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Salvage Therapy for Prostate Cancer: AUA/ASTRO/SUO Guideline Part II: Treatment Delivery for Non-metastatic Biochemical Recurrence After Primary Radical Prostatectomy

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Purpose: The summary presented herein covers recommendations on salvage therapy for recurrent prostate cancer intended to facilitate care decisions and aid clinicians in caring for patients who have experienced a recurrence following prior treatment with curative intent. This is Part II of a 3-part series focusing on treatment delivery for non-metastatic biochemical recurrence (BCR) after primary radical prostatectomy (RP). Please refer to Part I for discussion of treatment decision-making and Part III for discussion of evaluation and management of recurrence after radiotherapy (RT) and focal therapy, regional recurrence, and oligometastasis.

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

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

ABBREVIATIONS and Acronyms

95% CI = 95% Confidence interval
ADT = Androgen deprivation therapy
ASTRO = American Society for Radiation Oncology
AUA = American Urological Association
BCR = Biochemical recurrence
GnRH = Gonadotropin-releasing hormone
HR = Hazard ratio
LHRH = Luteinizing hormone-releasing hormone
mpMRI = Multiparametric MRI
MRI = Magnetic resonance imaging
OCM = Other-cause mortality
OS = Overall survival
PET = Positron emission tomography
PFS = Progression-free survival
PSA = Prostate-specific antigen
PSADT = PSA doubling time
PSMA = Prostate specific membrane antigen
QOL = Quality of life
RP = Radical Prostatectomy
RT = Radiation therapy
SDM = Shared decision-making
WPRT = Whole Pelvic Radiation Therapy

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Conclusions: 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.

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

PART II of this guideline series presents recommendations on treatment delivery for non-metastatic BCR after primary RP. This summary presents those recommendations.

GUIDELINE STATEMENTS

Treatment Delivery for Non-metastatic BCR after Primary RP

13. **Clinicians should offer androgen deprivation therapy (ADT) in addition to salvage radiation therapy (RT) for patients with BCR following RP and any high-risk features (eg, higher post-prostatectomy prostate-specific antigen [PSA] such as PSA ≥ 0.7 ng/mL, Gleason Grade Group 4-5, PSA doubling time [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,[1,2] RTOG 9601,[3] and NRG/RTOG 0534 SPPORT,[4] which compared salvage RT plus ADT vs salvage RT alone.

GETUG-AFU 16[1,2] 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 vs salvage RT alone. Patients were enrolled with a PSA of 0.2 to 2.0 ng/mL (median 0.30). With a median follow-up of 9.3 years, patients who received ADT with salvage RT had improved 10-year progression-free survival (PFS) (64% vs 49%; hazard ratio [HR]: 054; 95% confidence interval [CI]: 0.43-0.68; $P < .0001$) and metastasis-free survival (75% vs 69%; HR: 0.73; 95% CI: 0.54-0.98; $P = .034$). There was no difference between the cohorts in 10-year overall survival (OS) or prostate cancer-specific mortality.

Meanwhile, RTOG 9601[3] 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 vs salvage RT alone. Patients were enrolled with a PSA of 0.2 to 4.0 ng/mL (median 0.6), and the median follow-up was 13 years. The addition of ADT to salvage RT improved 12-year OS (76% vs 71%; HR: 0.77; 95% CI: 0.59-0.99), prostate cancer death (5.8% vs 13.4%; HR: 0.49; 95% CI: 0.32-0.74), metastasis (14% vs 23%; HR: 0.63; 95% CI: 0.46-0.87), second BCR (44% vs 68%; HR: 0.48; 95% CI: 0.40-0.58), local progression (1.8% vs 4.7%; HR: 0.36; 95% CI: 0.15-0.85), and disease progression (47% vs 69%; HR: 0.51; 95% CI: 0.42-0.61). 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: 0.39-0.95) and a PSA of > 1.5 ng/mL (HR: 0.45; 95% CI: 0.25-0.81), but not among patients with a PSA of < 0.7 ng/mL (HR: 1.13; 95% CI: 0.77-1.65). A secondary analysis of RTOG 9601[5] reported that there was no difference in OS between the bicalutamide arm vs 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: 1.12-3.07; $P = .02$).

NRG/RTOG 0534 SPPORT[4] randomized 1142 patients to 3 arms: (1) salvage prostate bed RT (median PSA prior to RT 0.32, range: 0.20-0.60), (2) prostate bed RT plus short-term ADT (4-6 months; median PSA prior to RT 0.40, range: 0.23-0.68), (3) prostate bed RT plus short-term ADT plus pelvic RT (median PSA prior to RT 0.32, range: 0.20-0.60). Median follow-up was 8.2 years. The addition of ADT to salvage RT was associated with decreased likelihood of progression (HR: 0.64; 97.5% CI: 0.50-0.82), biochemical failure (HR: 0.65; 97.5% CI: 0.49-0.87), local failure (HR: 0.44; 97.5% CI: 0.20-0.97), and regional failure (HR: 0.51; 97.5% CI: 0.28-0.93). Adding ADT alone (ie, arm 2 vs arm 1) did not statistically significantly improve distant metastasis, prostate cancer death, or overall mortality; however, adding ADT and pelvic RT (ie, arm 3 vs arm 1) did improve distant metastases (HR: 0.55; 95% CI: 0.35-0.85; $P = .00098$) and prostate cancer death (HR: 0.54; 95% CI: 0.29-1.00; $P = .012$).

