Systematic Review and Meta-Analysis

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Adding radiotherapy to androgen deprivation therapy in men with node-positive prostate cancer after radical prostatectomy

A meta-analysis

Lijuan Guo, MD[a], Zhaowei Zhu, MD[b,*], Xuepei Zhang, MD[b,*]

Abstract

Background: Several studies have tested the addition of adjuvant radiotherapy (RT) to androgen deprivation therapy (ADT) in node-positive prostate cancer (PCa) after radical prostatectomy (RP). This meta-analysis aims to assess the effects of adding RT to ADT in the treatment of PCa patients with lymph node invasion.

Methods: We systematically searched PubMed and Embase through June 2018 for human studies comparing RT plus ADT versus ADT in men with node-positive PCa after RP. The primary end point was overall survival (OS). Secondary end point was cancer-specific survival (CSS). Hazard ratios (HRs) with 95% confidence intervals (CIs) for the effects of RT plus ADT on OS and CSS were combined across studies using meta-analysis.

Results: Five studies were selected for inclusion. Overall, 15,524 patients were enrolled in the 5 studies. This included 6309 (40.6%) patients receiving ADT, 4389 (28.3%) patients receiving adjuvant RT plus ADT, and 4826 (31.1%) patients receiving observation. In lymph node-positive PCa patients, the addition of adjuvant RT was associated with improved OS (HR: 0.74; 95% CI, 0.59–0.92; $P = .008$). Moreover, the addition of adjuvant RT was also associated with a dramatic CSS improvement (HR: 0.40; 95% CI, 0.27–0.59; $P = .000$).

Conclusions: Adding RT to ADT may be a clinically effective treatment option for men with lymph node-positive PCa after RP.

Abbreviations: 3D-CRT = 3-dimensional conformal RT, ADT = androgen deprivation therapy, CIs = confidence intervals, CSS = cancer-specific survival, HRs = hazard ratios, LNI = lymph node invasion, OS = overall survival, PCa = prostate cancer, RP = radical prostatectomy, RT = radiotherapy.

Keywords: androgen deprivation therapy, lymph node invasion, prostate cancer, radical prostatectomy, radiotherapy

1. Introduction

Prostate cancer (PCa) represents the most common genitourinary malignancy in male patients and the second leading cause of cancer-related death among men in the Europe and United States.[1,2] Radical prostatectomy (RP) is an effective treatment for patients with localized PCa.[3] Large series have demonstrated that RP may be a reasonable first step in a multimodal approach for patients with high-risk and locally advanced PCa.[3–6] Given the decline in PCa screening with the PSA test, there is general concern that PCa patients with lymph node invasion (LNI) may become a larger clinical entity in the future.[7–10] Although the number of positive lymph nodes is a strong predictor of survival in PCa patients following RP,[11–15] the ideal treatment paradigm for these patients is not well defined.

PCa patients with pathological LNI were once considered to harbor a systemic disease. Thus, early androgen deprivation therapy (ADT) was regarded as the treatment of choice and have dramatically improved outcomes in node-positive PCa patients.[16,17] The idea of testing adjuvant radiation therapy (RT) in the presence of LNI came from the evidence that node-positive PCa is not always a systemic and noncurable disease.[13–15,18,19] A retrospective study reported a significant protective role for adjuvant RT in patients with PCa and nodal metastases treated with RP and extended pelvic lymph node dissection.[20] Since then, various relevant studies on this association have also been published.[21–24]

Current guidelines recommend a variety of options including observation (expectant management), ADT, or a combination of adjuvant RT and ADT.[3] The aim of this systematic review is to conduct a meta-analysis of studies which evaluated the combination of RT with ADT versus ADT alone, in node-positive

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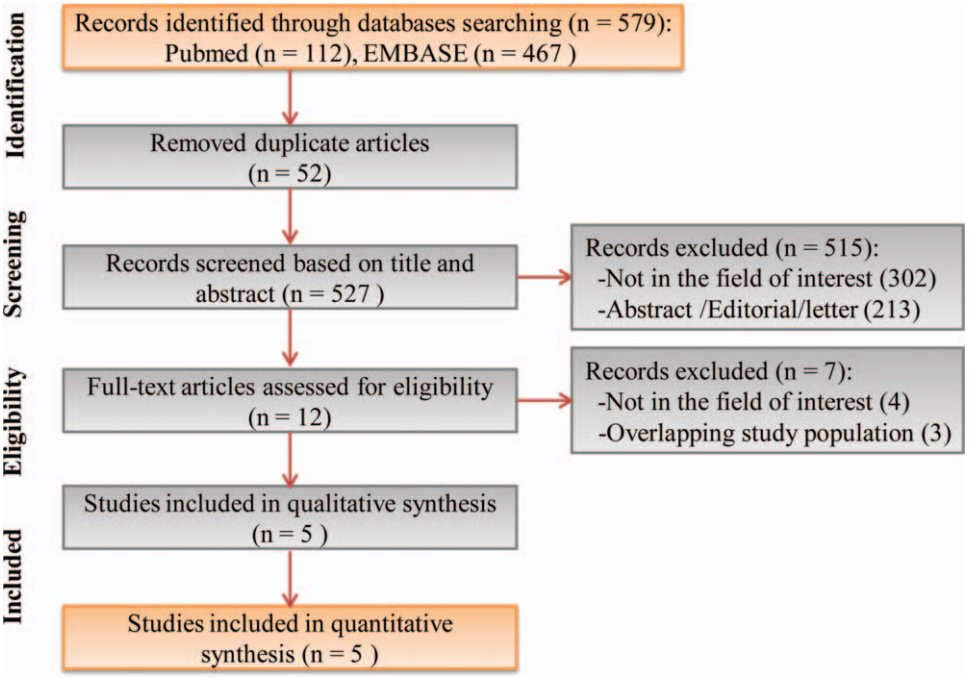

