trials included clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; blinding of patients, care providers, and outcome assessors; and appropriate analysis of outcomes.

Studies rated "medium risk of bias" were susceptible to some bias, though not necessarily enough to invalidate the results. These studies did not meet all the criteria for a rating of low risk of bias but had no flaw likely to cause major bias. Studies may have been missing information, making it difficult to assess limitations and potential problems. The "medium risk of bias" category is broad, and studies with this rating varied in their strengths and weaknesses. Therefore, the results of some medium risk of bias studies were likely to be valid, while others may only be possibly valid.

Studies rated "high risk of bias" had significant flaws that may have invalidated the results. They had a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of high risk of bias studies could be as likely to reflect flaws in study design and conduct as true difference between compared interventions. OHSU did not exclude studies rated high risk of bias *a priori*, but high risk of bias studies were considered to be less reliable than low or medium risk of bias studies.

Data Synthesis

OHSU constructed evidence tables with study characteristics, results, and risk of bias ratings for all included studies, and summary tables to highlight the main findings. Pooled estimates and other results from systematic reviews were reported and examined whether the findings of new studies were consistent with the reviews.

The strength of evidence for management interventions evaluated in this report were graded in accordance with AUA Guideline development methods as discussed in the following section.

Determination of Evidence Strength

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[6] system was used to determine the aggregate evidence quality for each outcome or group of related outcomes informing Key Questions. GRADE defines a body of evidence in relation to how confident guideline developers can be that the estimate of effects as reported by that body of evidence, is correct. Evidence is categorized as high, moderate, low, and very low, and assessment is based on the aggregate risk of bias for the evidence base, plus limitations introduced as a consequence of inconsistency, indirectness, imprecision, and publication bias across the

studies.[7] Additionally, certainty of evidence can be downgraded if confounding across the studies has resulted in the potential for the evidence base to overestimate the effect. Upgrading of evidence is possible if the body of evidence indicates a large effect or if confounding would suggest either spurious effects or would reduce the demonstrated effect.

The AUA employs a 3-tiered strength of evidence system to underpin evidence-based guideline statements. **Table 1** summarizes the GRADE categories, definitions, and how these categories translate to the AUA strength of evidence categories. In short, high certainty by GRADE translates to AUA A-category strength of evidence, moderate to B, and both low and very low to C.

TABLE 1: Strength of Evidence Definitions

AUA Strength of Evidence Category	GRADE Certainty Rating	Definition
A	High	• Very confident that the true effect lies close to that of the estimate of the effect
B	Moderate	• Moderately confident in the effect estimate • The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C	Low	• Confidence in the effect estimate is limited • The true effect may be substantially different from the estimate of the effect
	Very Low	• Very little confidence in the effect estimate • The true effect is likely to be substantially different from the estimate of effect

The AUA categorizes body of evidence strength as Grade A (e.g., well-conducted and highly-generalizable RCTs or exceptionally strong observational studies with consistent findings), Grade B (e.g., RCTs with some weaknesses of procedure or generalizability or moderately strong observational studies with consistent findings), or Grade C (e.g., RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes or observational studies that are inconsistent, have small sample sizes, or have other problems that potentially confound interpretation of data). By definition, Grade A evidence is evidence about which the Panel has a high level of certainty, Grade B evidence is evidence about which the Panel has a moderate level of certainty, and Grade C evidence is evidence about which the Panel has a low level of certainty.[8]

AUA Nomenclature: Linking Statement Type to Evidence Strength

The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (**Table 2**). Strong Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is substantial. Moderate Recommendations are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken because net benefit or net harm is moderate. Conditional Recommendations are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm, or

when the balance between benefits and risks/burden is unclear. All three statement types may be supported by any body of evidence strength grade. Body of evidence strength Grade A in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances and future research is unlikely to change confidence. Body of evidence strength Grade B in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but better evidence could change confidence. Body of evidence strength Grade C in support of a Strong or Moderate Recommendation indicates that the statement can be applied to most patients in most circumstances, but better evidence is likely to change confidence. Conditional Recommendations also can be supported by any evidence strength. When body of evidence strength is Grade A, the statement indicates that benefits and risks/burdens appear balanced, the best action depends on patient circumstances, and future research is unlikely to change confidence. When body of evidence strength Grade B is used, benefits and risks/burdens appear balanced, the best action also depends on individual patient circumstances and better evidence could change confidence. When body of evidence strength Grade C is used, there is uncertainty regarding the balance between benefits and risks/burdens, alternative strategies may be equally reasonable, and better evidence is likely to change confidence.

Where gaps in the evidence existed, the Panel provides guidance in the form of Clinical Principles or Expert Opinions with consensus achieved using a modified Delphi technique if differences in opinion emerged.[9] A Clinical Principle is a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. Expert Opinion refers to a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment.

Peer Review and Document Approval

An integral part of the guideline development process at the AUA is external peer review. The AUA conducted a thorough peer review process to ensure that the document was reviewed by experts who were knowledgeable in the area of salvage therapy for prostate cancer. In addition to reviewers from the AUA PGC, Science and Quality Council (SQC), and Board of Directors (BOD), the document was reviewed by external content experts. Additionally, a call for reviewers was placed on the AUA website from July 21st to August 3rd, 2023 to allow any additional interested parties to request a copy of the document for review. Additional notifications were sent through various AUA membership and patient advocacy channels to further promote the availability of the document for review. The draft Guideline was distributed to 153 peer reviewers. All peer review comments were blinded and sent to the Panel for review. In total, 97 reviewers provided comments, including 77 external reviewers. At the end of the peer review process, a total of 568 comments were received. Following comment discussion, the Panel revised the draft as needed. Once finalized, the Guideline was submitted to the AUA PGC, SQC, and BOD for final approval in addition to the approval bodies of collaborators ASTRO and SUO.

BACKGROUND

While definitive standard of care therapies cure most patients with clinically localized prostate cancer, the risk of recurrence, and even subsequent metastasis, is over 50% in patients with the highest disease risk features.[10] Understanding the evaluation and appropriate use of salvage therapies for patients with BCR is a critical area of prostate cancer care. In fact, a cure is still possible for many of these patients. Novel PET/CT and 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 QOL for these patients.

Terminology and Definitions

This Guideline is intended 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/ASTRO Localized Prostate Cancer Guideline and the AUA/SUO Advanced Prostate Cancer Guideline.[11, 12] For instance, while the Localized Prostate Cancer Guideline includes discussion of adjuvant therapy, it does not extend to the setting of PSA recurrence following local therapy. Conversely, the

TABLE 2: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

Evidence Grade	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears substantial -Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits > Risks/Burdens (or vice versa) -Net benefit (or net harm) appears moderate -Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (Net benefit or harm comparable to other options)	-Benefits = Risks/Burdens -Best action depends on individual patient circumstances -Future Research is unlikely to change confidence	-Benefits = Risks/Burdens -Best action appears to depend on individual patient circumstances -Better evidence could change confidence	-Balance between Benefits & Risks/Burdens unclear -Net benefit (or net harm) comparable to other options -Alternative strategies may be equally reasonable -Better evidence likely to change confidence
Clinical Principle	a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

Advanced Prostate Cancer Guideline specifically starts with the assumption that patients have exhausted all local therapy options. Given the early, maturing results regarding PET/CT scans at the time of BCR and with an awareness of the nuanced nature of stage migration in this context, metastatic disease detected only on PET/CT scans has been included in this Guideline rather than the current Advanced Prostate Cancer Guideline.

The prostate cancer field has made substantial advancements since the original AUA/ASTRO Guideline on Adjuvant and Salvage Radiotherapy published in 2013.[13] 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 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. As discussed within AUA/ASTRO's Localized Prostate Cancer Guideline, there are multiple resources that exist for patients with prostate cancer and their loved ones. 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 (e.g., 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], ZERO/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. The array of survivorship needs for an individual patient and caregiver may be broad and should be explored by the clinician and team to ensure that appropriate support, especially peer support, is offered.[11]

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. The Cancer Equity working group published recommendations for Elevating Equitable Cancer Care, which include suggestions for clinical practice guideline development.[14] These suggestions may help to reduce disparities in guideline-adherent cancer care and include the following relevant to this Guideline: (1) review guidelines for disparity issues that could eliminate or reduce disparity, (2) incorporate language recognizing existence of bias in care, (3) incorporate a framework to account for health disparities into panel processes, and (4) consider adding a health equity expert representative. The Panel has sought to be attentive to these recommendations in the process of developing the present Guideline.

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.[15-17] 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. It is known that, despite PSA as a known biomarker for early detection of prostate cancer, Black individuals with prostates continue to be screened at a lower rate than non-Hispanic White counterparts.[18] Separately, it has been found that inequities exist with respect to access to prostate cancer imaging, and these inequities also exist with respect to novel molecular imaging.[19-21] An analysis of a single U.S. tertiary medical center found that when it comes to molecular imaging scans, Black people were more likely than White people to undergo PET scans with ^{18}F-fluciclovine versus ^{68}Ga-PSMA-11, with no other significant differences documented among any other demographic

characteristics.[19] 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. In addition, it has been found that Black patients are underrepresented in prostate cancer clinical trials compared to their known prostate cancer incidence.[22, 23] Many older studies did not include information surrounding racial composition of participants, thus treatment recommendations or clinical outcomes may not be broadly applicable to all diverse populations with prostate cancer. Prior evaluations of patients with prostate cancer in the Veterans Health Administration have 1) included a relative enrichment of Black patients (compared to standard trials or analyses of registries) and 2) found that, within an equal-access healthcare setting, many of the disparities associated with treatment response and outcomes among Black patients disappeared.[24-27] These findings must be validated further but suggest that it is critical that trials and studies going forward capture and report on race/ethnicity as well as other social determinants of health so that all outcomes are fully understood and all diverse individuals benefit from prostate cancer research breakthroughs.