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 (eg, ≥ 0.7 ng/mL). That said, analysis of NRG/RTOG 0534 SPPORT, using more contemporary radiation techniques and ADT

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(consisting of 4-6 months of combined androgen blockade), points toward a potential alternative PSA threshold of 0.35 ng/mL, albeit in an underpowered secondary analysis. Thus, 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).

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).[6-13] 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,[1,2] 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.[14-16] It is, however, noted that margin status is one of the more inconsistent risk indicators for benefit of addition of ADT. In this analysis, the impact of ADT on improved PFS was similar for each of these groups (low [HR: 0.47; 95% CI: 0.28-0.80] and high [HR: 0.56; 95% CI: 0.44-0.73]). This was also true when evaluating the impact of ADT on metastasis-free survival in each group (low [HR: 0.58; 95% CI: 0.29-1.17] and high [HR: 0.77; 95% CI: 0.55-1.06]).

In RTOG 9601,[3] the addition of ADT was associated with improved OS for patients with Gleason score 7 (HR: 0.69; 95% CI: 0.49-0.98) and Gleason score 8 to 10 (HR: 0.76; 95% CI: 0.44-1.30), but not in patients with Gleason score 2 to 6 (HR: 0.95; 95% CI: 0.57-1.59). This association was also observed in patients with a positive surgical margin (HR: 0.73; 95% CI: 0.54-0.98; $P = .04$).

In NRG/RTOG 0534 SPPORT,[4] the addition of ADT to RT was associated with greater benefit with regard to 8-year freedom from progression (vs RT alone) for patients with Gleason score < 8 (76% vs 64%; $P < .0001$) rather than patients with Gleason score 8 to 9 (47% vs 45%; $P = .06$). However, associations of ADT plus RT with outcomes were similar when patients were stratified according to pathology (pT2 and negative margins vs 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. 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[17] 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 the subject of ongoing cooperative group studies (eg, NRG GU006, 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.[18-20] However, if there is macroscopic disease detected, addition of ADT should generally 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[3] 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: 0.77-1.65; $P = .53$), nor in those with negative surgical margins (HR: 0.87; 95% CI: 0.53-1.41; $P = .56$) or Grade Group 1 (HR: 0.95; 95% CI: 0.57-1.59; $P = .84$). The aforementioned secondary analysis of RTOG 9601,[5] 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 from bicalutamide for patients treated with what would be considered "early" salvage RT (HR: 1.16; 95% CI: 0.79-1.70; $P = .46$). In fact, these patients experienced a 2-fold increased hazard of

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

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

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

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OCM (subdistribution HR: 1.94; 95% CI: 1.17-3.20; $P = .01$).

Given the competing risks associated with ADT, the Panel believes that patients without any high-risk features (eg, pathological or surgical Gleason Grade Group 4-5, persistently elevated post-operative PSA, seminal vesical involvement, extracapsular extension, PSADT $\leq$ 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 a shared decision-making (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, $P <$ .001), coronary heart disease (adjusted HR: 1.16, $P < .001$), myocardial infarction (adjusted HR: 1.11, $P = .03$), and sudden cardiac death (adjusted HR: 1.16, $P = .004$), per a large population-based cohort of 73,196 fee-for-service Medicare enrollees diagnosed with locoregional prostate cancer.[21] 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,[22] weight gain, and dementia.[23] These risks increase with longer-term ADT use.[23] 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,[1,2] the addition of ADT was associated with worse sexual function, although these differences disappeared at 5 years. The addition of ADT was associated with an increased risk of grade $\geq$ 2 hot flashes (8% vs 0%) and grade $\geq$ 2 hypertension (2% vs < 1%). There were no significant differences between RT vs RT + ADT in terms of urinary or bowel symptoms. Moreover, in RTOG 9601,[3] bicalutamide was associated with a higher risk of grade $\geq$ 3 gynecomastia (3.7% vs 0%) and impotence (7.5% vs 4.2%), with no difference in bladder or bowel toxicity. In NRG/RTOG 0534 SPPORT,[4] the addition of ADT to salvage RT was associated with a significant increase in acute adverse events grade $\geq$ 2 ($P < .0001$). At the same time, a secondary analysis of RTOG 9601[5] 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: 1.16-5.74; $P = .02$). 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,[21,24,25] 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,[26] with cancer-specific survival (CSS) closely related to the number of positive lymph nodes found at the time of surgery.[27-30] The only randomized trial in this specific patient population is ECOG 3886, which reported that adjuvant lifelong ADT was associated with improved CSS 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.[31] In several more recent retrospective series, the addition of RT to ADT in this patient population has been associated with improved outcomes.[32-34] One study[34] of 703 patients treated between 1986 and 2002 at 2 large academic institutions matched patients treated with ADT alone vs ADT plus RT. With a mean follow-up of 100 months, patients who received RT and ADT had improved CSS and OS at 10 years after surgery compared to ADT alone (86% vs 70%, and 74% vs 55%, respectively; $P = .004$ and $P < .001$). 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: 4-158 months). In a separate study evaluating RT + ADT in this setting compared to observation or ADT alone,[35] RT + ADT was associated with better OS than ADT alone (HR: 0.46; 95% CI: 0.32-0.55; $P <$ .0001) and observation alone (HR: 0.41; 95% CI: 0.27-0.64; $P < .0001$). The median duration of ADT when combined with RT was 5.9 years (interquartile range: 3.55-8.91). Of note, the ongoing NRG-GU008 (INNOVATE, NCT04134260) randomized trial is

