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Long-term oncologic outcomes of postoperative adjuvant versus salvage radiotherapy in prostate cancer: Systemic review and meta-analysis of 5-year and 10-year follow-up data

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Purpose: To evaluate the oncologic outcomes between adjuvant radiotherapy (ART) and salvage radiotherapy (SRT) in patients with locally advanced prostate cancer or with adverse pathologic factors including positive surgical margin and high Gleason score.

Materials and Methods: We searched the literature published from January 2000 until December 2014 at MEDLINE, PubMed, Web of Science, Embase, ProQuest, and Cochrane Library. To be specific, included were studies comparing ART and SRT settings if they followed up oncologic outcomes more than 5 years.

Results: Overall, 3 retrospective, nonrandomized, observational studies, 1 matched control analysis, and 3 prospective randomized controlled studies met our inclusion criteria including a total of 2,380 patients (1,192 ART vs. 1,188 SRT). Higher favorable results were found in ART than in SRT was seen in the 5-year and 10-year biochemical recurrence (BCR)-free survival (risk ratio [RR], 0.61 and 0.70; 95% confidence interval [CI], 0.54–0.69 and 0.63–0.76). ART had a significantly higher 5-year progression-free survival rate than that in SRT (RR, 0.64; 95% CI, 0.51–0.80), but this was not the same for the 10-year progression-free survival rate (RR, 0.88; 95% CI, 0.72–1.08). There was no significant difference for the 5-year and 10-year overall survival rates between ART and SRT (RR, 0.80 and 0.94; 95% CI, 0.59–1.07 and 0.80–1.11).

Conclusions: ART showed favorable results in BCR-free survival during the 5-year follow-up period. However, the 10-year progression-free survival and overall survival did not show any difference between ART and SRT.

Keywords: Prostatic neoplasms; Adjuvant radiotherapy; Salvage therapy; Treatment outcome

INTRODUCTION

Radical prostatectomy (RP) is considered as the "gold standard" treatment of localized prostate cancer. However, when the prostate cancer cells extend beyond the prostatic fascia or invade the seminal vesicles, progression, including

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the biochemical or radiological recurrence after RP, is reported in 10%–50% [1,2]. The predictors of this progression are baseline prostate-specific antigen (PSA), positive surgical margins, Gleason score, and invasion of seminal vesicle [1]. With this, the role of postoperative radiotherapy after RP in patients with these predictors remains controversial. In addition, patient selection and exact disease staging remain undiscovered, with concerns about overtreatment of patients never destined to recur in adjuvant setting, or undertreatment of patients with unrecognized metastatic or recurred lesions in salvage setting. Moreover, the accurate timing of postoperative radiotherapy, either the adjuvant or salvage setting, remains debated.

There are a few studies about the efficacy of both settings including retrospective and prospective trials. However, efficacy varies according to each study, with most of these studies carrying the limitation of being a small-sized study with short-term follow-up periods. We systemically analyzed the efficacy between both settings in patients with the above predictors with more than a 5-year follow-up period.

MATERIALS AND METHODS

1. Search method and protocol for considering studies

We performed literature review in January 2015 to evaluate long-term postoperative oncologic results between adjuvant radiotherapy (ART) and salvage radiotherapy (SRT) in patients with locally advanced prostate cancer or with adverse pathologic factors including positive surgical margin and high Gleason score. The main sources included the database of Central, MEDLINE, PubMed, Web of Science, Embase, ProQuest, and Cochrane Library. The following terms and their combinations were used in the MeSH database—Prostatic Neoplasms, Prostatectomy, Radiotherapy, Adjuvant radiotherapy, Salvage therapy, ART, SRT—while the recruited articles were handled by manual searching to identify eligibility. Two researchers (JYK and CHL) searched the articles independently using each database. This study was conducted under PNUH-IRB approval (No. E2014118).

2. Eligibility criteria

When the researcher considers the abstract of the study as eligible, all references of the full text are reviewed. All patients should have undergone RP. The eligible criteria for the ART group were as follows: (1) less than 0.2 ng/mL of serum PSA at the start of radiotherapy; (2) postoperative radiotherapy should be performed within 6 months after operation; (3) neoadjuvant radiotherapy should not be performed; (4) patients with more than one of the following factors: 1. capsular invasion of prostate cancer cell; 2. seminal vesicle invasion; 3. lymphatic invasion; 4. high Gleason score; and 5. positive surgical margin. The radiotherapy was started more than 0.2 ng/mL of PSA for the SRT group. All patients with metastatic prostate cancer were excluded. Review articles, letters, opinions, case reports, laboratory and animal studies, and original articles with a short-term follow-up period (less than a 5-year outcome) were also excluded.