As practitioners and stakeholders invested in treatment of people with prostate cancer, it is critical to recognize and address health disparities to achieve improved health equity for all minoritized populations.[28] At the congressional level, the PSA Screening for HIM Act was introduced in the 116th, 117th and now 118th Congress. The Act requires private insurance plans to cover preventive prostate cancer screenings for Black men and men with a familial history of prostate cancer, not already covered under the recommendations of USPSTF, without imposing any cost-sharing requirement. This act proposes to address health inequities related to PSA screening and can be read in full: https://www.congress.gov/bill/118th-congress/house-bill/1826). All prostate cancer care providers and healthcare organizations should be aware of the well-documented inequities that exist and pursue strategies that mitigate biases and barriers to care. This is particularly imperative for the care related to the present Guideline—although some of the recommendations here incorporate novel techniques or technology that may not be accessible to all prostate cancer patients at this time, the Panel believes these recommendations represent the best evidence to date for prostate cancer management. All stakeholders should strive to ensure equal access for quality care for all people with prostate cancer.

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 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 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*)**

The Panel recommends informing patients that the effectiveness of salvage RT decreases with increasing PSA. Collective data from retrospective observational studies including over 6,000 patients indicate that salvage RT outcomes are superior when delivered at lower PSA levels.

In terms of secondary biochemical failure (e.g., biochemical failure after salvage radiation), studies have compared outcomes based on a pre-salvage RT PSA level threshold of 0.5 ng/mL[29-34] as well as a threshold of 0.2 ng/mL.[33, 35, 36] While patient populations and treatment approaches were heterogenous across series, 5 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).[30-34] Moreover, an analysis of 1,108 patients who underwent salvage RT pooled from 10 academic centers with a median follow-up of 65.2 months 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.[36] Further, on multivariable analysis, pre-salvage RT PSA level was statistically significantly associated with the risk of secondary biochemical failure.[36]

Seven studies (N=5,555) reported on the outcome of metastatic progression-free survival (PFS) among patients receiving earlier versus later salvage RT, and all found earlier salvage RT was associated with improved metastatic PFS.[32, 34-39] In addition, several studies reported on prostate cancer-specific survival/mortality stratified by PSA at time of receipt of salvage RT.[32, 34, 35, 39, 40] Three found a positive association, with the two largest studies (n=1,106 and n=1,040) 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 level of >0.5 ng/mL (10-year cumulative incidence: 6% versus 13%; adjusted HR: 0.62; 95% confidence interval [CI]: 0.39 to 0.97[32] and adjusted HR: 0.31; 95% CI: 0.15 to 0.62 [incidence not reported by PSA group]).[39] Meanwhile, three studies reported the associated with pre-salvage RT with the outcome of overall survival (OS) and demonstrated mixed results. That is, one study (n=1,106)[32] 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% versus 82% versus 61%, respectively; p<0.001).[35] In a third study, Tilki et al. examined the association between the salvage RT PSA level and all-cause mortality. These investigators reported that the 10-year all-cause mortality was 14.5% for people who received salvage RT at a PSA of >0.25 ng/mL versus 10.4% for PSA of ≤0.25 ng/mL.[40] On multivariable analysis, salvage RT below a 0.25 threshold was associated with reduced all-cause mortality (HR: 1.49; p=.008).[40]

Finally, 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 3** 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. It is critical to highlight that the Panel supports clinicians engaging the patient using SDM when discussing the timing of salvage RT, communicating the potential impact of salvage RT on continence and potency as well as the risk of disease progression associated with delaying additional local therapy.

TABLE 3: High-risk Features in the Setting of BCR to be Considered for Patient Counseling and Management**

• **Grade Group 4-5**
• **Stage pT3b-4**
• **Surgical margin status***
• **Node-positive disease**
• **Short 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**
***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 Panel recognizes that the above does not represent an exhaustive list of relevant prognostic variables**

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 an 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 regarding the intervention being considered by both patient and clinician. Assessment of this balance is particularly important in the management of BCR after prostatectomy in which the natural history is

heterogeneous and often prolonged.[41-45] Patient comorbidity status is particularly critical to incorporate into SDM as well. Cardiac comorbidity status has been associated with a nearly five-fold increased risk of all-cause mortality among people with BCR.[46] Thus, it is critical to consider competing risks of mortality and the potential adverse health-related QOL impacts of salvage therapy.[47-52]

Potential harms of salvage RT include its potential impact on both acute and late functional outcomes (urinary, sexual, and bowel function)[50-52] and the long-term risks of hemorrhagic cystitis and secondary malignancies.[53, 54] Patients should be made aware of these potential side effects as part of the SDM process. To facilitate discussions regarding the risks of secondary therapy, clinicians should ascertain urinary, bowel, and sexual function prior to salvage treatment using standardized instruments (e.g., Expanded Prostate Cancer Index Composite [EPIC]-26, Functional Assessment of Cancer Therapy Prostate [FACT-P], International Index of Erectile Function [IIEF], Sexual Health Inventory for Men [SHIM], The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ]-PR25).[55-60] 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 and followed for 18 months, 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.[61] 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.[62] Differences in QOL outcomes after salvage RT are likely at least partially related to treatment technique and technology at different institutions. The only randomized data come from the SWOG 8794 trial, which compared observation after RP versus adjuvant RT.[63] 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[39, 64] as well as the likelihood of disease control with salvage radiation.[65] 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.[11]

5. **Clinicians should use prognostic factors (e.g., 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*)**

It is critical to informed decision-making that patients understand that the treatments for PSA recurrence may adversely impact QOL; further, there should be an understanding of cancer risk, and specifically the likelihood of metastases and death from prostate cancer (see Table 3). 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.[41-44, 46, 66-68] For example, in a cohort of 2,426 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 ≥10 years.[42] A shorter interval from primary therapy to BCR is also a clear risk factor for subsequent metastasis regardless of the mode of primary treatment.[69, 70] Similarly, numerous series have demonstrated an association between higher Grade Group and increased risk of metastases and death.[42-44, 46, 66-68] 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,[42] this was not observed in

other studies.[39, 41, 46, 66, 68, 71] 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.[39, 41-44, 46, 66, 68]

Several prognostic models have been developed to assess the risk of death from prostate cancer among patients with BCR by combining clinicopathologic variables. One nomogram developed in a multi-institutional cohort of 2,254 patients with BCR after prostatectomy included PSA parameters as well as surgical pathology and reported an (internally validated) concordance index of 0.77.[64] More recently, a risk group model was proposed to stratify subsequent survival outcomes among patients with BCR after surgery or RT.[72] The model, which for patients after prostatectomy was based on pathologic Grade Group and PSADT, has been validated for the outcomes of metastases and death from prostate cancer in a cohort of 1,040 patients with BCR after surgery.[39] Nevertheless, 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.

In addition, a tissue-based genomic score from RP specimens is associated with metastasis risk.[73] Again, however, the ability of a genomic score to inform the likelihood of response to salvage local therapy beyond its prognostic value remains to be established. 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,[71] the impact of PSMA-PET findings on the outcomes of contemporary patients with a detectable PSA ≥0.1 ng/mL remains to be determined and is the subject of ongoing randomized trials.[74, 75]

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 ≥0.2 ng/mL and a confirmatory value of >0.2 ng/mL.[1] Ultrasensitive PSA assays can provide PSA levels below 0.1 ng/mL (some down to 0.001 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 ≥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 (e.g., 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 ≥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 there are no prospective trials evaluating the use of ultrasensitive PSA to identify patients at higher risk of systemic progression or to direct subsequent therapies, some evidence supports that a higher detectable ultrasensitive PSA is associated with a greater risk of ultimately progressing to a PSA of 0.2 ng/mL or above.[76-79] However, 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 ≥0.1 ng/mL or consecutive rises at any PSA level) in values prior to instituting salvage therapies as has been done previously in prospective trials assessing salvage RT.[51]

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*)**

PET radiotracers have changed the landscape for imaging biochemically recurrent prostate cancer. The approval of new PET radiotracers has been based on

studies demonstrating improved sensitivity and disease detection rates for biochemically recurrent prostate cancer compared to conventional imaging as well as resultant changes in management.[80-82] 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 (e.g., ^{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-flotufolastat (formerly ^{18}F-rhPSMA 7.3) and differ in physical properties (e.g., radioisotope, radiochemistry, and biodistribution). The positive predictive value (PPV) and correct localization rates for detecting BCR compared to histopathology with PSMA-PET/CT ranges from 83% to 87%.[81-83]

Importantly, PSMA-PET/CT detection rates increase with increasing PSA levels.[81, 84] Across the different PSMA-PET radiotracers investigated in prospective cohort studies, detection rates range from 31% to 42% for PSA <0.5 ng/mL, 45% to 57% for PSA ≥0.5 to <1 ng/mL, 57% to 84% for PSA ≥1 to <2 ng/mL, and 77% to 86% for ≥2 to <5 ng/mL. For PSA ≥5 ng/mL, ^{68}Ga-PSMA-11 or gozetotide and ^{18}F-piflufolastat had detection rates of 90% to 97%, while ^{18}F-flotufolastat had verified detection rates of 61% between PSA ≥5 to <10 ng/mL and 84% for PSA ≥10 ng/mL.[81, 83, 85] 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.[84]