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evaluating the utility of RT + GnRH agonist/antagonist for two years vs RT + GnRH agonist/antagonist + apalutamide for two 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 vs salvage therapy alone following RP.[1-4,17] 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).[1-4,17] 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. [1-4,17] With 8 to 13 years of follow-up, all 3 studies demonstrated a 40% to 60% improvement in freedom from clinical progression[1-4] 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 nine cohort studies demonstrated superior BCR-free survival and OS among patients receiving concurrent ADT and salvage RT compared to salvage RT alone.[36] The shortest durations of ADT across these three trials ranged from four to six months.[4] Even shorter durations of ADT have not been demonstrated to improve patient outcomes. As such, the Panel recommends that four to six 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.[1-4,17] 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[1,2] classification (eg, Grade Group 4-5, positive surgical margin, seminal vesicle involvement, PSADT $\leq$ 6 months).[3] 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.[3,17] 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 vs 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*)**

The best evidence to date for this question is from the NRG/RTOG 0534 SPPORT RCT.[4] 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.[37,38]

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 (4-6 months) 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: 0.27-0.94; $P = .007$) and distant metastasis (HR: 0.52; 95% CI: 0.34-0.81; $P < .001$) in arm 3 compared to arm 1. Further, 5-year freedom from progression increased by 6.1% (SE 2.2%; $P = .0027$) with the addition of pelvic lymph node RT to prostate bed RT + short-term ADT (arm 3 vs 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% vs 78%; $P = .054$) but not for those with a PSA between 1.0 and 2.0 ng/mL (61% vs 71%; $P = .24$).

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.

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The NRG/RTOG 0534 SPPORT trial[4] showed that pelvic nodal RT modestly increased any acute grade ≥ 2 adverse event (44% vs 36%; OR: 1.39; 95% CI: 1.10-1.77), any acute grade ≥ 3 adverse event (11% vs 7%; OR: 1.60; 95% CI: 1.06-2.42), acute grade ≥ 2 blood or bone marrow adverse events (5% vs 2%; OR: 3.01; 95% CI: 1.45-6.26), acute grade ≥ 3 blood or bone marrow adverse events (3% vs $< 1\%$; OR: 15.38; 95% CI: 2.03-116.85), and acute grade ≥ 2 gastrointestinal adverse events (7% vs 4%; OR: 1.76; 95% CI: 1.03-3.03). For gastrointestinal adverse events, the largest event difference between groups was mostly for diarrhea, while the difference was related to lymphopenia for blood or bone marrow events. A small difference in late grade ≥ 2 blood or bone marrow events (4% vs 2%; OR: 2.60; 95% CI: 1.23-5.47) was also reported, with the differences related to leukopenia and lymphopenia. However, overall late toxicities were not different between prostate bed RT alone vs prostate bed plus pelvic lymph node RT plus ADT ($P = .26$). 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 vs ADT alone in patients undergoing salvage RT. That said, two RCTs have compared docetaxel plus ADT vs 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 (75 mg/m^2 every 3 weeks for up to 10 cycles) with ADT for 18 months compared to ADT alone.[39] 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 vs 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, vs ADT alone (n = 250).[40] There was no statistically significant difference in PSA PFS, 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 androgen receptor (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 vs ADT alone in patients undergoing salvage RT for high-risk BCR after primary RP (primary completion estimated September 2024).[41] The EMBARK trial (NCT02319837) compares three arms: enzalutamide with ADT vs placebo with ADT vs enzalutamide monotherapy for BCR after primary RP or RT, but this study does not require salvage RT.[42] The phase 3 ECOG/ACRIN EA8191 (INDICATE, NCT04423211) study contains four arms, two of which (arms A and B) are comparing apalutamide with ADT vs 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 2 years of abiraterone acetate to ADT and primary RT for eligible patients.[43] 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.

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