How can we best manage biochemical failure after radical prostatectomy?

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Biochemical recurrence (BCR) is common after radical prostatectomy, but effective treatment options for men with BCR after curative treatment remain controversial. Although prostate-specific antigen is widely used as a surrogate marker for prostate cancer survival, it cannot fully differentiate between prostate-cancer-specific survival and overall survival. Thus, it is challenging for physicians to determine the timing of treatment to halt or slow the clinical progression of disease in patients with BCR while avoiding overtreatment for patients whose disease may not progress beyond BCR. Adjuvant therapy for radical prostatectomy or radiotherapy in intermediate- or high-risk localized prostate cancer has a benefit in terms of disease progression and survival but is not recommended in low-risk prostate cancer because of the significant adverse effects related to radiotherapy and androgen-deprivation therapy (ADT). Salvage radiotherapy (SRT) is also recommended for patients with BCR after radical prostatectomy. Several options for management of BCR after radical prostatectomy include SRT to the prostatic bed and/or pelvis, continuous or intermittent ADT, or observation. Patients’ comorbidity, preferences, and cancer-related factors must be considered when deciding the best management strategy. Modern imaging technology such as positron emission tomography imaging of prostate-specific membrane antigen-positive regions enables earlier detection of disease progression, thus enhancing decision making for future disease management.

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accepted after radical prostatectomy, the most common definition is a prostate-specific antigen (PSA) level of ≥0.2 ng/mL [1]. In case of radiotherapy, the RTOG-ASTRO Phoenix Consensus Conference recommended that a rise of ≥2 ng/mL or above the nadir PSA is considered to be the standard definition for biochemical failure [2]. Issues with the conventional determination, however, are related to the fact that BCR only means an increased PSA level without providing any evidence of metastasis in conventional imaging studies such as computed tomography (CT) or bone scan. In recent years, more accurate diagnostic methods have been introduced. The role of positron emission tomography (PET) imaging with \(^{11}C\)-choline and \(^{18}F\)-fluciclovine in evaluating patients with prostate cancer has grown in importance. Importantly, \(^{68}Ga\)-Ga-prostate-specific membrane antigen (PSMA)-11 was approved in the United States by the Food and Drug Administration in 2020 as the first \(^{68}Ga\)-radiopharmaceutical for the PET imaging of PSMA-positive prostate cancer [3]. Since then, Ga-PSMA-11 has been widely used as a new radiotracer to evaluate patients with BCR and metastasis. The combination of PET/CT and PSMA-PET imaging can improve overall survival and prostate-cancer-specific survival. Nonetheless, evidence from multiple studies suggests that BCR might include occult metastasis, implying the importance of developing more accurate detection methods of BCR for patient’s survival and quality of life.

### Table 1. Summary of management of biochemical failure after radical prostatectomy

| BCR | Definition |
|-----|------------|
|     | After RP, the most common definition is a PSA level of ≥0.2 ng/mL. |
| ADT | Immediate vs. delayed |
|     | Immediate ADT improved overall survival compared with delayed ADT. |
|     | **PSADT & Gleason score** |
|     | High-risk BCR: PSADT <10–12 months, Gleason score ≥8, BCR interval ≤18 months. |
|     | Intermediate vs. continuous |
|     | Intermediate ADT may be a good alternative because it delays androgen resistance and can improve quality of life. |
| SRT | Early SRT at low PSA levels after RP is associated with enhanced freedom from BCR and metastasis. |
|     | **Dose-intensified vs. conventional-dose SRT** |
|     | Therapeutic efficacy of dose-intensified SRT (70–72 Gy) was similar to conventional-dose SRT (60–64 Gy). |
|     | **Target volume for SRT** |
|     | Treating both the prostate bed and the pelvic lymph nodes in patients receiving SRT following RP might have potential benefit. |
| ADT with SRT | The combination of SRT and ADT or antiandrogen therapy for these patients prolongs survival. |
|     | Therefore, this combination treatment modality provides a rational approach to delay metastasis and to improve overall survival among patients with BCR. |
| Timing of SRT | There was no any clinical benefit of immediate ADT compared to early SRT. Adjuvant radiotherapy increased genitourinary toxicity and erectile dysfunction, whereas early SRT reduces overtreatment and radiotherapy-related toxicity. |

BCR, biochemical recurrence; RP, radical prostatectomy; PSA, prostate-specific antigen; ADT, androgen deprivation therapy; PSADT, PSA doubling time; SRT, salvage radiotherapy.