While there is relatively little high-quality evidence comparing PSMA-PET/CT versus conventional imaging for key oncologic outcomes, 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.[86] At a lower median PSA level (0.32 ng/mL, range of 0.2 to 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.[87] The benefit of PSMA-PET/CT appears to be detecting tumor harboring in nonenlarged lymph nodes and bone metastases[86] and disease outside the pelvis.[88]

^{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.[89-91] The EMPIRE-1 RCT compared the impact of ^{18}F-fluciclovine PET/CT versus conventional imaging on oncologic outcomes.[92-94] One hundred and sixty-five 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. For the 79 patients in the ^{18}F-fluciclovine PET/CT arm, ^{18}F-fluciclovine PET/CT had higher detection rates compared to conventional imaging (79.7% versus 13.9%; p<0.001), prostate bed (69.6% versus 5.1%; p<0.001), and pelvic lymph nodes (38% versus 10.1%; p<0.001),[92] 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% versus 51.2%; p<0.001).[93, 94] 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;[95-99] 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. Several ongoing investigations are assessing how management changes related to this more sensitive imaging may impact oncologic outcomes. 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 versus conventional imaging on oncologic outcomes.[92-94] The 3-year event-free survival was significantly longer in the cohort who underwent salvage RT based on ^{18}F-fluciclovine PET/CT (75.5% versus 63.0%; p=0.003), a difference that persisted at 4 years of follow-up (75.5% versus 51.2%; p<0.001).[93, 94] Patients with extra-pelvic or distant metastases detected on the ^{18}F-fluciclovine PET/CT were excluded from salvage radiation. This cohort represented 5% of patients in the ^{18}F-fluciclovine PET/CT arm (4 of 80) who would have likely failed salvage pelvic RT. This may have subsequently enriched the ^{18}F-fluciclovine arm to have seemingly better outcomes; however, this is also confounded by the fact that the ^{18}F-fluciclovine-PET/CT only imaged up to the diaphragm, and unknown disease could have been present in this arm as well.

In addition, a medium risk of bias study compared outcomes in 610 patients who underwent salvage RT to the prostatic fossa with or without prior PET/CT imaging.[100] Two-hundred ninety-eight patients who underwent PSMA-PET/CT with ^{18}F-piflufolastat or ^{18}F-PSMA-1007 for radiation planning versus 312 historical controls without PSMA-PET/CT imaging. 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 to 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.[92] In addition, radiation treatment volume also incorporated PET uptake areas if these areas fell outside the original contours.[93] While technically EMPIRE-1 did not randomize patients with positive PET scans to salvage RT that incorporated versus ignored the positive PET findings, such randomization would likely be considered unethical. Nevertheless, it is important to note that the intervention arm of the trial did include two components: 1) PET/CT, and 2) salvage RT strictly guided by the PET findings. The improvement in oncologic outcomes observed in EMPIRE-1 is, therefore, likely explained by the selective use of more aggressive salvage RT as guided by the PET/CT, including addition of pelvic RT in 14 patients and incorporation of PET-positive areas in treatment planning contours. 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*)

PET/CT has been shown to be superior to conventional imaging, using CT and ^{99m}Tc-methylene diphosphonate bone scintigraphy, for detection of locoregional and distant recurrences in the setting of BCR following RP or RT (see references in preceding Statements #8-10). 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. Local prostate bed recurrence and pelvic nodal metastases were identified in 61 of 87 patients (70.1%) and 50 of 70 patients (71.4%), respectively. The reference standard for recurrent disease included pathologic confirmation, treatment change, and imaging follow-up for determination of recurrent tumor. 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.[96] 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 in two other independent studies included in this Guideline.[95, 99]

Newer U.S. Food and Drug Administration (FDA) approved PSMA-PET agents ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL have generally supplanted older PET agents such as choline in the U.S. (at the time of this AUA Guideline writing, a third PSMA agent has also been approved for use in this space, ^{18}F-rhPSMA-7.3). 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 to 27.45 ng/mL) and negative conventional imaging were prospectively recruited and imaged with ^{18}F-DCFPyL PET/CT imaging and pelvic MRI.[88] For prostate bed recurrences, sensitivity was numerically higher with MRI (83% versus 57%), while specificity (52% versus 86%) and PPV (66% versus 81%) were numerically higher with PET/CT (only specificity was statistically significant, p=0.02). Moreover, the combination of ^{18}F-DCFPyL and MRI improved PPV for detecting prostate bed recurrences by 30% (p=0.09). Similar results have also been obtained with a ^{68}Ga-PSMA-based tracer.[99]

Based on potential enhanced detection of prostate bed recurrences, the Panel concluded 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.[85] 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. Even though PET/CT is more sensitive than conventional imaging, microscopic disease may still be undetectable. 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.[101] 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.

TREATMENT DELIVERY FOR NON-METASTATIC BCR AFTER PRIMARY RP

13. Clinicians should offer ADT in addition to salvage RT for patients with BCR following RP and any high-risk features (e.g., higher post-prostatectomy PSA such as PSA ≥0.7ng/mL, Gleason Grade Group 4 to 5, PSADT ≤6 months, persistently detectable post-operative PSA, seminal vesicle involvement). (*Moderate Recommendation; Evidence Level: Grade B*)

Evidence to support ADT in patients being treated with salvage RT for BCR after RP comes from three randomized trials: GETUG-AFU 16,[47, 48] RTOG 9601,[102] and NRG/RTOG 0534 SPPORT,[103] which compared salvage RT plus ADT versus salvage RT alone.

GETUG-AFU 16[47, 48] enrolled 743 patients between 2006 to 2010 and evaluated short-term ADT (6 months) plus salvage RT to the prostate bed ± pelvic lymph node irradiation versus salvage RT alone. Patients were enrolled with a PSA of 0.2 to 2.0 ng/mL. The median follow-up was 9.3 years. At randomization, the median PSA was 0.30 ng/mL. At 10 years, patients who received ADT with salvage RT had improved 10-year PFS (64% versus 49%; HR: 054; 95% CI: 0.43 to 0.68; p<0.0001) as well as metastasis-free survival (75% versus 69%; HR: 0.73; 95% CI: 0.54 to 0.98; p=0.034). Of note, there were no differences between the cohorts in 10-year OS or prostate cancer-specific mortality.

Meanwhile, RTOG 9601[102] enrolled 760 patients between 1998 to 2003 and tested long-term bicalutamide (150 mg daily for 2 years) plus salvage RT to the prostate bed versus salvage RT alone. Patients were enrolled with a PSA of 0.2 to 4.0 ng/mL, and the median follow-up was 13 years. At randomization, the median PSA was 0.6 ng/mL. The addition of ADT to salvage RT improved 12-year OS (76% versus 71%; HR: 0.77; 95% CI: 0.59 to 0.99), prostate cancer death (5.8% versus 13.4%; HR: 0.49; 95% CI: 0.32 to 0.74), metastasis (14% versus 23%; HR: 0.63; 95% CI: 0.46 to 0.87), second BCR (44% versus 68%; HR: 0.48; 95% CI: 0.40 to 0.58), local progression (1.8% versus 4.7%; HR: 0.36; 95% CI: 0.15 to 0.85), and disease progression (47% versus 69%; HR: 0.51; 95% CI: 0.42 to 0.61). Notably, upon stratifying by PSA at time of enrollment, the addition of ADT to salvage RT was associated with improved OS specifically among patients with a pre-salvage RT PSA of 0.7 to 1.5 ng/mL (HR: 0.61; 95% CI: 0.39 to 0.95) and a PSA of >1.5 ng/mL (HR: 0.45; 95% CI: 0.25 to 0.81), but not among patients with a PSA of <0.7 ng/mL (HR: 1.13; 95% CI: 0.77 to 1.65). A secondary analysis of RTOG 9601[104] reported that there was no difference in OS between the bicalutamide arm versus placebo for patients with a pre-salvage RT PSA of 0.2 to 0.6 ng/mL, but there was a 9.4% estimated increase in other-cause mortality (OCM) for the bicalutamide arm at 12-years (95% CI: 1.12 to 3.07; p=0.02).

NRG/RTOG 0534 SPPORT[103] randomized 1,142 patients to 3 arms: 1) salvage prostate bed RT (median PSA prior to RT 0.32, range: 0.20 to 0.60), 2) prostate bed RT plus short-term ADT (4 to 6 months; median PSA prior to RT 0.40, range: 0.23 to 0.68), 3) prostate bed RT plus short-term ADT plus pelvic RT (median PSA prior to RT 0.32, range: 0.20 to 0.60). Patients were enrolled with PSA of 0.1 to 2.0 ng/mL following prostatectomy, and the median follow-up was 8.2 years. The study reported that addition of ADT to salvage RT was associated with decreased likelihood of progression (HR: 0.64; 97.5% CI: 0.50 to 0.82), biochemical failure (HR: 0.65; 97.5% CI: 0.49 to 0.87), local failure (HR: 0.44; 97.5% CI: 0.20 to 0.97), and regional failure (HR: 0.51; 97.5% CI: 0.28 to 0.93). Adding ADT alone (i.e., arm 2 versus arm 1) did not statistically significantly improve distant metastasis, prostate cancer death, or overall mortality; however, adding ADT and pelvic RT (i.e., arm 3 versus arm 1) did improve distant metastases (HR: 0.55; 95% CI: 0.35 to 0.85; p=.00098) and prostate cancer death (HR: 0.54; 95% CI: 0.29 to 1.00; p=.012).

