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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.

Keywords: Prostatectomy; Prostatic neoplasms; Radiotherapy; Recurrence; Salvage therapy

INTRODUCTION

It is informative for both urologists and patients to identify biochemical recurrence (BCR) after radical prostatectomy or radiotherapy with respect to survival and quality of life. A plethora of studies have reported the pros and cons of various therapeutic options. This review describes the diagnosis of BCR and determination process of androgen-deprivation therapy (ADT) and salvage radiotherapy (SRT). We discuss current therapeutic regimens for patients with BCR and the benefits and potential caveats of each option. Finally, we describe modern imaging techniques to detect disease progression, which will help guide decision making for future management. Table 1 summarizes the management of biochemical failure after radical prostatectomy.

DIAGNOSIS OF BCR

Numerous definitions have been proposed with respect to BCR, and among these, the following criterion is broadly

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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 ART 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.

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. PET/CT influences management planning and demonstrates a significantly higher disease detection rate than conventional imaging including CT and magnetic resonance imaging (MRI) [4-7]. Mazrani et al. [7] analyzed the literature including 20 prospective studies on ^{68}Ga- and ^{18}F-PSMA PET/CT and PET/MRI. Sensitivity of PSMA PET was 66.6% in 2,110 patients. Treatment strategy was changed in 42.7% after PET/CT. However, long-term follow-up data are lacking demonstrating whether changes in treatment strategies based on PSMA-PET imaging can improve overall 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.

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,

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extraprostatic 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 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 08.03/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 [38,61]. However, half of patients receiving SRT will have further disease progression, particularly high-risk cancer [38,61-63].

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. Dess 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

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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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AUTHORS' CONTRIBUTIONS

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REFERENCES

1. Cookson MS, Aus G, Burnett AL, Canby-Hagino ED, D'Amico AV, Dmochowski RR, et al. Variation in the definition of biochemical recurrence in patients treated for localized prostate cancer: the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel report and recommendations for a standard in the reporting of surgical outcomes. J Urol 2007;177:540-5.
2. Roach M 3rd, Hanks G, Thames H Jr, Schellhammer P, Shipley WU, Sokol GH, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965-74.
3. Hennrich U, Eder M. [^{68}Ga]Ga-PSMA-11: the first FDA-approved ^{68}Ga-radiopharmaceutical for PET imaging of prostate cancer. Pharmaceuticals (Basel) 2021;14:713.
4. Savir-Baruch B, Werner RA, Rowe SP, Schuster DM. PET imaging for prostate cancer. Radiol Clin North Am 2021;59:801-11.
5. Ekmekcioglu Ö, Busstra M, Klass ND, Verzijlbergen F. Bridging the imaging gap: PSMA PET/CT has a high impact on treatment planning in prostate cancer patients with biochemical recurrence-a narrative review of the literature. J Nucl Med 2019;60:1394-8.
6. Wang R, Shen G, Huang M, Tian R. The diagnostic role of ^{18}F-choline, ^{18}F-fluciclovine and ^{18}F-PSMA PET/CT in the detection of prostate cancer with biochemical recurrence: a meta-analysis. Front Oncol 2021;11:684629.
7. Mazrani W, Cook GJR, Bomanji J. Role of 68Ga and 18F PSMA PET/CT and PET/MRI in biochemical recurrence of prostate cancer: a systematic review of prospective studies. Nucl Med Commun 2022;43:631-7.
8. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. The Medical Research Council Prostate Cancer Working Party Investigators Group. Br J Urol 1997;79:235-46.
9. Studer UE, Whelan P, Albrecht W, Casselman J, de Reijke T,

Hauri D, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006;24:1868-76.