3. Type of outcome measures

We measured 5-year and 10-year biochemical recurrence-free survival (BRFS). Biochemical recurrence was defined as a detectable or rising serum PSA after RP that is more than 0.2 ng/mL with a consecutive confirmatory increasing of PSA at least 2 weeks apart after the lowest postoperative value was measured. BRFS was measured from RP to the start of any other treatment for prostate cancer. We also evaluated 5-year and 10-year progression-free survival (PFS) between ART and SRT. PFS was measured from RP to radiologic progression (computed tomography or bone scan). Finally, we analyzed 5-year and 10-year overall survival (OS). OS was measured from RP to death from any cause.

4. Data collection and analysis

Two authors (JYK and HKH) evaluated the articles independently. Disagreement between two authors was solved by discussion with an independent expert (HKH). Data from included studies were assessed the quality of by authors (CHL, JYK).

5. Statistical analysis

This systemic review was performed using Review Manager ver. 5.3 (Review Manager, The Cochrane Collaboration, Copenhagen, Denmark). Dichotomous variables were analyzed by risk ratio. We used the Mantel-Haenszel method to evaluate the risk ratio of the outcomes, and this was used as a statistical value for outcomes. The risk ratio and mean difference with a 95% confidential interval (CI) were used in the analysis. Also, I^2 statistics were used to evaluate heterogeneity. More than 75% of I^2 was defined as high statistical heterogeneity. If high heterogeneity was found, the random effects model was used, and otherwise, the fixed effects model was performed. Sensitivity analyses were performed for high-quality studies, and funnel plots were used to screen for publication bias.

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RESULTS

1. Data collection and description

A total of 7 articles including 2,380 patients (1,192 ART vs. 1,188 SRT) were finally included in this systemic review. All articles were collected as full text form from mentioned databases. All authors reviewed and agreed to the selection and quality of assessment of studies (Fig. 1).

2. Characteristics of included studies

The characteristics of each study are shown in Table 1. There are 3 recently reported randomized controlled studies and 4 retrospective studies including 1 matched-control analysis. The methodological quality was assessed by Newcastle-Ottawa scale to retrospective studies and reporting biases by the Review Manager including selection, detection, attrition, and reporting bias for randomized controlled studies [3].

3. Sensitivity analysis and publication bias

Sensitivity analysis was performed in 4 retrospective and 3 randomized controlled studies (Fig. 2). The funnel plots were symmetrical in all included studies. All included studies were inside the 95% CIs, with an even distribution around the vertical, indicating no obvious publication bias. Each funnel plot of comparison for each outcome is shown at Figs. 3, 4.

4. Five-year outcomes

All 7 studies including 2,380 patients provided data about 5-year BRFS with a 95% CI. The compressive analysis shows a significant difference between ART and SRT (RR,

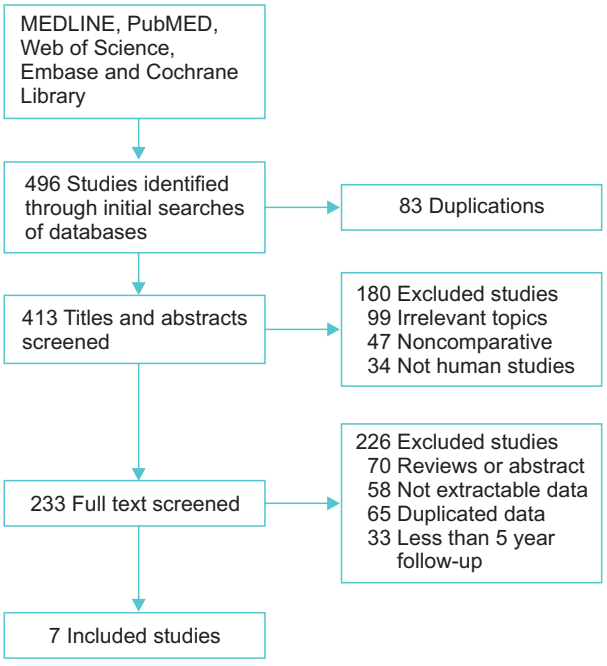

Fig. 1. Flow diagram.