Although these collective data consistently demonstrate a benefit of ADT with salvage RT, including reducing metastasis, an optimal threshold of PSA to identify patients most likely to benefit from adding ADT has not been rigorously defined. Based on the RTOG 9601 data, the Panel recommends offering ADT to patients being treated with salvage RT who have a higher post-prostatectomy PSA, including a PSA of ≥0.7 ng/mL. That said, analysis of NRG/RTOG 0534 SPPORT, using more contemporary radiation techniques and ADT (consisting of 4 to 6 months of combined androgen blockade), points toward a potential alternative PSA threshold of 0.35 ng/mL, albeit in an underpowered secondary analysis of outcomes. Thus, while there remains uncertainty about the use of concurrent ADT with salvage radiation in patients with PSA values <0.7 ng/mL, ADT should be

offered in patients with a higher post-prostatectomy PSA including those above 0.7 ng/mL. For patients with a PSA <0.7 ng/mL, where the benefit is less well defined, PSA alone should not be used to determine when to add ADT to salvage radiation regimens, and other factors must be taken into account (**see Table 3**).

14. **For patients with BCR following RP without any high-risk features, clinicians may offer radiation alone. (*Conditional Recommendation; Evidence Level: Grade C*)**

Several clinical and pathologic features among patients with BCR have been associated with worse long-term clinical outcomes (**see Table 3**).[39, 41, 42, 46, 66-68, 71] As such, the Panel recommends that these variables should be considered as part of the decision to offer ADT with salvage RT. Of note, these variables have been evaluated in post-hoc analyses of the RTOG 9601, GETUG-AFU 16, and NRG/RTOG 0534 trials with conflicting results, although such subgroup analyses are often underpowered.

In GETUG-AFU 16,[47, 48] patients defined as low-risk were compared to those categorized as high-risk. Risk categories were characterized based on prior data evaluating risk factors for biochemical recurrence after surgery, including time to relapse after surgery, PSADT, seminal vesicle involvement, margin status, and Gleason score,[44, 105, 106] although it is understood that margin status is one of the more inconsistent risk indicators for benefit of addition of ADT. In fact, the impact of ADT on improved PFS was similar for each of these groups (low [HR: 0.47; 95% CI: 0.28 to 0.80] and high [HR: 0.56; 95% CI: 0.44 to 0.73]). This was also true when evaluating the impact of ADT on metastases-free survival in each group (low [HR: 0.58; 95% CI: 0.29 to 1.17] and high [HR: 0.77; 95% CI: 0.55 to 1.06]).

In RTOG 9601,[102] the addition of ADT was associated with improved OS for patients with Gleason score 7 (HR: 0.69; 95% CI: 0.49 to 0.98) and Gleason score 8 to 10 (HR: 0.76; 95% CI: 0.44 to 1.30), but not in patients with Gleason score 2 to 6 (HR: 0.95; 95% CI: 0.57 to 1.59). Similarly, this association was also observed in patients with a positive surgical margin (HR: 0.73; 95% CI: 0.54 to 0.98; p=0.04).

In NRG/RTOG 0534 SPPORT,[103] the addition of ADT to RT was associated with greater benefit with regard to 8-year freedom from progression (versus RT alone) for patients with Gleason score <8 (76% versus 64%; p<0.0001) rather than patients with Gleason score 8 to 9 (47% versus 45%; p=0.06). However, associations of ADT plus RT with outcomes were similar when patients were stratified according to pathology (pT2 and negative margins versus others) as well as the presence of seminal vesicle involvement.

Future studies are required to refine which patients specifically benefit from the addition of ADT to salvage RT and which patients may be spared the toxicities of intensified treatment. Furthermore, in addition to the established clinicopathologic prognostic variables detailed above, the potential exists to utilize biomarkers in the selection of patients for the addition of ADT to salvage RT. Evolving data with biomarkers have suggested a potential role in this setting. For example, a separate ancillary analysis of pathological samples from 352 patients in RTOG 9601 using the validated post-prostatectomy genomic classifier[107] found that absolute benefits in distant metastasis, prostate-cancer specific mortality, and OS at 12 years with ADT were different by validated post-prostatectomy genomic classifier score. While such data suggest that genomic classifier scores may help estimate the magnitude of benefit from ADT with salvage RT for different patients, the body of evidence is still maturing at this time, and subject of ongoing cooperative studies (e.g., NRG GU-006, BALANCE, NCT03371719). In addition, the utility of PSMA-PET in the post-operative space for BCR is evolving with no clear guidelines on whether ADT should be incorporated into treatment depending on a positive or negative PSMA-PET scan.[108-110] However, if there is macroscopic disease detected, generally addition of ADT should be considered.

While an individualized approach to adding ADT to salvage RT is evolving, there is a subset of patients with BCR who may be treated with salvage RT without ADT. Indeed, RTOG 9601[102] did not find an OS benefit from adding ADT to salvage RT in patients with a PSA <0.7 ng/mL at trial entry (HR: 1.13; 95% CI: 0.77 to 1.65; p=0.53), nor in those with negative surgical margins (HR: 0.87; 95% CI: 0.53 to 1.41; p=0.56) or low Grade Group 1 (HR: 0.95; 95% CI: 0.57 to 1.59; p=0.84). The aforementioned secondary analysis of RTOG 9601,[104] which included post-hoc analyses by the median trial entry PSA of 0.60 ng/mL, similarly did not find a significant improvement in OS for patients treated with what would be considered “early” salvage RT who received bicalutamide (HR: 1.16; 95% CI: 0.79 to 1.70; p=0.46). In fact, these patients experienced a two-fold increased hazard of OCM (subdistribution hazard ratio [sHR]: 1.94; 95% CI: 1.17 to 3.20; p=0.01).

Given the competing risks associated with ADT, the Panel believes that patients without any high-risk features (e.g., features included in **Table 3** such as pathological or surgical Gleason Grade Group 4 to 5, persistently elevated post-operative PSA, seminal vesical involvement, extracapsular extension, PSADT ≤6 months, PSMA-PET/CT + disease) may be offered salvage RT without ADT after a discussion of the pros and cons of omission of ADT as part of an SDM approach.

15. Clinicians should discuss treatment side effects and the impact of medical comorbidities when patients are being considered for ADT (as well as duration) with salvage RT, utilizing an SDM approach. (*Clinical Principle*)

Despite the demonstrated oncologic benefits outlined, the addition of ADT to salvage RT can increase treatment side effects, which merits appropriate patient counseling. In particular, the risk-benefit ratio must be evaluated for each patient, including medical comorbidities, life expectancy, QOL considerations, and patient preferences. Gonadotropin-releasing hormone (GnRH) agonists have been found to be associated with an increased risk of incident diabetes (adjusted HR: 1.44, p<0.001), coronary heart disease (adjusted HR: 1.16, p<0.001), myocardial infarction (adjusted HR: 1.11, p=0.03), and sudden cardiac death (adjusted HR: 1.16, p=0.004), per a large population-based cohort of 73,196 fee-for-service Medicare enrollees diagnosed with locoregional prostate cancer.[111] Patients with coronary risk factors starting ADT may be referred for co-management with a cardiologist. ADT is also known to impact bone mineral density loss,[112] weight gain, and dementia.[113] These risks increase with longer-term ADT use.[113] The discussion surrounding the addition of ADT to salvage RT as well as proposed duration of ADT should be balanced with both the clinician and patient coming to a decision together about the care plan.

In GETUG-AFU 16,[47, 48] the addition of ADT was associated with worse sexual function, although these differences disappeared at five years. The addition of ADT was associated with an increased risk of grade ≥2 hot flashes (8% versus 0%) and grade ≥2 hypertension (2% versus <1%). There were no significant differences between RT versus RT + ADT in terms of urinary or bowel symptoms. Moreover, in RTOG 9601,[102] bicalutamide was associated with a higher risk of grade ≥3 gynecomastia (3.7% versus 0%) and impotence (7.5% versus 4.2%), with no difference in bladder or bowel toxicity. In NRG/RTOG 0534 SPPORT,[103] the addition of ADT to salvage RT was associated with a significant increase in all acute adverse events grade ≥2 (p<0.0001). At the same time, a secondary analysis of RTOG 9601[104] noted that the odds of combined grades 3 to 5 cardiac and neurologic events were significantly increased in the arm assigned to 2 years of bicalutamide (odds ratio [OR]: 2.48; 95% CI: 1.16 to 5.74; p=0.02). As this is a secondary analysis of only one study that used long-term high-dose bicalutamide, which is not commonly used today, these results might not be generalizable to all patients, especially those who receive short-term luteinizing hormone-releasing hormone (LHRH) agonists or antagonists. Nevertheless, given the known effects of ADT on cardiac events, dementia, fracture risk, and metabolic syndrome,[111, 114, 115] the potential morbidity of ADT needs to be addressed in all SDM discussions.

16. For patients with pN1 disease being treated with post-operative RT, clinicians should include ADT rather than treating with RT alone. (*Clinical Principle*)

The optimal management for patients with pN1 disease post-RP remains to be defined. Pathologic node-positive disease at time of RP is a risk factor for recurrence,[116] with cancer-specific survival closely related to the number of positive lymph nodes found at the time of surgery.[117-120] The only randomized trial in this specific patient population is ECOG 3886, which reported that adjuvant lifelong ADT was associated with improved cancer specific survival and OS, albeit in a relatively limited number of patients and with the reference comparator arm consisting of what would today be considered very late salvage therapy.[121] In several more recent retrospective series, the addition of RT to ADT in this patient population has been associated with improved outcomes.[122-124] One study[124] of 703 patients treated between 1986 and 2002 at 2 large academic institutions matched patients treated with ADT alone versus ADT plus RT. With a mean follow-up of 100 months, patients who received RT and ADT had improved cancer-specific survival and OS at 10 years after surgery compared to ADT alone (86% versus 70%, and 74% versus 55%, respectively; p=0.004 and p<0.001). The duration of ADT in combination with RT in this context has not been defined, and ADT duration was highly heterogeneous in the aforementioned study. Of all patients, 44% underwent

orchiectomy, and the remaining 56% were treated with median duration of ADT of 37.5 months (range: 4 to 158 months). In a separate study evaluating RT + ADT in this setting compared to observation or ADT alone,[125] RT + ADT was associated with better OS than ADT alone (HR: 0.46; 95% CI: 0.32 to 0.55; p<0.0001) and observation alone (HR: 0.41; 95% CI: 0.27 to 0.64; p<0.0001). The median duration of ADT when combined with RT was 5.9 years (interquartile range: 3.55 to 8.91). Of note, the ongoing NRG-GU008 (INNOVATE, NCT04134260) randomized trial is evaluating the utility of RT + GnRH agonist/antagonist for 2 years versus RT + GnRH agonist/antagonist + apalutamide for 2 years and will help define the optimal hormonal therapy in patients with node-positive disease.