FACTORS INFLUENCING THE TIMING OF ADT

1. **Immediate versus delayed ADT**

   Given that survival is improved with early intervention compared with delaying until the development of symptoms or disease progression, ADT has been a well-known regimen for early intervention [8-10]. However, determining the optimal timing for ADT is challenging when patients are asymptomatic but have BCR after failure of curative local therapy. Although cure or improved survival after local curative treatment for prostate cancer is expected [11-13], BCR in an asymptomatic patient is an important clinical issue because it is highly likely that those patients will eventually present with disease progression and/or exhibit symptoms. ADT is recommended to patients with prostate cancer who have a rising PSA level after curative therapy, but the op-
timal timing for its use is still uncertain. Duchesne et al. [14] evaluated whether immediate ADT improved overall survival compared with delayed therapy (TOAD trial). They used a randomization algorithm to unbiasedly assign participants (1:1) to immediate ADT (ADT within 8 weeks) or to delayed ADT (wait at least 2 years). Immediate ADT significantly improved overall survival compared with the delayed arm in patients with BCR. However, cardiovascular adverse events were more frequent in the immediate therapy arm than in the delayed therapy arm. With respect to the TOAD trial results, physicians must discuss with patients whether to proceed with observation or ADT very seriously. Further, given that more than 40% of patients with BCR did not need management for 6 years [14], it is not entirely clear whether starting ADT at the time of BCR is more beneficial than delaying the therapeutic intervention until patients become symptomatic, metastatic, or have a PSA doubling time (PSADT) of <6 months.

2. PSA doubling time and Gleason score

The PSADT is an important factor for determining ADT after curative treatment of localized disease. Pound et al. [15] investigated the natural history of metastatic progression in patients with BCR after radical prostatectomy. There were no patients who received ADT until disease progression. Interestingly, the median time from BCR to metastasis was 8 years. Since this report, two more studies have confirmed that the PSADT is a risk factor for patient’s outcome [16,17]. But the amount of data provided by these reports was insufficient to fully confirm the PSADT as a risk factor because of the small number of patients and inappropriate adjuvant/salvage management before metastasis. Antonarakis et al. [18] performed a well-designed cohort study with long-term follow-up (since 1981). They demonstrated that risk for metastasis was the highest for patients with Gleason score ≥8 (vs. Gleason score <8) and PSADT <3 months (vs. ≥3 months). These findings lead to an interesting question: Which group of patients with BCR after radical prostatectomy have the highest risk? Most definitions of high-risk BCR include as follows PSADT <10–12 months, Gleason score ≥8, and BCR interval ≤18 months following local treatment, and additional considerations including high initial PSA and pathologic findings (seminal vesicle invasion, extraprostatic extension, and intraductal carcinoma) [19-21].

3. Intensity of ADT (intermittent vs. continuous)

Since Huggins and Hodges’s research work of 1941 [22], ADT has been the gold standard treatment for metastatic prostatic cancer. With the development of diverse forms of medical castration, however, ADT began to be used in patients with nonmetastatic prostate cancer [23-25]. The conventional method for ADT is continuous administration, with repeated depot injections to ensure testosterone deprivation [26]. However, owing to morbidity and poor quality of life, intermittent ADT has been proposed. Intermittent ADT is achieved by the cyclical administration of ADT in patients with a favorable PSA response [26]. Bruchovsky et al. [27] identified the effect of intermittent ADT on androgen-dependent cancer cells. When they applied intermittent ADT to hormone-dependent cells, the cells showed multiple apoptotic processes. Then, many researchers demonstrated that consecutive castration and exposure to androgen produces and delays onset of androgen resistance [28,29].