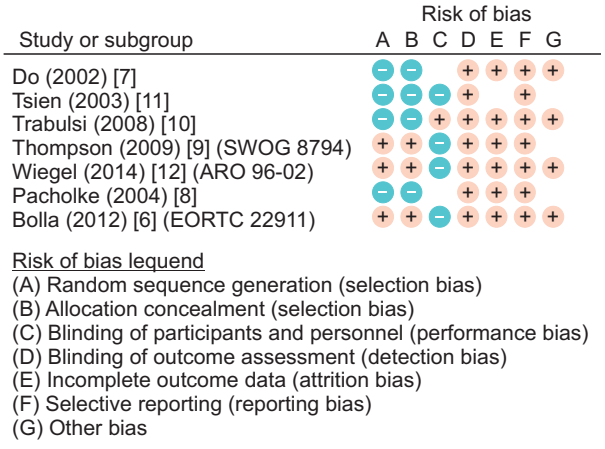

Fig. 2. Publication bias analysis of included studies.

Table 1. Characteristics of included studies

Study	Included number of patients	No. of Patients with ART	No. of patients with SRT	Follow-up period (mo), median (range)	Dose of radiation (Gy), median (range)	Type of study
Do et al. (2002) [7]	115	42	73	80.6 (20–157) for all	64.8 (59.4–68.4)	Retrospective
Tsien et al. (2003) [11]	95	38	57	116.4 (54–170.4) for ART 74.4 (12–151.2) for SRT	Median, 64.8	Retrospective
Thompson et al. (2009) [9]	425	214	211	Median, 152.4 for ART Median, 150 for SRT	Range, 60–64	Prospective
Wiegel et al. (2014) [12]	388	148	159	111.3 (2.3–167.8) for ADT 113.2 (1.3–161.4) for SRT	Median, 60	Prospective
Pacholke et al. (2004) [8]	163	107	56	70 (4–153) for all	Median, 60	Retrospective
Bolla et al. (2012) [6]	1,005	502	503	127.2 (2–199.2) for all	Median, 60	Prospective
Trabulsi et al. (2008) [10]	449	211	238	97 (30–207) for ADT 94 (26–190) for SRT	Median, 60.0 for ART Median, 64.8 for SRT	Retrospective

ART, adjuvant radiotherapy; SRT, salvage radiotherapy.