17. When providing ADT to patients undergoing salvage RT, clinicians should provide a minimum of four to six months of hormonal therapy. (*Clinical Principle*)

GETUG-AFU-16, RTOG 9601, and NRG/RTOG 0534 SPPORT all compared salvage RT with ADT versus salvage therapy alone following RP.[47, 48, 102, 103, 107] However, the 3 studies utilized different forms and durations of ADT: 6 months of goserelin (GETUG-AFU-16), 24 months of high-dose bicalutamide (150 mg daily, RTOG 9601), and 4 to 6 months of flutamide or bicalutamide plus LHRH agonist (NRG/RTOG 0534 SPPORT).[47, 48, 102, 103, 107] The timing of ADT administration all differed between studies with RTOG 9601 and GETUG-AFU-16 starting ADT at initiation of salvage RT and with NRG/RTOG 0534 SPPORT initiating ADT 2 months prior to salvage RT. [47, 48, 102, 103, 107] With 8 to 13 years of follow-up, all 3 studies demonstrated a 40% to 60% improvement in freedom from clinical progression[47, 48, 102, 103] with the addition of concurrent ADT to salvage RT. Moreover, the RTOG 9601 and NRG/RTOG 0534 SPPORT studies demonstrated a survival advantage of concurrent ADT with salvage RT, and a systematic review of GETUG-AFU, RTOG 9601, and 9 cohort studies demonstrated superior BCR-free survival and OS among patients receiving concurrent ADT and salvage RT compared to salvage RT alone.[126] The shortest durations of ADT across these 3 trials ranged from 4 to 6 months.[103] Even shorter durations of ADT have not been demonstrated to improve patient outcomes. As such, the Panel recommends that 4 to 6 months should be considered the minimum duration of ADT treatment in patients selected for concurrent ADT with salvage RT. ADT could be initiated concurrently or up to two months prior to initiating salvage RT based on the three clinical trial protocols.

18. For patients with high-risk features, clinicians may extend ADT to 18 to 24 months. (*Expert Opinion*)

As noted, three previous clinical trials compared different durations and types of ADT with salvage RT to salvage RT alone.[47, 48, 102, 103, 107] The variation in type of ADT and treatment duration does not allow for a robust comparative analysis. RTOG 9601, which randomized patients to long-term (24 months) high-dose bicalutamide, included 18% of patients with Grade Group 4 to 5 cancer and 70% of patients considered high-risk based on the GETUG-AFU-16[47, 48] classification (e.g., Grade Group 4 to 5, positive surgical margin, seminal vesicle involvement, PSADT ≤6 months).[102] On stratified analysis, longer-term duration of ADT was associated with lower likelihood of progression and death in patients with high-risk factors, including Grade Group 4 to 5 cancer, positive surgical margins, and higher PSA at the time of RT.[102, 107] Thus, for patients with high-risk features requiring salvage RT, clinicians may extend ADT duration to 18 to 24 months while data matures from the RADICALS-HD trial (NCT00541047), which directly compares short-term versus long-term ADT with salvage RT.

19. In patients with BCR following RP undergoing salvage RT with ADT, clinicians may use expanded radiation fields that include the regional lymph nodes. (*Conditional Recommendation; Evidence Level: Grade B*)

When proceeding with salvage RT with ADT to the prostate bed in patients with BCR following RP, it is important to consider whether to irradiate the pelvic lymph nodes as well. The best evidence to date for this question is from the NRG/RTOG 0534 SPPORT RCT.[103] Prior to these results, pelvic nodal RT had not been rigorously evaluated in the salvage setting, and early prospective, randomized data from the intact prostate cancer setting were controversial.[127, 128]

NRG/RTOG 0534 SPPORT had 3 arms and evaluated the utility of salvage prostate bed RT alone (arm 1), prostate bed RT with short-term (4 to 6 month) ADT (arm 2), and prostate bed RT, short-term ADT, and pelvic

lymph node RT (arm 3). Pertinent to this Guideline statement, there was a lower risk of prostate cancer death (HR: 0.51; 95% CI: 0.27 to 0.94; p=0.007) and distant metastasis (HR: 0.52; 95% CI: 0.34 to 0.81; p<0.001) in arm 3 compared to arm 1. Further, 5-year freedom from progression increased by 6.1% (standard error [SE] 2.2%; p=0.0027) with the addition of pelvic lymph node RT to prostate bed RT + short-term ADT (arm 3 versus arm 2). However, there was no significant difference between the three arms with respect to OS. While subgroup analysis results of this trial are hypothesis-generating, the addition of pelvic node RT appeared to be associated with improved freedom from progression for patients with a pre-salvage RT PSA of 0.1 to 1.0 ng/mL (73% versus 78%; p=0.054) but not for those with a PSA between 1.0 and 2.0 ng/mL (61% versus 71%; p=0.24).

20. Clinicians should discuss with patients that including treatment of regional lymph nodes with salvage RT may increase the risk of side effects, particularly in the short term, compared to prostate bed RT alone. (*Moderate Recommendation; Evidence Level: Grade A*)

The addition of pelvic nodal RT to prostate bed RT has the potential to increase the risk of side effects, and the balance of risks and benefits should be considered by the patient and the clinician as part of the SDM process. However, the data are conflicting regarding the possible increase in toxicity.

The NRG/RTOG 0534 SPPORT trial[103] showed that pelvic nodal RT modestly increased any acute grade ≥2 adverse event (44% versus 36%; OR: 1.39; 95% CI: 1.10 to 1.77), any acute grade ≥3 adverse event (11% versus 7%; OR: 1.60; 95% CI: 1.06 to 2.42), acute grade ≥2 blood or bone marrow adverse events (5% versus 2%; OR: 3.01; 95% CI: 1.45 to 6.26), acute grade ≥3 blood or bone marrow adverse events (3% versus <1%; OR: 15.38; 95% CI: 2.03 to 116.85), and acute grade ≥2 gastrointestinal adverse events (7% versus 4%; OR: 1.76; 95% CI: 1.03 to 3.03). For gastrointestinal adverse events, the largest event difference between groups was mostly for diarrhea, while for blood or bone marrow events, the difference was related to lymphopenia. A small difference in late grade ≥2 blood or bone marrow events (4% versus 2%; OR: 2.60; 95% CI: 1.23 to 5.47) was also reported, with the differences related to leukopenia and lymphopenia. However, overall late toxicities were no different between prostate bed RT alone versus prostate bed plus pelvic lymph node RT plus ADT (p=0.26). These small differences might be further reduced with the use of modern radiation techniques.

21. Clinicians should not recommend the addition of docetaxel in patients undergoing salvage RT and ADT. (*Strong Recommendation; Evidence Level: Grade B*)

No studies have reported comparative outcomes of docetaxel with standard ADT versus ADT alone in patients undergoing salvage RT. That said, two RCTs have compared docetaxel plus ADT versus ADT alone in patients with BCR after RP, in which some of the patients included also received salvage RT. The TAX 3503 study randomized patients (n=413) with BCR after primary RP to docetaxel (75mg/m^2 every 3 weeks for up to 10 cycles) with ADT for 18 months compared to ADT alone.[129] Patients were eligible based on a PSA ≥1.0 ng/mL or PSADT of ≤9 months. No statistically significant differences were identified between the group that received docetaxel versus the group that received no docetaxel with respect to PFS or OS. A second study randomized patients with BCR after RP or RT to docetaxel 70 mg/m^2 IV every 3 weeks for up to 6 cycles with ADT, versus ADT alone (n=250).[130] There was an observed difference in PSA PFS that did not reach statistical significance, whereas no difference was observed in radiographic PFS or OS. In both studies the addition of docetaxel was associated with increased likelihood of adverse effects, including Grade 3 to 4 neutropenia, febrile neutropenia, hair loss, fatigue, diarrhea, edema, and peripheral neuropathy. Thus, given the absence of direct investigation of docetaxel in the salvage RT setting, together with the outlined data demonstrating a lack of benefit and increased toxicities of docetaxel in patients with BCR, the Panel strongly recommends against the addition of docetaxel in patients undergoing salvage RT and ADT.

22. For pN0 patients, clinicians should recommend the use of intensified AR suppression with salvage RT only within a clinical trial setting. (*Clinical Principle*)

Several ongoing studies are assessing the role of intensified AR suppression (defined as newer AR pathway inhibitors such as abiraterone acetate, enzalutamide, apalutamide, and darolutamide) with salvage RT. RTOG 3506 (STEEL, NCT03809000) is comparing enzalutamide with ADT versus ADT alone in

patients undergoing salvage RT for high-risk BCR after primary RP (primary completion estimated September 2024).[131] The EMBARK trial (NCT02319837) compares three arms: enzalutamide with ADT versus placebo with ADT versus enzalutamide monotherapy for BCR after primary RP or RT, but this study does not require salvage RT.[132] The phase 3 ECOG/ACRIN EA8191 (INDICATE, NCT04423211) study contains 4 arms, 2 of which (arms A and B) are comparing apalutamide with ADT versus ADT without apalutamide in conjunction with salvage RT or salvage RT with metastases-directed RT in patients with BCR after primary RP.