Although continuous ADT shows therapeutic efficacy in prostate cancer, toxicity must be considered with respect to quality of life, including sexual dysfunction, hot flashes, osteoporosis, sarcopenia, and cardiovascular adverse events [30-36]. In that sense, intermittent ADT may be a good alternative as it delays androgen resistance and can improve quality of life. Crook et al. [37] enrolled 1,386 patients with PSA greater than 3 ng/mL, and intermittent ADT was applied in 8-month cycles. Of note, the results showed that intermittent ADT is not inferior to continuous ADT and provides better quality of life scores for libido, urinary symptoms, and hot flashes [37]. Regarding several issues with intensification of ADT, along with duration of therapy (6–9 months), frequency of PSA checks, and metastatic work-up, in-depth discussion was held at the 2022 American Society of Clinical Oncology (ASCO) meeting. Intensification with abiraterone with intermittent ADT did not provide clear benefit of the combination treatment (ABICURE study in 2022 ASCO meeting), whereas the EMBARK study (enzalutamide with intermittent ADT) is still ongoing and has not yet released the results. It will be interesting to see whether the results of the EMBARK study will support the ABICURE study results or have a different outcome. Nevertheless, the above issues should be taken into consideration when choosing intermittent ADT for patients with BCR.

**SALVAGE RADIOTHERAPY**

SRT following radical prostatectomy to the prostate bed is a potentially curative option for patients with BCR [38]. Generally, patients with a PSA level ≥0.2 ng/mL are treated by SRT in multi-institutional series. Three randomized trials of adjuvant radiotherapy (ART) versus observation following radical prostatectomy demonstrated a better clinical outcome to ART in patients with positive surgical margins,
extraprosthetic extension, and/or seminal vesicle invasion [39-41]. Tendulkar et al. [42] updated a previously published multi-institutional series for SRT after radical prostatectomy and concluded that early SRT at low PSA levels after radical prostatectomy is associated with enhanced freedom from BCR and metastasis. Several points should be considered when applying SRT to patients, such as radiation dose, target volume, use of ADT with SRT, and timing of SRT.

1. Dose-intensified vs conventional-dose SRT

Although SRT has been considered to be a potentially curative treatment for BCR to the prostate bed and/or the pelvic nodes [42-44], well-designed, randomized comparative studies are lacking. Recently, the SAKK 09/10 trial was conducted to compare dose-intensified SRT with conventional SRT [45]. SAKK 09/10 was a prospective, open-label, multicenter, randomized phase 3 clinical trial of dose-intensified SRT versus conventional-dose SRT in prostate cancer patients with BCR without objective disease at 28 European hospitals. Patients with evidence of BCR (two consecutive rises in PSA with final PSA >0.1 ng/mL, or 3 consecutive rises) and PSA ≤2 ng/mL at randomization were enrolled. Radical prostatectomy was done within 12 weeks of randomization. SRT was applied to a total dose of 64 Gy in 32 fractions in the standard arm (arm A) and to 70 Gy in 35 fractions in the experimental arm (arm B). The SAKK 09/10 trial demonstrated three main findings: (1) dose-intensified SRT for BCR is not superior to conventional-dose SRT regarding freedom from biochemical progression; (2) SRT-related late genitourinary and gastrointestinal toxicities were more common in the dose-intensified SRT arm; and (3) dose intensification showed no significant impact on patients’ symptoms. Importantly, the findings of the SAKK 09/10 trial do not support earlier data from retrospective studies showing that SRT dose intensification improves prognosis [42,43,46-49]. There might be various reasons to explain such discrepancy, which may include selection bias (e.g., patients who received dose-intensified SRT), technical issues linked to radiation, and shorter follow-up period.

The TROG 0803/ANZUP RAVES trial compared ART with SRT using 64 Gy without ADT or elective radiation of the pelvic lymph nodes and reported a 5-year freedom from biochemical progression rate of 87% [50]. The trial comprised subjects with lower PSA levels than in the SAKK 09/10 cohort and the target volume for radiation (both prostate and pelvic lymph-node) was larger than in the SAKK 09/10 trial [51] potentially reducing occult micrometastatic regions in lymph nodes. Another trial including 144 patients who underwent SRT and ART compared doses of 66 and 72 Gy. The study showed no differences between the two dosages in biochemical progression-free survival or acute and late genitourinary or gastrointestinal toxicities after short-term follow-up [52].

