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Salvage Therapy for Prostate Cancer: AUA/ASTRO/SUO Guideline Part III: Salvage Therapy After Radiotherapy or Focal Therapy, Pelvic Nodal Recurrence and Oligometastasis, and Future Directions

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

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

Results: In a collaborative effort between AUA, ASTRO, and SUO, the Salvage Therapy for Prostate Cancer Guideline Panel developed evidence- and consensus-based guideline statements to provide guidance for the care of

ABBREVIATIONS and Acronyms

95% CI = 95% Confidence interval
ADT = Androgen deprivation therapy
AR = Androgen receptor
ARSI = Androgen receptor signaling inhibitors
ASTRO = American Society for Radiation Oncology
AUA = American Urological Association
BCR = Biochemical recurrence
CR = Clinical recurrence
CT = Computed tomography
HDR = High-dose-rate
HIFU = High-intensity focused ultrasound
IRE = Irreversible electroporation
LDR = Low-dose-rate
MDT = Metastasis-directed therapy
MRI = Magnetic resonance imaging
ORIOLE = Observation Versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer
OS = Overall survival
PET = Positron emission tomography
PFS = Progression-free survival
PSA = Prostate-specific antigen
PSMA = Prostate specific membrane antigen
RP = Radical Prostatectomy
RT = Radiation therapy
SABR = Stereotactic ablative radiotherapy
SBRT = Stereotactic body radiation therapy
SDM = Shared decision-making
STOMP = Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence
SUO = Society of Urologic Oncology
WPRT = Whole pelvic radiation therapy

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patients who experience BCR after initial definitive local therapy for clinically localized disease.

Conclusions: 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.

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

PART III of this guideline series presented recommendations on evaluation and management of suspected non-metastatic recurrence after radiotherapy and focal therapy, evaluation and management of regional recurrence, management for molecular imaging metastatic recurrence, and future directions. This summary presents those recommendations.

GUIDELINE STATEMENTS

Evaluation and Management of Suspected Non-metastatic Recurrence after Radiation Therapy (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 androgen deprivation therapy (ADT) alone.[1] BCR may also be an increasingly common 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.[2]

The rationale to document local recurrence with prostate biopsy includes the potentially significant side effects from any local salvage therapy following prior radiation treatment.[3-8] 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 (eg, if there is diffuse bilateral cancer recurrence versus isolated to a lobe or region, or if there is positive seminal vesicle involvement).[9]

Further, the increasing availability and application of positron emission tomography (PET)/computed tomography (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, high intensity focused ultrasound (HIFU), or reirradiation as part of a shared decision-making (SDM) 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 stereotactic body radiation therapy (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 staging applying conventional imaging, any local salvage therapy approach has similar ~50% long-term rates of freedom from subsequent BCR in appropriately selected patients.[3-6,10]

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 of the most common salvage treatment modalities—surgery (RP),

ablation (cryoablation and HIFU) and reirradiation (SBRT, permanent LDR brachytherapy, and temporary HDR brachytherapy)[2]—reported that 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.[11] 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.[12] The post-treatment follow-up after salvage whole-gland cryoablation or HIFU has mostly been measured applying the Phoenix definition (nadir + 2 ng/mL), which is used for RT but has not been validated in this setting.[13,14]

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.[2-4]

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.[15] 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 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.[16] Typically, "clinically significant" has been defined based on a combination of biochemical, radiographic, and histologic data following treatment.[15] 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.[17] 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.[18] 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 (refer to Part II of this series).

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.[18] 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 reirradiation may be of benefit. In this scenario, depending on the anatomic findings and again with limited evidence, options include salvage lymphadenectomy, reirradiation (eg, with stereotactic ablative radiotherapy [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%).[19] In addition, the analysis for cancer specific mortality was unadjusted for potential confounders.

A small randomized trial compared metastasis-directed therapy (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.[20] MDT in this study included nodal excision as well as SBRT to metastatic sites, and in one case lung metastasectomy. The trial enrolled patients with prostate-specific antigen (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.[21] 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, BCR and ADT-free survival following salvage bilateral extended pelvic lymphadenectomy. Clinical recurrence-free and BCR-free survival at 10-years of follow-up were 31% and 11%, respectively.[22]

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.[23] In this oligometastatic setting there have been attempts to incorporate MDT in order to minimize or delay the need for systemic therapy and prolong

progression-free survival (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.[24,25] 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.[26] Several retrospective cohort series have been primarily hypothesis-generating in terms of the potential oncologic benefit of MDT. There is a small (n = 63) study demonstrating improved PSA progression and delayed time to ADT initiation.[27] The other, a large cohort (n = 2049), showed improvement in cancer specific mortality, which was muted when a propensity-matched analysis was completed.[21]

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: 0.40-0.90). Importantly, there were no grade 2 events in the MDT group and no differences noted in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 or Global Health Scores.[20] A second randomized phase 2 trial, Observation Versus Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer (ORIOLE) trial,[28] 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 $\geq$ 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: 0.15-0.68), as well as improvements in PFS (median not reached versus 5.8 months; HR: 0.30; 95% CI: 0.11-0.81). 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: 0.29-0.66; P value $<$ .001).[29-31] 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 and/or overall survival. 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,[32] 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.[33]

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 efforts. 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 prostate-specific membrane antigen (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 androgen receptor (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.[34]

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.

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