The Panel acknowledges the data from STAMPEDE trial of non-metastatic, high-risk prostate cancer patients supporting use of two years of abiraterone acetate to ADT and primary RT for eligible patients.[133] However, given that the median PSA of patients enrolled on the STAMPEDE trial was 34 to 40 ng/mL and that definitive trials in the salvage RT setting are ongoing and data are not yet mature, the Panel recommends that use of intensified AR suppression in combination with salvage RT be limited to the clinical trial setting.

EVALUATION AND MANAGEMENT OF SUSPECTED NON-METASTATIC RECURRENCE AFTER RT

23. For patients with BCR following primary RT or ablative therapy who have no evidence of metastatic disease and are candidates for local salvage therapy, clinicians should perform a prostate biopsy to evaluate for local recurrence. (*Clinical Principle*)

Historically, there has been limited utilization of local salvage therapy for patients with BCR after primary RT. In fact, up to 90% of individuals with recurrence after radiation treatment do not receive local salvage therapy and instead are managed with ADT alone.[134] BCR may also be an increasingly seen scenario for patients who undergo primary ablative therapy instead of prostatectomy or primary RT. That said, for patients who demonstrate isolated local recurrence after prior definitive radiation treatment or following partial or whole-gland ablative therapy, local salvage therapy may be a more effective management option than observation or ADT.[135]

The rationale to document local recurrence with prostate biopsy includes the potentially significant side effects from any local salvage therapy following prior radiation treatment.[136-141] Prostate biopsy should be performed before any local retreatment to confirm the presence of recurrent prostate cancer and should include biopsy of the seminal vesicles and targeted biopsy of suspicious areas that may be identified on imaging. The details of prostate biopsy are important to guide the choice and extent of local salvage therapy (e.g., if there is diffuse bilateral cancer recurrence versus isolated to a lobe or region, or if there is positive seminal vesicle involvement).[142]

Further, the increasing availability and application of PET/CT imaging may enhance the ability to detect metastatic disease and allow improved selection of patients for possible local salvage therapy. However, the performance of PET/CT imaging for diagnosis of local recurrence following definitive RT or prior ablative therapy remains undefined, and there is a recognized false-positive rate of PET/CT; it remains imperative that local salvage therapy should only be performed after pathologic confirmation of prostate cancer and should not be attempted based solely on positive imaging findings.

24. In patients with a biopsy-documented prostate cancer recurrence after primary RT who are candidates for salvage local therapy, clinicians should offer RP, cryoablation, HIFU, or reirradiation as part of a shared decision-making approach. (*Moderate Recommendation; Evidence Level: Grade C*)

Options for local salvage therapy for biopsy-confirmed recurrent prostate cancer after primary RT include salvage RP, salvage ablation using cryoablation or HIFU, or salvage reirradiation, which has most commonly been approached with low-dose-rate (LDR) brachytherapy, high-dose-rate (HDR) brachytherapy, or SBRT. Local salvage therapy is generally undertaken with curative intent, and oncologic outcomes between these different modalities have been mainly examined in retrospective cohorts, although a limited number of prospective non-randomized studies have been performed. When patient evaluation has been based on applying conventional imaging, any local salvage therapy approach has similar ~50% long-term rates of freedom from subsequent BCR in appropriately selected patients.[136-139, 143]

Counseling regarding local salvage therapy after primary RT should emphasize that there are likely to be higher risk of treatment-related adverse events, particularly impacting patients' urinary, sexual, and bowel function

compared to initial local treatment applying these same therapies in the primary setting. An SDM approach should apply in counseling a patient regarding management of locally recurrent prostate cancer.

A recent meta-analysis performed a systematic review of the most common salvage treatment modalities: surgery (RP), ablation (cryoablation and HIFU) and reirradiation (SBRT, permanent LDR brachytherapy, and temporary HDR brachytherapy).[135] Efficacy between treatments is largely similar at two-year and five-year follow-up.

Salvage RP can be performed via an open or robotic approach and should incorporate lymphadenectomy to provide complete pathologic staging. Salvage RP is a technically challenging operation even in the hands of experienced surgeons and is associated with greater risk for urinary incontinence compared to other local salvage treatments.[144] Salvage ablation applying cryoablation or HIFU, are modalities that traditionally have been applied as whole-gland treatments, although these may also be performed as partial gland ablation or focal ablation. As cryoablation or HIFU toxicity may correlate with the extent of ablation, it is suggested that morbidity from local salvage therapy with a focal cryoablation or HIFU may be lower compared to whole gland ablation, albeit without diminished oncologic outcomes.[145] The post-treatment follow-up after salvage whole-gland cryoablation or HIFU has mostly been measured applying the Phoenix definition (nadir + 2ng/mL), which has not been validated in this setting.[2, 146]

Salvage reirradiation can be performed via SBRT, LDR brachytherapy, or HDR brachytherapy, and the salvage RT approach chosen is generally different from the original radiation treatment. The rates and severity of complications for these salvage local treatments are similar, with largely similar degrees of genitourinary and gastrointestinal toxicity.[135-137]

In comparison to salvage RP, the meta-analysis suggests there is similar severe urinary function toxicity with HIFU, both roughly 21% to 23%, with cryoablation modestly less (~15%), and significantly lower degree of severe urinary function toxicity for any manner of reirradiation, estimated 5.6% to 9.6%. The overall rates of severe bowel function toxicity are low across all salvage treatment modalities.

EVALUATION AND MANAGEMENT OF SUSPECTED NON-METASTATIC RECURRENCE AFTER FOCAL THERAPY

25. In patients for whom salvage local therapy is being considered following focal ablation, clinicians should offer whole gland treatment by RP or RT. (*Expert Opinion*)

The use of focal ablative therapy has increased for localized prostate cancer in recent years. Median reported rates of clinically significant cancer following ablation, as compiled from multiple studies, are approximately 15% (range 0% to 22%) following HIFU, 8.5% (range 0% to 33%) following irreversible electroporation (IRE), 16.5% (range 4% to 40%) following focal laser ablation, 10% to 13% for photodynamic therapy, and up to 20% following cryoablation.[147] The recurrence rate is likely to differ between different ablation treatment modalities, and there is currently no consensus on the optimal approach for focal ablation. A recent investigational phase 2b study of MRI-guided focused ultrasound focal therapy reported a 40% risk of clinically significant cancer present on biopsy at 2 years post-treatment.[148] Typically, “clinically significant” has been defined based on a combination of biochemical, radiographic, and histologic data following treatment.[147] Salvage treatment should be largely reserved for Grade Group 2 and higher recurrences and in individuals with life expectancy greater than 5 to 10 years.

Limited data exist to inform the optimal approach for patients with recurrence following primary focal ablation.[149] Based on the multifocal nature of prostate cancer, the Panel believes that patients should be offered salvage RP or RT to the whole gland to manage clinically significant locally recurrent prostate cancer following primary focal ablative therapy.

EVALUATION AND MANAGEMENT OF REGIONAL RECURRENCE

26. In patients with pelvic nodal recurrence following primary RP, clinicians should offer ADT plus salvage RT to the prostate bed and pelvic lymph nodes. (*Expert Opinion*)

The clinical scenario of isolated pelvic nodal recurrence following RP is becoming increasingly common given the

clinical use of new PET/CT radiotracers. There is currently only 1 published prospective study, the GETUG P07 OLIGOPELVIS single-arm phase 2 trial of men with 5 or fewer pelvic nodes detected via fluorocholine PET imaging following primary prostate/prostate-bed directed therapy, which treated patients with salvage comprehensive nodal irradiation and 6 months of ADT.[150] The OLIGOPELVIS trial provides some interesting benchmarking data that are roughly consistent with retrospective published studies; however, it was non-randomized. The utility of whole pelvic radiation therapy (WPRT) is being addressed by the PEACE-V STORM trial (NCT03569241). However, until better prospective data are available, the consensus of this Panel is that patients may gain a substantial clinical benefit from salvage comprehensive RT (which includes the prostate bed and pelvis) plus ADT, similar to other settings where salvage treatment is needed after RP (see Statements 16-19).

27. **In patients with pelvic nodal recurrence following primary RT who did not receive prior pelvic nodal RT, clinicians should offer salvage pelvic nodal RT plus ADT. (*Expert Opinion*)**

Similar to the clinical scenario described in Statement #26, isolated pelvic nodal recurrence following primary RT is increasing, especially with use of PET/CT. The prospective GETUG P07 OLIGOPELVIS single-arm phase 2 trial examined only a very small number of these specific patients (n=6) in a non-randomized fashion with salvage comprehensive nodal irradiation and 6 months of ADT demonstrating generally low toxicity and favorable disease control.[150] Given the dearth of data in this space, the consensus of this Panel is that a significant fraction of these patients may benefit from salvage therapy in the form of WPRT and ADT (if prior pelvic RT was not given). Once again, as the Panel believes in the potential of long-term disease control with salvage therapy, the combination of salvage WPRT and ADT was determined to be preferable to ADT alone. At the same time, the Panel recognizes there will be situations in which the pelvic lymph nodes were radiated at the time of primary prostate RT, and for such patients who develop isolated pelvic nodal recurrence, there is a paucity of evidence that re-irradiation may be of benefit. In this scenario, depending on the anatomic findings and again with limited evidence, options include salvage lymphadenectomy, re-irradiation (e.g., with SABR]), or ADT alone.