In conclusion, the therapeutic efficacy of dose-intensified SRT was similar to that of conventional-dose SRT, but dose-intensified SRT showed more common genitourinary and gastrointestinal toxicity. To improve outcomes and reduce toxicity for patients with BCR after radical prostatectomy, future clinical trials should select patient more precisely to allow personalized SRT.

2. Target volume for SRT

Radiotherapy to the prostate bed is a standard treatment after radical prostatectomy in patients with high-risk prostate cancer [53]. Clinical trials suggest that radiotherapy for patients with a rising PSA level is recommended. It has also been validated as an adjuvant to radical prostatectomy [39-41]. A recent issue related to the target volume is whether the pelvic lymph nodes need to be included.

The SPPORT trial compared whole-pelvis with prostate-bed radiotherapy in patients with BCR after radical prostatectomy. The early findings showed improved PSA control in the whole-pelvis treatment arm [54].

PSMA PET/CT study in patients with BCR after surgery has shown that the pelvic lymph nodes are a frequent site of relapsing disease [55]. The NRG Oncology/RTOG 0534 SPPORT trial in patients receiving SRT found better results for PSA control for whole-pelvis compared with prostate-bed radiotherapy with acceptable toxicity from pelvis radiotherapy [56].

The pattern of disease progression after SRT has not been well investigated. Brand et al. [57] found that pelvic lymph nodes are a common site of recurrence in patients receiving SRT to the prostate bed. In their series, approximately 11% of patients receiving postoperative radiotherapy experienced only pelvic lymph node metastasis, but the number may increase with longer-term follow-up. These findings emphasize the potential benefit of treating both the prostate bed and the pelvic lymph nodes in patients receiving SRT following radical prostatectomy.

3. ADT with SRT

More than 30% of patients experience subsequent recurrence after radical prostatectomy [58-60]. Many data suggest that SRT after BCR may be associated with long-term disease progression [58,61]. However, half of patients receiving SRT will have further disease progression, particularly high-risk cancer [58,61-63].

The combination of SRT and ADT or antiandrogen ther-
apy for these patients prolongs survival [64-67]. Therefore, this combination treatment modality provides a rational approach to delay metastasis and to improve overall survival among patients with BCR. In randomized trials, the antiandrogenic agent bicalutamide showed efficacy against prostate cancer [67,68]. Accordingly, the NRG Oncology Radiation Therapy Oncology Group performed a randomized, double-blind, placebo-controlled trial (RTOG 9601) to investigate whether the addition of bicalutamide for 24 months during and after SRT could prolong overall survival compared with SRT plus placebo. The results showed that SRT with bicalutamide is associated with significantly lower rates of BCR and metastasis than placebo [69]. Shipley et al. [70] conducted a double-blind, placebo-controlled trial from 1998 to 2003. Seven hundred sixty patients with radical prostatectomy were enrolled; inclusion criteria were a tumor stage of T2 with a positive surgical margin or T3 with extra-capsular extension, no node-positive disease, and a detectable PSA level of 0.2 to 4.0 ng/mL. The experimental subjects underwent radiotherapy and received either antiandrogen therapy for 24 months of bicalutamide (150 mg/d) or daily placebo tablets during and after radiotherapy. The group that received antiandrogen therapy for 24 months showed significantly longer overall survival and cancer-specific survival than the placebo group, further supporting the beneficial effects of bicalutamide in patients with SRT.

Because hormonal therapy is accompanied by morbidity, such as cardiovascular adverse events, it is important to identify the role of the PSA level before SRT to reduce these adverse effects. Hess et al. [71] performed a randomized study to evaluate SRT with bicalutamide according to the pre-SRT PSA level. Overall survival benefit was observed in patients with PSA greater than 1.5 ng/mL, but not in those with PSA of 1.5 ng/mL or less. In patients with PSA of 0.61 to 1.5 ng/mL, there was an overall survival benefit associated with the antiandrogenic agent. But there was no survival benefit in those receiving early SRT (PSA <0.6 ng/mL), and an increase in cardiac and neurologic toxic effects. These findings suggest that the PSA level before SRT with antiandrogen therapy must be considered when determining the benefit of antiandrogen therapy.