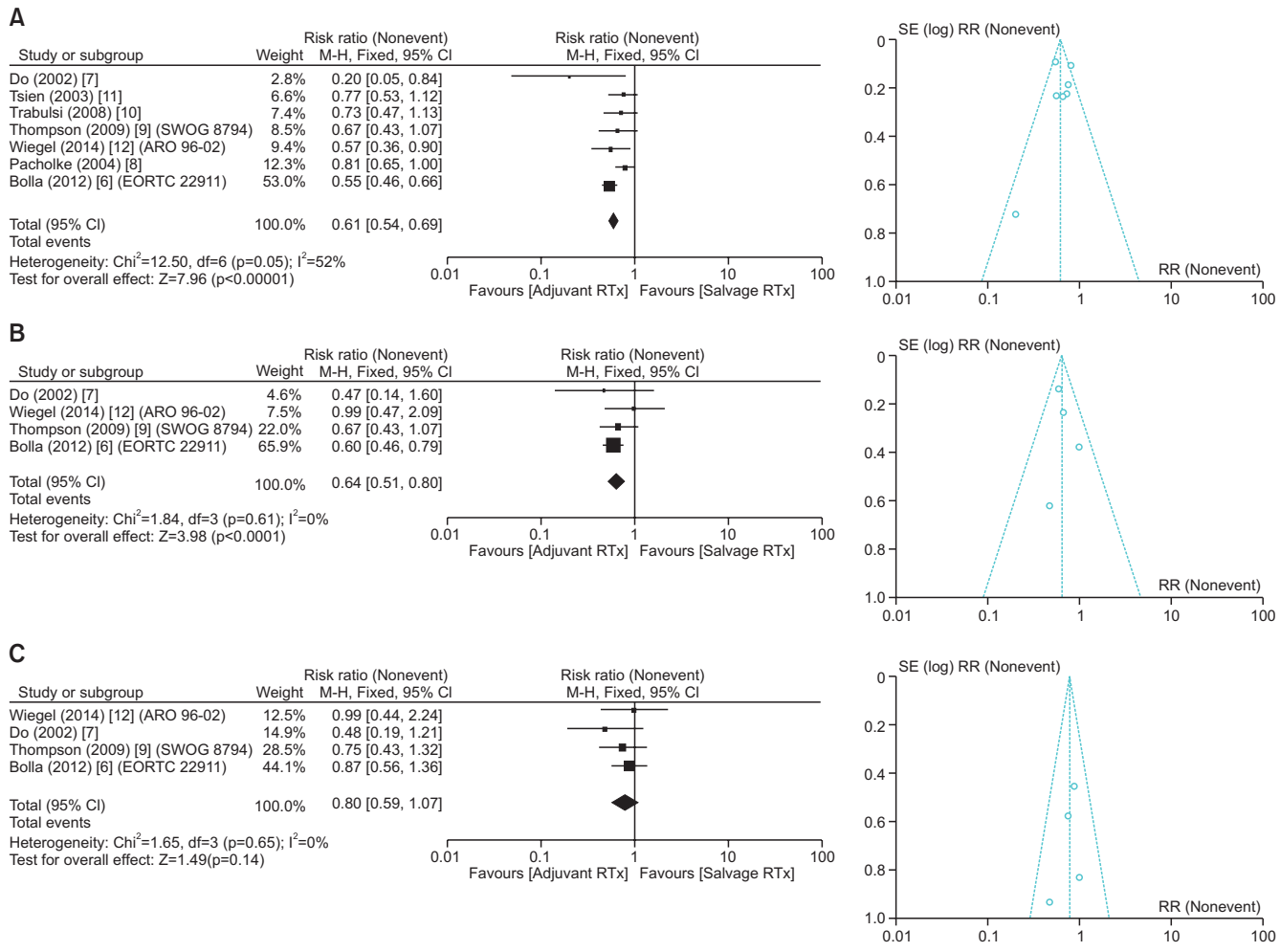

Fig. 3. Forest and funnel plots of each parameter at 5-year follow-up. (A) 5-year biochemical recurrence free survival. (B) 5-year progression free survival. (C) 5-year overall survival. M-H, Mantel-Haenszel test; CI, confidence interval; df, degree of freedom; SWOG, Southwest Oncology Group; ARO, Arbeitsgemeinschaft Radiologische Onkologie; EORTC, European Organization for the Research and Treatment of Cancer; RR, risk ratio; RTx, radiotherapy.

0.61; 95% CI, 0.54–0.69; p<0.000001; I^2=52%), which means a 39% reduction of 5-year biochemical recurrence in ART compared to SRT. We can get the 5-year PFS from 4 studies. In the meta-analysis of these studies, ART shows significant favorable results in PFS compared to SRT (RR, 0.64; 95% CI, 0.51–0.80; p<0001; I^2=0%). We analyze 5-year OS from the same 4 studies. However, there was no significant difference in 5-year OS between ART and SRT (RR, 0.80; 95% CI, 0.59–1.07; p=0.14; I^2=0%) (Fig. 3).

5. Ten-year outcomes

A total of 6 studies including 2,285 patients provided data about 10-year BRFS with a 95% CI. The systemic analysis shows a significant difference between ART and SRT (RR, 0.70; 95% CI, 0.63–0.76; p<0.00001; I^2=71%), which means a 30% reduction of 10-year biochemical recurrence in ART compared to SRT. We can obtain the 10-year PFS from 4 studies. In the comprehensive analysis of these studies, ART does not show any significant favorable results in PFS compared to SRT (RR, 0.88; 95% CI, 0.72–1.08; p=0.24; I^2=9%). We evaluate 10-year OS from the same 4 studies. There was no significant difference in 10-year OS between ART and SRT (RR, 0.94; 95% CI, 0.80–1.11; p=0.48; I^2=52%) (Fig. 4).