28. **Clinicians may offer salvage pelvic lymphadenectomy for patients with evidence of pelvic lymph node recurrence after RP or RT; however, these patients should be counseled regarding the uncertain oncologic benefit from surgery in this setting. (*Conditional Recommendation; Evidence Level: Grade C*)**

The decision to perform salvage lymphadenectomy for recurrent pelvic lymph node disease after primary RP or RT should involve appropriate counseling regarding both the unknown oncologic benefit and the potential risks associated with salvage lymphadenectomy. Currently, only one retrospective cohort study has reported comparative outcomes from lymphadenectomy to what was considered standard of care with ADT. The study included 265 patients with oligometastatic recurrence identified on ^{11}C-choline PET/CT. Salvage lymphadenectomy was performed in those with pelvic nodal disease and compared to ADT alone. The authors defined salvage lymphadenectomy as extended bilateral pelvic lymph node dissection in all patients, with additional excision of any PET avid retroperitoneal lymph nodes. Performance of salvage lymphadenectomy was associated with improved second-line systemic therapy-free survival and reduced cancer specific mortality compared to ADT alone. However, there were several limitations to this study, including the fact that patients undergoing salvage lymphadenectomy were more likely to have pelvic disease only compared to those receiving ADT (91% versus 51%).[151] In addition, the analysis for cancer specific mortality was unadjusted.

A small randomized trial compared MDT (including removal of suspicious pelvic lymph nodes only and bilateral salvage pelvic lymph node dissection [full template node dissection]) with no MDT for oligometastatic recurrent prostate cancer.[152] MDT in this study did not only include nodal excision, but also included SBRT to metastatic sites, and in one case lung metastasectomy. The trial enrolled patients with PSA recurrence and oligometastatic disease diagnosed on ^{11}C-choline PET/CT. MDT was associated with improved ADT-free survival; however, the study did not stratify results by type of MDT, thus the direct impact of salvage lymphadenectomy remains unknown. Similarly, a large retrospective cohort study compared MDT to standard of care and found MDT to be associated with improved 5-year cancer-specific survival and reduced 10-year cancer-specific mortality.[153] Again, however, this study

did not stratify outcomes by salvage therapy type; therefore, the direct impact of salvage pelvic lymph node dissection remains unclear. Lastly, a large multi-center retrospective review evaluated cancer-specific mortality, clinical recurrence (CR), BCR and ADT-free survival following salvage bilateral extended pelvic lymphadenectomy. CR-free and BCR-free survival at 10-years of follow-up were 31% and 11%, respectively.[154]

In this context, the Panel believes that clinicians may offer salvage lymphadenectomy for select patients with recurrent pelvic lymph node disease; however, the uncertain oncologic benefit and the surgical risks of salvage lymphadenectomy must be acknowledged.

MANAGEMENT FOR MOLECULAR IMAGING METASTATIC RECURRENCE

29. In patients with evidence of regional or metastatic oligorecurrence following primary therapy (RP or RT), clinicians may perform SABR MDT but should consider the risk of toxicity versus benefits. (*Conditional Recommendation; Evidence Level: Grade C*)

The standard treatment for metastatic prostate cancer includes intensified systemic therapy in addition to ADT based on high-quality evidence.[12] In this oligometastatic setting, there have been attempts to incorporate MDT in order to minimize or delay the need for systemic therapy and prolong PFS, with the ultimate intent to improve OS. Oligometastatic definitions vary, and this term generally means limited skeletal or nodal metastases, but there is no defined number of metastases that is universally accepted. Several clonal evolution studies have been completed that have demonstrated that metastases are capable of spreading not only from the primary tumor but also from other metastatic sites.[155, 156] This led to the evaluation of the MDT concept in several retrospective cohort studies and phase 1 single arm studies to determine the risk of toxicity and feasibility.

In the POPSTAR trial, 33 patients with oligometastatic prostate cancer were treated with single fraction SBRT, with 14% of patients experiencing grade 2 toxicity and 3% experiencing grade 3 toxicity. Local PFS was >90% out to 2 years.[157] Several retrospective cohort series have been primarily hypothesis-generating in terms of the potential oncologic benefit of MDT. There is a smaller (n=63) study demonstrating improved PSA progression and delayed time to ADT initiation.[158] The other, a large cohort (n=2,049), showed improvement in cancer specific mortality, which was muted when a propensity-matched analysis was completed.[153]

Two phase 2 randomized trials have been completed that evaluated MDT in the setting of PSA recurrence and with staging evaluation showing oligometastases post prior local therapy. The control arm of these trials was continued observation versus the experimental MDT. The Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence (STOMP) study was a small trial (n=62) and the first to evaluate the effect of MDT on initiation of ADT in the oligometastatic recurrence post local therapy setting. Patients were enrolled after a PSA recurrence with up to three lymph node or bone metastases identified on ^{11}C-choline PET. MDT consisted of targeted pelvic lymph node dissection or radiation. Meeting the primary endpoint, MDT was found to be associated with improvement in ADT-free survival (21 months versus 13 months; HR: 0.60; 95% CI: 0.40 to 0.90). Importantly, there were no grade 2 events in the MDT group and no differences noted in the EORTC QLQ C30 or Global Health Scores.[152] A second randomized phase 2 trial, Observation Versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE) trial,[159] enrolled 54 patients with up to 3 metastases identified on conventional imaging (CT, bone scan, MRI). Although all patients had PSMA-PET, the investigators were blinded to the results of this additional imaging study. MDT was given as SBRT in 3 to 5 fractions. The primary outcome was a composite endpoint of progression (PSA ≥2 ng/mL, radiographic progression, symptomatic progression, initiation of ADT, death, or withdrawal). At 6 months, MDT was associated with decreased risk of progression (19% versus 61%; RR: 0.32; 95% CI: 0.15 to 0.68), as well as improvements in PFS (median not reached versus 5.8 months; HR: 0.30; 95% CI: 0.11 to 0.81). Recently, longer-term outcomes of MDT from STOMP and ORIOLE trials demonstrated median PFS was still prolonged with MDT compared with observation (pooled HR: 0.44; 95% CI: 0.29 to 0.66; P value <.001).[160-162] These trials have demonstrated a signal of benefit for MDT, and further phase 3 trials (NCT04641078, NCT04302454, NCT03569241) are underway to determine if these interventions will result in meaningful oncologic endpoints, such as metastasis-free survival and/or OS. In addition, work is being done to

evaluate the role of ADT in the setting of MDT, as the role of concomitant therapy remains unclear.

Although these trials were completed in asymptomatic patients with minimal lymph node or bone metastases, patients with symptomatic recurrences/metastases may also receive MDT to improve pain, prevent ureteral obstruction, and prevent risk of impending fractures. Understandably, these patients are unlikely to present with low PSA recurrences (at the time of salvage treatment considerations) and more likely to present with more advanced recurrences, which is beyond the scope of this Guideline. In light of these data as well as the low risk of toxicity from MDT, the Panel believes that MDT may be offered to patients with oligorecurrent disease who are motivated to achieve time off of systemic therapy. Importantly, the Panel recognizes that establishing a definitive oncologic benefit to MDT, with or without concurrent systemic therapy, will require additional clinical trial testing and so endorses continued efforts to develop evidence and enroll patients on such trials where available.

30. **In patients with BCR who have non-regional disease seen on PET/CT but no visible disease on conventional imaging, clinicians may omit salvage RT to the prostate bed and should discuss the uncertain role of systemic therapy in this setting. (*Expert Opinion*)**

The incorporation of PET/CT scans, which are more sensitive than conventional imaging, into routine care of prostate cancer patients raises relevant clinical questions that require further research. Historically, patients with BCR after RP and negative conventional imaging received salvage RT with curative intent as standard of care. A portion of these patients had subclinical metastatic disease that would be visible with PET/CT today. Whether these patients with conventional imaging negative, but PET/CT positive metastatic disease benefit from salvage RT is unknown. It may be reasoned that patients with metastatic prostate cancer are unlikely curable with local therapy; therefore, omitting salvage RT is reasonable. Indeed, in the EMPIRE-1 trial,[93] patients randomized to the ^{18}F-fluciclovine PET/CT arm and found to have visible metastatic disease did not receive salvage RT. At the same time, however, treating these patients using an oligometastatic disease paradigm, which could include salvage RT to the prostate bed and metastatic areas, remains a reasonable approach. Currently, data on comparative oncologic outcomes from each of these management approaches are lacking to inform decision-making.

Meanwhile, the benefits of systemic therapy, including treatment intensification beyond ADT with the use of chemotherapy and androgen receptor signaling inhibitors (ARSIs), has been demonstrated in clinical trials for patients with metastatic disease on conventional imaging. Whether these benefits exist for patients with conventional imaging negative and PET/CT only detected disease has not been proven to date. Therefore, discussion between the clinician and patient is needed using a conventional SDM process, communicating the trade-offs between the toxicity from systemic therapy versus possible but unproven benefit of early systemic therapy before the patient has demonstrated metastatic disease on conventional imaging. Simply applying clinical trial data to conventional imaging negative patients risks potential overtreatment of many of these patients.[163]

FUTURE DIRECTIONS

Optimizing and personalizing the approach to salvage therapy remains an ongoing area of work in the field of genitourinary oncology and represents an area of research and clinical care that requires well-coordinated, multi-disciplinary care. 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.