10. Schröder FH, Kurth KH, Fossa SD, Hoekstra W, Karthaus PP, De Prijck L, et al. Early versus delayed endocrine treatment of T2-T3 pN1-3 M0 prostate cancer without local treatment of the primary tumour: final results of European Organisation for the Research and Treatment of Cancer protocol 30846 after 13 years of follow-up (a randomised controlled trial). Eur Urol 2009;55:14-22.
11. Lu-Yao GL, Kim S, Moore DF, Shih W, Lin Y, DiPaola RS, et al. Primary radiotherapy vs conservative management for localized prostate cancer--a population-based study. Prostate Cancer Prostatic Dis 2015;18:317-24.
12. Wolff RF, Ryder S, Bossi A, Briganti A, Crook J, Henry A, et al. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. Eur J Cancer 2015;51:2345-67.
13. Amiya Y, Sasaki M, Shima T, Tomiyama Y, Suzuki N, Murakami S, et al. Long-term outcomes of nonpalpable prostate cancer (T1c) patients treated with radical prostatectomy. Prostate Int 2015;3:27-30.
14. Duchesne GM, Woo HH, Bassett JK, Bowe SJ, D'Este C, Frydenberg M, et al. Timing of androgen-deprivation therapy in patients with prostate cancer with a rising PSA (TROG 03.06 and VCOG PR 01-03 [TOAD]): a randomised, multicentre, non-blinded, phase 3 trial. Lancet Oncol 2016;17:727-37. Erratum in: Lancet Oncol 2016;17:e223. Erratum in: Lancet Oncol 2017;18:e510.
15. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999;281:1591-7.
16. Slovin SF, Wilton AS, Heller G, Scher HI. Time to detectable metastatic disease in patients with rising prostate-specific antigen values following surgery or radiation therapy. Clin Cancer Res 2005;11(24 Pt 1):8669-73.
17. Okotie OT, Aronson WJ, Wieder JA, Liao Y, Dorey F, DeKERNION JB, et al. Predictors of metastatic disease in men with biochemical failure following radical prostatectomy. J Urol 2004;171(6 Pt 1):2260-4.
18. Antonarakis ES, Chen Y, Elsamanoudi SI, Brassell SA, Da Rocha MV, Eisenberger MA, et al. Long-term overall survival and metastasis-free survival for men with prostate-specific antigen-recurrent prostate cancer after prostatectomy: analysis of the Center for Prostate Disease Research National Database. BJU Int 2011;108:378-85.
19. Virgo KS, Rumble RB, de Wit R, Mendelson DS, Smith TJ, Taplin ME, et al. Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer: ASCO guideline update. J Clin Oncol 2021;39:1274-305.
20. Lowrance WT, Breau RH, Chou R, Chapin BF, Crispino T, Dreicer R, et al. Advanced prostate cancer: AUA/ASTRO/SUO Guideline PART I. J Urol 2021;205:14-21.
21. Lowrance WT, Breau RH, Chou R, Chapin BF, Crispino T, Dreicer R, et al. Advanced prostate cancer: AUA/ASTRO/SUO Guideline PART II. J Urol 2021;205:22-9.
22. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. J Urol 2002;168:9-12.
23. Roach M 3rd, Bae K, Speight J, Wolkov HB, Rubin P, Lee RJ, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol 2008;26:585-91.
24. Horwitz EM, Bae K, Hanks GE, Porter A, Grignon DJ, Brereton HD, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol 2008;26:2497-504.
25. Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. Lancet Oncol 2010;11:1066-73.
26. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol 2017;71:630-42.
27. Bruchovsky N, Rennie PS, Coldman AJ, Goldenberg SL, To M, Lawson D. Effects of androgen withdrawal on the stem cell composition of the Shionogi carcinoma. Cancer Res 1990;50:2275-82.
28. Akakura K, Bruchovsky N, Goldenberg SL, Rennie PS, Buckley AR, Sullivan LD. Effects of intermittent androgen suppression on androgen-dependent tumors. Apoptosis and serum prostate-specific antigen. Cancer 1993;71:2782-90.
29. Sato N, Gleave ME, Bruchovsky N, Rennie PS, Goldenberg SL, Lange PH, et al. Intermittent androgen suppression delays progression to androgen-independent regulation of prostate-specific antigen gene in the LNCaP prostate tumour model. J Steroid Biochem Mol Biol 1996;58:139-46.
30. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol 2006;24:4448-56.
31. D'Amico AV, Denham JW, Crook J, Chen MH, Goldhaber SZ,