DISCUSSION

About one-fourths of patients who underwent RP showed biochemical or radiologic recurrence in the 10-year follow-up [4]. If the patient with high-risk factors, including high-serum PSA or pathologically local advanced (T3 or T4) or adverse pathologic factors, high Gleason score, or positive surgical margin, these patients have an increased risk of biochemical recurrence or radiologic progression in the future. There are two radiotherapeutic modalities for these high-risk patients, depending on physician belief [5]. One modality is to treat patients with high-risk factors

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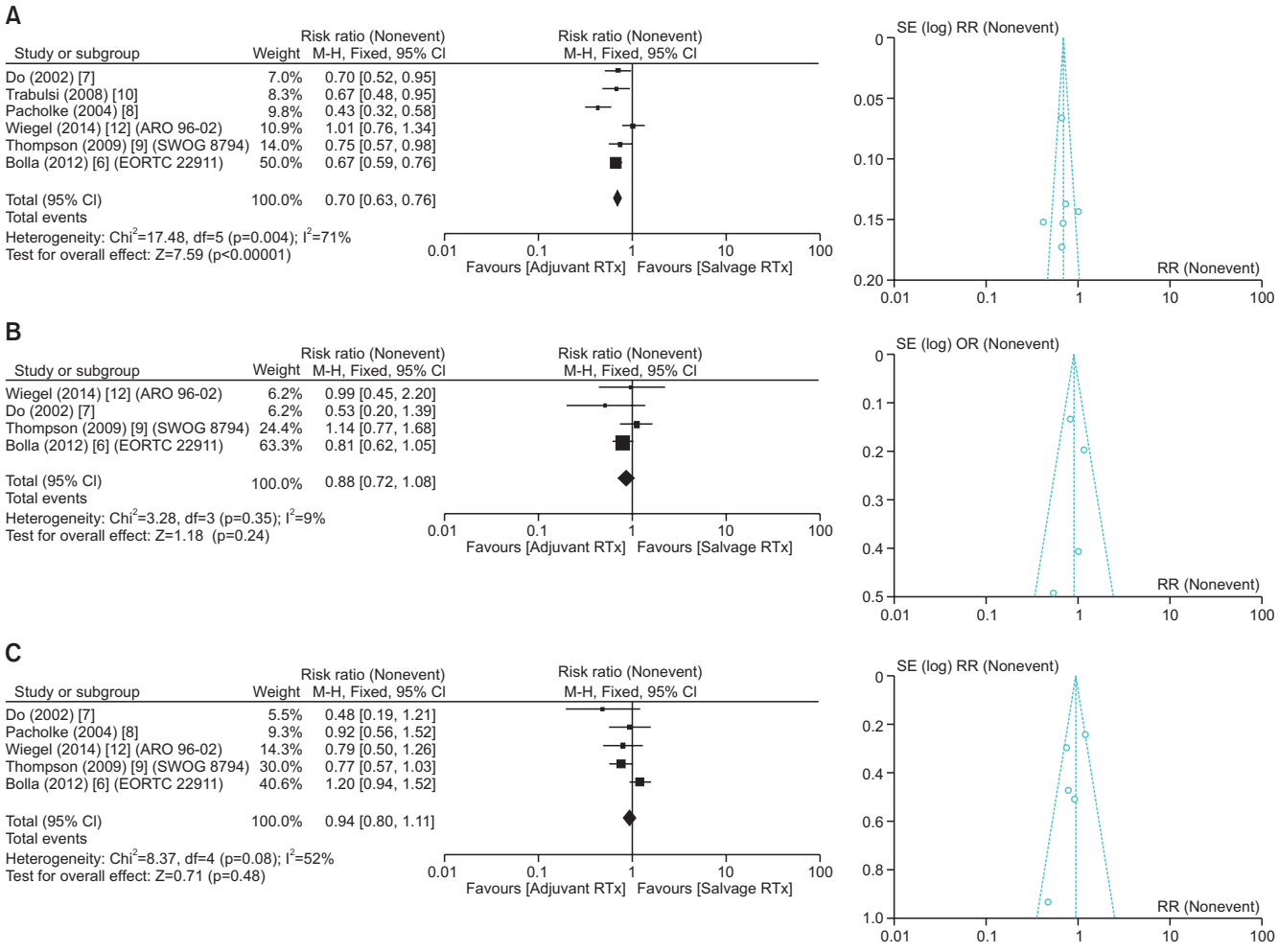

Fig. 4. Forest and funnel plots of each parameter at 10-year follow up. (A) 10-year biochemical recurrence free survival. (B) 10-year progression free survival. (C) 10-year overall survival. M-H, Mantel-Haenszel test; CI, confidence interval; df, degree of freedom; SWOG, Southwest Oncology Group; ARO, Arbeitsgemeinschaft Radiologische Onkologie; EORTC, European Organization for the Research and Treatment of Cancer; RR, risk ratio; RTx, radiotherapy.