As examples of these opportunities, the field will soon see the completion of studies involving the use of PSMA-PET/CT both to optimize patient selection and radiation planning for managing locoregional recurrences. Nevertheless, as newer and more sensitive imaging agents and modalities become available, further studies will be needed to define appropriate utilization in patients being considered for salvage therapy. With continued investigation of molecular biomarkers, the field will also gain insight into the optimization of systemic therapies, particular suppression of AR activation, for example, in using genomic classifiers. Indeed, NRG-GU006 (BALANCE, NCT03371719), which evaluates the role of

luminal-basal subtyping to personalize the use of hormonal manipulation in salvage RT, is due to mature.

In addition, there is renewed interest in balancing the harms and benefits of early AR suppression in prostate cancer, fueled by studies showing the benefits of treatment intensification for patients with metastatic disease. In addition to optimizing the duration of AR suppression, there is now interest in understanding the role of intensified AR suppression in the setting of salvage RT. Early results from the completed phase 2 studies point to potential benefit, but there is still need to develop trials in this space and to follow fully accrued studies as they mature. (NCT02319837, NCT03009981) Similarly, there is now evidence from the EMBARK study to support early intensified AR suppression for patients at particularly high risk of developing metastasis.[164] This topic will be addressed in a future update to the Advanced Prostate Cancer Guideline.

Continuous and deliberate efforts for multidisciplinary care in prostate cancer will be required to optimize and improve the oncologic and functional outcomes of patients treated with salvage therapies in the future.

Abbreviations

95%CI	95% confidence interval
ADT	Androgen deprivation therapy
AR	Androgen receptor
ARSI	Androgen receptor signaling inhibitors
AS	Active surveillance
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
AUAER	American Urological Association Education and Research, Inc.
BCR	Biochemical recurrence
BOD	Board of Directors
CR	Clinical 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
GnRH	Gonadotropin-releasing hormone
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HDR	High-dose rate
HIFU	High-intensity focused ultrasound
HR	Hazard ratio
HRQOL	Health-related quality of life
IIEF	International Index of Erectile Function
IRE	Irreversible electroporation
LDR	Low-dose rate
LHRH	Luteinizing hormone-releasing hormone
MDT	Metastasis-directed therapy
mpMRI	Multiparametric MRI
MRI	Magnetic resonance imaging
OCM	Other-cause mortality
OR	Odds ratio
ORIOLE	Observation Versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PGC	Practice Guidelines Committee
PICOTS	populations, interventions, comparators, outcomes, timing, and settings
PSA	Prostate-specific antigen
PSADT	PSA doubling time
PSMA	Prostate specific membrane antigen
QOL	Quality of life
QUADAS- 2	Quality Assessment of Diagnostic Accuracy Studies-2
RCT	Randomized controlled trial
ROBINS-I	Risk of Bias in Non-Randomized Studies of Intervention
RP	Radical Prostatectomy
RT	Radiation therapy
SABR	Stereotactic ablative radiotherapy
SBRT	Stereotactic body radiation therapy
SDM	Shared decision-making
SHIM	Sexual Health Inventory for Men
SQC	Science & Quality Council
STOMP	Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence
SUO	Society of Urologic Oncology
WPRT	Whole Pelvic Radiation Therapy

SALVAGE THERAPY FOR PROSTATE CANCER PANEL, CONSULTANTS, AND STAFF

Panel

Todd M. Morgan, MD (Chair)
University of Michigan
Ann Arbor, MI

Ronald C. Chen, MD, MPH (Vice Chair)
University of Kansas
Kansas City, KS

Stephen A. Boorjian, MD (PGC Representative)
Mayo Clinic
Rochester, MN

Ben J. Nathanson (Patient Advocate)
AnCan
Teaneck, NJ

Mark K. Buyyounouski, MD, MS
Stanford University
Stanford, CA

Brian F. Chapin, MD
MD Anderson Cancer Center
Houston, TX

David Y.T. Chen, MD
Fox Chase Cancer Center-Temple Health
Philadelphia, PA

Heather H. Cheng, MD, PhD
University of Washington
Seattle, WA

Heather A. Jacene, MD
Harvard University
Boston, MA

Sophia C. Kamran, MD
Harvard University
Boston, MA

Amy N. Luckenbaugh, MD
Vanderbilt University
Nashville, TN

Yaw A. Nyame, MD, MS, MBA
University of Washington
Seattle, WA

Edwin M. Posadas, MD
Cedars-Sinai
Los Angeles, CA

Phuoc T. Tran, MD, PhD
University of Maryland
Baltimore, MD

Consultant
Roger Chou, MD
Pacific Northwest Evidence-based Practice Center

Staff
Erin Kirkby, MS
Sennett K. Kim
Brooke Bixler, MPH
Leila Rahimi, MHS
Lauren J. Pak, MHS, MS

CONFLICT OF INTEREST DISCLOSURES

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Consultant/Advisor: Todd Morgan, Foundation Medicine; **Ronald Chen**, Astellas; **Stephen Boorjian**, Ferring, ArTara, Prokarium; **Brian Chapin**, Janssen and Janssen, Merck, Pfizer, Johnson and Johnson; **Heather Jacene**, Advanced Accelerator Applications, Blue Earth Diagnostics, Spectrum Dynamics; **Phuoc Tran**, RefleXion Medical, Bayer Healthcare

Scientific Study or Trial: **Stephen Boorjian**, SUO-CTC; **Brian Chapin**, Blue Earth Diagnostics, Regeneron; **Heather Cheng**, Clovis, Janssen, Medivation, Color Foundation, Sanofi, AstraZeneca, Phosplatin; **Heather Jacene**, Telix, Blue Earth Diagnostics; **Sophia Kamran**, Prostate Cancer Foundation; **Edwin Posadas**, Pfizer

Meeting Participant/Lecturer: Amy Luckenbaugh, UroGen; **Edwin Posadas**, Bayer, Movant

Investment Interest: **David Chen**, Pfizer

Health Publishing: **Mark Buyyounouski**, Wolters Kluwer, Elsevier; **Heather Jacene**, American Journal of Radiology

Leadership Position: **Heather Jacene**, SNMMI; **Sophia Kamran**, ASTRO, ASCO GU Symposium, American Board of Radiology

Other: **Ben Nathanson**, AnCan Foundation; **Heather Jacene**, SNMMI; **Sophia Kamran**, Sanofi Genzyme; **Phuoc Tran**, Janssen-Taris Biomedical, Natsar Pharm

PEER REVIEWERS

We are grateful to the persons listed below who contributed to the Guideline by providing comments during the peer review process. Their reviews do not necessarily imply endorsement of the Guideline.

AUA (Board of Directors, Science and Quality Council, Practice Guidelines Committee, Journal of Urology)
Erin Bird, MD
Sam Chang, MD
Thomas Chi, MD
Michael Cookson, MD
David Ginsberg, MD
Damara Kaplan, MD
Kathleen Kobashi, MD
Janet Kukreja, MD
Edward Messing, MD
Matthew Nielsen, MD
Vernon Pais, Jr., MD
Phillip Pierorazio, MD
Christopher Porter, MD
Glenn Preminger, MD
Hassan Razvi, MD
Angela Smith, MD
Arun Srinivasan, MD
Thomas Stringer, MD
Arthur Tarantino, MD
James Ulchaker, MD

External Reviewers (Non-AUA Affiliates)
Jack Andrews, MD
John Antonucci, MD
Alan Babcock
Leslie Ballas, MD
Dan Barocas, MD
Alejandro Berlin, MD
Marc Bjurlin, DO
Alvin Cabrera, MD
Marty Chakoian
Anthony D'Amico, MD
Robert Dess, MD
James Eastham, MD
William Franklin
Martin Gewirtz
Patrick Gomella, MD
Tomas Griebling, MD
Aditya Halthore, MD
Sam Haywood, MD
Eric Horwitz, MD
Peter Kafka
Robert J. Karnes, MD
Aaron Katz, MD
Bridget Koontz, MD
Timothy Korytko, MD
Robert Lee, MD
Anna Likhacheva, MD
Leonard Marks, MD
Shelby Moneer
Scott Morgan, MD
David Morris, MD
Steven Nordstrom
William Parker, MD
Gary Peters
Ashley Ross, MD
Kilian Salerno, MD
James Schraidt, Esq.
Randy Vince, MD
MaryBeth Westerman, MD
Jeffrey Wood

Public Commenters (Via public notice on AUA website)
Andre Abreu, MD
Mario Alvarez-Maestro, MD
Kara Babaian, MD
John Banerji, MD
Amit Bhattu, MD
Danny Darlington, MD
Joongwon Choi, MD
Eugene Cone, MD
Atreya Dash, MD
Daben Dawam, MD
Jean Fouda, MD
Maximilien Goris-Gbenou, MD
Gustavo Guimaraes, MD
Sumit Isharwal, MD
Venkates Kamaraj, MD
Sanjay Kumar, MD
Nathan Lawrentschuk, MD
Stanley Liauw, MD
Derek Lomas, MD
Kevin Lu, MD
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Maniyur Raghavendran, MD
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Martin Sanda, MD

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Vivek Sharma, MD
Hamidreza Shemshaki, MD
Kirill Shiranov, MD
Jas Singh, MD
Abhishek Solanki, MD
Akshay Sood, MD
Donald Urban, MD
Joseph Wagner, MD
Chris Wambi, MD
Michael Whalen, MD
Guobing Xiong, MD

DISCLAIMER

This document was written by the Salvage Therapy for Prostate Cancer Panel of the American Urological Association Education and Research, Inc., which was created in 2022. The PGC of the AUA selected the Panel Chair. Panel members were selected by the Panel and PGC Chair.

Membership of the panel included specialists with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis-based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the early detection of prostate cancer setting.

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses (“off label”) that are not approved by the FDA, or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not in-tended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management that are too new to be addressed by this guideline as necessarily experimental or investigational.

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