https://doi.org/10.4111/icu.20220294

Lamb DS, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. J Clin Oncol 2007;25:2420-5.
32. Spry NA, Galvão DA, Davies R, La Bianca S, Joseph D, Davidson A, et al. Long-term effects of intermittent androgen suppression on testosterone recovery and bone mineral density: results of a 33-month observational study. BJU Int 2009;104:806-12.
33. Green HJ, Pakenham KI, Headley BC, Yaxley J, Nicol DL, Mactaggart PN, et al. Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: a randomized controlled trial. BJU Int 2002;90:427-32.
34. Cherrier MM, Rose AL, Higano C. The effects of combined androgen blockade on cognitive function during the first cycle of intermittent androgen suppression in patients with prostate cancer. J Urol 2003;170:1808-11.
35. Higano C, Shields A, Wood N, Brown J, Tangen C. Bone mineral density in patients with prostate cancer without bone metastases treated with intermittent androgen suppression. Urology 2004;64:1182-6.
36. Harle LK, Maggio M, Shahani S, Braga-Basaria M, Basaria S. Endocrine complications of androgen-deprivation therapy in men with prostate cancer. Clin Adv Hematol Oncol 2006;4:687-96.
37. Crook JM, O'Callaghan CJ, Duncan G, Dearnaley DP, Higano CS, Horwitz EM, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med 2012;367:895-903. Erratum in: N Engl J Med 2012;367:2262.
38. Trock BJ, Han M, Freedland SJ, Humphreys EB, DeWeese TL, Partin AW, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA 2008;299:2760-9.
39. Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009;181:956-62.
40. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012;380:2018-27.
41. Wiegel T, Bartkowiak D, Bottke D, Bronner C, Steiner U, Siegmann A, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol 2014;66:243-50.
42. Tendulkar RD, Agrawal S, Gao T, Efstathiou JA, Pisansky TM, Michalski JM, et al. Contemporary update of a multi-institutional predictive nomogram for salvage radiotherapy after radical prostatectomy. J Clin Oncol 2016;34:3648-54.
43. Stish BJ, Pisansky TM, Harmsen WS, Davis BJ, Tzou KS, Choo R, et al. Improved metastasis-free and survival outcomes with early salvage radiotherapy in men with detectable prostate-specific antigen after prostatectomy for prostate cancer. J Clin Oncol 2016;34:3864-71.
44. Gandaglia G, Briganti A, Clarke N, Karnes RJ, Graefen M, Ost P, et al. Adjuvant and salvage radiotherapy after radical prostatectomy in prostate cancer patients. Eur Urol 2017;72:689-709.
45. Ghadjar P, Hayoz S, Bernhard J, Zwahlen DR, Hölscher T, Gut P, et al. Dose-intensified versus conventional-dose salvage radiotherapy for biochemically recurrent prostate cancer after prostatectomy: the SAKK 09/10 randomized phase 3 trial. Eur Urol 2021;80:306-15.
46. Ohri N, Dicker AP, Trabulsi EJ, Showalter TN. Can early implementation of salvage radiotherapy for prostate cancer improve the therapeutic ratio? A systematic review and regression meta-analysis with radiobiological modelling. Eur J Cancer 2012;48:837-44.
47. King CR. The timing of salvage radiotherapy after radical prostatectomy: a systematic review. Int J Radiat Oncol Biol Phys 2012;84:104-11.
48. Pisansky TM, Agrawal S, Hamstra DA, Koontz BF, Liauw SL, Efstathiou JA, et al. Salvage radiation therapy dose response for biochemical failure of prostate cancer after prostatectomy-a multi-institutional observational study. Int J Radiat Oncol Biol Phys 2016;96:1046-53.
49. Shelan M, Abo-Madyan Y, Welzel G, Bolenz C, Kosakowski J, Behnam N, et al. Dose-escalated salvage radiotherapy after radical prostatectomy in high risk prostate cancer patients without hormone therapy: outcome, prognostic factors and late toxicity. Radiat Oncol 2013;8:276.
50. Kneebone A, Fraser-Browne C, Duchesne GM, Fisher R, Frydenberg M, Herschtal A, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. Lancet Oncol 2020;21:1331-40.
51. Malone S, Croke J, Roustan-Delatour N, Belanger E, Avruch L, Malone C, et al. Postoperative radiotherapy for prostate cancer: a comparison of four consensus guidelines and dosimetric evaluation of 3D-CRT versus tomotherapy IMRT. Int J Radiat Oncol Biol Phys 2012;84:725-32.
52. Qi X, Li HZ, Gao XS, Qin SB, Zhang M, Li XM, et al. Toxicity and biochemical outcomes of dose-intensified postoperative radiation therapy for prostate cancer: results of a randomized phase III trial. Int J Radiat Oncol Biol Phys 2020;106:282-90.
53. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG,

De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618-29.