with ART, based on pathological information of the prostatectomy specimen with an undetectable serum PSA (less than 0.2 ng/mL). The other modality is SRT, which is to closely follow up with serum PSA and perform the radiotherapy after biochemical or radiologic progression. The appropriate timing of postoperative radiotherapy, either ART or SRT, remains controversial. Although the patients can show favorable biochemical or radiologic recurrence results in the ART setting, the risk of overtreatment and toxicity of radiotherapy can pose as a problem. At the same time, although SRT may reduce the risk of overtreatment and toxicity of radiotherapy, appropriate timing of radiotherapy can be missed. This systemic review and meta-analysis included 7 studies with long-term data assessing the oncologic outcomes of both radiotherapies on 2,380 patients with high-risk prostate cancer [6-12].

Although increasing serum PSA after radiotherapy is a controversial surrogate marker for prostate cancer outcome, all the included studies showed favorable results in ART compared to SRT in 5-year and 10-year BRFS. As PSA elevation often acts as a trigger for hormone deprivation therapy, it is no surprise that a reduction in hormone deprivation therapy use of similar magnitude was also observed. Given the multiple adverse effects associated with hormone deprivation therapy, including osteoporosis, cardiovascular events, and other metabolic events, the potential hormone therapy sparing effect of ART is compelling. However, the toxicity from radiotherapy should also be considered. In current meta-analysis, ART has a reduction of risk of 39% and 31% in 5-year and 10-year BRFS, respectively, compared to SRT.

Median radiologic progression was about 6 years after radiotherapy in Southwest Oncology Group (SWOG) trial, which suggested that more than a 6-year follow-up is necessary [9]. Most of the included studies showed favorable results in ART at the 5-year follow-up. However,

unlike other studies, the Arbeitsgemeinschaft Radiologische Onkologie trial did not show any difference in the 5-year PFS. In current comprehensive analysis, 5-year PFS is better in ART compared to SRT. However, this trend did not persist in 10-year PFS between ART and SRT.

Long-term OS is the most important outcome for any cancer therapy. Prostate cancer showed a relatively indolent natural course, which anticipated that long-term (more than 5 years) follow-up is necessary to assess the postprostatectomy differences in patients with prostate cancer. We included the data from more than a 5-year follow-up in this meta-analysis. OS outcome was similar among included studies except the SWOG trial, which showed more favorable results in ART [9]. This discordance among included studies may be induced from variations in quality of surgery or unrecognized selection of the patients. However, all included studies did not show any significant difference between both settings. In addition, salvage treatment may cause different outcomes after radiotherapy. In current meta-analysis, 5-year and 10-year OS also did not show any difference in both groups.

The present systemic review has the following limitations that must be taken into account. The first limitation is that we heterogeneously recruit randomized controlled studies and retrospective studies. In retrospective studies, the initiation timing of radiotherapy is somewhat different in each study, and findings were also shown in randomized controlled studies. Recent report showed men who received SRT for a slow PSA doubling time had a risk of all-cause mortality that was not significantly different from men who underwent ART [13]. Most men who had a slow PSA doubling time had a Gleason score of less than 8 and either pT2R1 or pT3R0 disease. Therefore, the number of risk factors might act as bias in outcome between ART and SRT. The second limitation is that there is a difference in dose and modality (2-dimensional, 3-dimensional, or intensity modulated radiation therapy) of radiation compared to recent practice, which may alter oncologic outcomes. Reduced dose of radiation (less than 64 Gy) was done in European Organization for the Research and Treatment of Cancer and SWOG trial [6,9]. The third limitation is that the information about the adverse events of both RT therapies is insufficient. In OS, adverse events would be significant confounding factors for 5-year and 10-year. However, the prevalence of long-term genitourinary and gastrointestinal adverse events was uncommon [11]. Usually, the genitourinary and gastrointestinal adverse events by RT tend to late one-set. Therefore, we could estimate that the prevalence rate of adverse events of ART is higher than that of SRT. Finally, concomitant hormonal treatments were different in each studies, which also affect the result of long-term outcome between both settings.

CONCLUSIONS

This systemic review and meta-analysis showed ART showed significantly favorable results in 5-year PFS compared to SRT, but not in 10-year PFS and 5-year and 10-year OS. Therefore, postprostatectomy ART was not superior to SRT in long-term survival in patients with high-risk prostate cancer.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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