The SPPORT trial was the largest international, multicenter, randomized case-control study, including 283 radiation oncology cancer centers [72]. Patients with persistently detectable or initially undetectable and rising PSA ranging from 0.1 to 2.0 ng/mL after prostatectomy were enrolled and assigned to three groups (group 1, prostate bed radiotherapy [PBRT] alone; group 2, PBRT plus short-term ADT; and group 3, pelvic lymph node radiotherapy [PLNRT] plus PBRT plus short-term ADT). Short-term ADT (antiandrogen and/or luteinizing hormone–releasing hormone agonists) was applied to the patients for 4 to 6 months. Although overall survival did not differ among the three groups, group 3 (PLNRT plus PBRT plus short-term ADT) showed better freedom from disease progression than groups 1 and 2. However, acute (<3 months after SRT) toxic events were more common in group 3 than in groups 1 and 2. The SPPORT trial demonstrated that SRT to the prostate bed adding PLNRT when combined with short-term ADT reduces meaningful disease progression after radical prostatectomy.

4. Timing of SRT

To prevent disease progression, it is critical to determine the right timing of postoperative radiotherapy. ART can be a well-accepted option for patients with high-risk localized prostate cancer even with extremely low PSA levels (e.g., PSA zero). Although ART might be more effective in terms of disease progression empirically, SRT can avoid unnecessary treatment and can reduce radiation toxicity. Decision-making for ART (PSA zero) or early (after BCR) or late (after radiological failure) SRT is very challenging and therefore is still an important issue for debate. Phase 3 randomized trials demonstrated that immediate postoperative radiotherapy to the prostate bed shows significant improvement of local control and BCR-free survival compared with deferred radiotherapy [39,73-75]. The EORTC trial 22911 was the first study demonstrating the efficacy of irradiation with respect to BCR and clinical relapse after local surgery [73] and included long-term follow-up data of immediate versus deferred radiotherapy. After more than 10 years of follow-up, the researchers reported that immediate postoperative irradiation significantly improved BCR-free survival compared with deferred treatment although clinical progression-free survival was not maintained.

The getug-17 French trial compared ART with early SRT in terms of clinical outcome and toxicity. That trial did not find any clinical benefit of immediate ART compared with early SRT. ART increased genitourinary toxicity and erectile dysfunction, whereas early SRT reduced overtreatment and radiotherapy-related toxicity [50].

Recently, the methodology in radiotherapy and ADT following prostatectomy has been evolving rapidly. The original RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery) questioned, “Is immediate postoperative radiotherapy required?” The first randomization study, called RADICALS-RT, compared ART with SRT [76]. The aim of RADICALS-RT was to identify the adequate timing of radiotherapy for patients with BCR. This trial did
not show any benefit of ART compared with SRT; on the other hand, ART increased the risk for genitourinary and gastrointestinal morbidity. Without having definite, reliable evidence supporting that ART has more benefits than harm, SRT should be the standard of care for BCR after radical prostatectomy currently.

The second randomization study investigating the optimal duration of ADT, RADICALS-HD, was done with patients for either ART or SRT. Randomization was to hormone duration of 0, 6, and 24 months of hormone therapy. The first outcome data will be reported in late 2022. It will be interesting to see whether the RADICALS-HD data provide insights into the efficacy of short-term ADT and whether short-term ADT shows similar therapeutic efficacy to 24 months of ADT.

CONCLUSIONS

BCR is common after radical prostatectomy and affects 20% to 40% of patients. Although the diagnosis of BCR is based on the PSA level, this should not be the only surrogate marker for follow-up and potential treatment. Initiation of ADT and/or SRT should be balanced with the patient’s age, comorbidities, and preferences; with potential adverse effects; and with several risk factors, such as short PSADT, high Gleason score, and short BCR interval.

When initiating ADT for BCR, intermittent ADT shows similar overall survival and improves quality of life compared with continuous ADT. When considering radiotherapy for BCR, SRT should be the standard of care after radical prostatectomy. ART is also effective in terms of disease progression, but genitourinary and gastrointestinal toxicities hamper treatment effect. Impact of PSMA PET/CT or PSMA PET/MRI on accelerating treatment decision needs further validation from more ample clinical research.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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