54. Reis Ferreira M, Khan A, Thomas K, Truelove L, McNair H, Gao A, et al. Phase 1/2 dose-escalation study of the use of intensity modulated radiation therapy to treat the prostate and pelvic nodes in patients with prostate cancer. Int J Radiat Oncol Biol Phys 2017;99:1234-42.
55. Han S, Woo S, Kim YJ, Suh CH. Impact of ^{68}Ga-PSMA PET on the management of patients with prostate cancer: a systematic review and meta-analysis. Eur Urol 2018;74:179-90.
56. Pollack A, Karrison TG, Balogh AG Jr, Low D, Bruner DW, Wefel JS, et al. Short term androgen deprivation therapy without or with pelvic lymph node treatment added to prostate bed only salvage radiotherapy: the NRG Oncology/RTOG 0534 SPPORT trial. Int J Radiat Oncol Biol Phys 2018;102:1605.
57. Brand DH, Parker JI, Dearnaley DP, Eeles R, Huddart R, Khoo V, et al. Patterns of recurrence after prostate bed radiotherapy. Radiother Oncol 2019;141:174-80.
58. Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990-2013. JAMA 2015;314:80-2.
59. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-13. Erratum in: N Engl J Med 2012;367:582.
60. Mullins JK, Feng Z, Trock BJ, Epstein JI, Walsh PC, Loeb S. The impact of anatomical radical retropubic prostatectomy on cancer control: the 30-year anniversary. J Urol 2012;188:2219-24.
61. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007;25:2035-41. Erratum in: J Clin Oncol 2007;25:4153.
62. Pisansky TM, Kozelsky TF, Myers RP, Hillman DW, Blute ML, Buskirk SJ, et al. Radiotherapy for isolated serum prostate specific antigen elevation after prostatectomy for prostate cancer. J Urol 2000;163:845-50.
63. Valicenti RK, Thompson I Jr, Albertsen P, Davis BJ, Goldenberg SL, Wolf JS, et al. Adjuvant and salvage radiation therapy after prostatectomy: American Society for Radiation Oncology/American Urological Association guidelines. Int J Radiat Oncol Biol Phys 2013;86:822-8.
64. Pilepich MV, Caplan R, Byhardt RW, Lawton CA, Gallagher MJ, Mesic JB, et al. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-31. J Clin Oncol 1997;15:1013-21.
65. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295-300.
66. Hanks GE, Pajak TF, Porter A, Grignon D, Brereton H, Venkatesan V, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. J Clin Oncol 2003;21:3972-8. Erratum in: J Clin Oncol 2004;22:386.
67. Iversen P, Tyrrell CJ, Kaisary AV, Anderson JB, Baert L, Tammela T, et al. Casodex (bicalutamide) 150-mg monotherapy compared with castration in patients with previously untreated nonmetastatic prostate cancer: results from two multicenter randomized trials at a median follow-up of 4 years. Urology 1998;51:389-96.
68. Tyrrell CJ, Kaisary AV, Iversen P, Anderson JB, Baert L, Tammela T, et al. A randomised comparison of 'Casodex' (bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol 1998;33:447-56.
69. Shipley WU, Hunt D, Lukka HR, Major P, Heney NM, Grignon D, et al. Initial report of RTOG 9601, a phase III trial in prostate cancer: effect of anti-androgen therapy (AAT) with bicalutamide during and after radiation therapy (RT) on freedom from progression and incidence of metastatic disease in patients following radical prostatectomy (RP) with pT2-3,N0 disease and elevated PSA levels. J Clin Oncol 2011;29(7 suppl):1.
70. Shipley WU, Seiferheld W, Lukka HR, Major PP, Heney NM, Grignon DJ, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. N Engl J Med 2017;376:417-28.
71. Dess RT, Sun Y, Jackson WC, Jairath NK, Kishan AU, Wallington DG, et al. Association of presalvage radiotherapy PSA levels after prostatectomy with outcomes of long-term antiandrogen therapy in men with prostate cancer. JAMA Oncol 2020;6:735-43.
72. Pollack A, Karrison TG, Balogh AG, Gomella LG, Low DA, Bruner DW, et al. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. Lancet 2022;399:1886-901.
73. Bolla M, van Poppel H, Collette L, van Cangh P, Vekemans K, Da Pozzo L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet 2005;366:572-8.

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74. Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009;27:2924-30.
75. Thompson IM Jr, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 2006;296:2329-35.
76. Parker C, Clarke N, Logue J, Payne H, Catton C, Kynaston H, et al. RADICALS (Radiotherapy and Androgen Deprivation in Combination after Local Surgery). Clin Oncol (R Coll Radiol) 2007;19:167-71.