Figure 1. Flow diagram for study selection process.

PCa after RP, to assess the impact of this therapeutic option in terms of survival outcomes.

2. Methods

2.1. Identification of eligible studies

A literature search was carried out using PubMed and Embase databases in June 2018. The following terms were used: adjuvant radiotherapy, ADT, LNI, node-positive disease, PCa, and radical prostatectomy. No limitations were placed with respect to publication year. Our search was not restricted to the English language. Considering that this was a meta-analysis study, we just retrieved results from previous studies. Thus, the meta-analysis study did not involve patient consent and ethical approval was not necessary.

Two investigators independently performed study selection (GLJ and ZZW). Disagreements were settled by a third author (ZXP). Titles and abstracts were used to screen for initial study inclusion. Full-text review was used where abstracts were insufficient to determine if the study met inclusion or exclusion criteria. One author (GLJ) performed all data abstraction with independent verification performed by another author (ZZW).

Following the literature search, all duplicates were excluded. Commentaries, editorials, review articles, and those not subject to peer review were also excluded. References of relevant review articles were checked to identify additional eligible studies. In the event of multiple publications from the same study population, the most recent information was considered in the meta-analysis. To perform treatment comparisons, all studies had to include a control arm comprising treatment with ADT alone. In addition, they had to include an experimental arm which comprised adjuvant RT and ADT. Finally, only 5 retrospective cohort studies were included in this systematic review and meta-analysis.

2.2. Data collection and study quality

We used preferred reporting items for systematic reviews and meta-analyses for reporting of this systematic review and meta-analysis. For each eligible study, the following information were collected, if available:

- Main inclusion criteria: age, stage, previous treatment, Gleason score, preoperative PSA, number of lymph nodes removed and examined, number of positive lymph nodes
- Details of study treatment: type of ADT allowed, RT technique, timing of treatment
- Study design: primary end point, secondary end point, study hypothesis
- Patients enrollment and follow-up: date of start and date of end of accrual; number of patients assigned to control arm (ADT alone), number of patients assigned to experimental arm (adjuvant RT and ADT), median follow-up
- Overall survival (OS): number of deaths in each arm, median OS, hazard ratio (HR) with 95% confidence interval (CI)
- Cancer-specific survival (CSS): number of events in each arm, median CSS, HR with 95% CI

2.3. Statistical methods

Primary end point of the study was OS. Secondary end point was CSS. For both OS and CSS, the summary measure was HR (with 95% CI). Touijer et al demonstrated that adjuvant RT + ADT was associated with better CSS than observation or ADT alone. We used the method of Song et al[25] to perform the indirect treatment comparison between adjuvant RT + ADT and ADT alone. CIs are widely used in reporting statistical analyses of research data, and are usually considered to be more informative than *P*-values from significance tests. However, 2 published articles reported estimated

Table 1

Characteristics of the 5 trials included in the meta-analysis.

	Da PLF 2009	Briganti A 2011	Touijer KA 2018	Abdollah F 2018	Gupta M 2018
Main inclusion criteria					
Stage	PCa patients with LNI	pT2–4 pN+ M0 PCa patients	PCa patients with LNM	pN1 M0 PCa patients	PCa patients with LNM
Previous treatment	RP and ePLND	RP and PLND	RP and ePLND	RP and PLND	RP and PLND
Treatment					
ADT (both arms)	LHRH analogue	Orchiectomy, LHRH agonist or antiandrogen	Bilateral orchiectomy or LHRH agonist	NA	Medical or surgical hormonal suppression
RT (experimental arm)	Prostatic bed 26%; pelvis plus prostatic bed 74%	Whole-pelvis and prostatic bed	Whole-pelvis	The pelvis was included for 78% of these patients	Prostatic bed and pelvic lymph nodes
Timing of treatment	NA	RT: within 3 mo after surgery; ADT: immediately after RP	Within 6 mo of surgery	With 1 yr from surgery	NA
Study design					
Primary endpoint	BCR-free survival	CSS	OS	OS	OS
Seconday endpoint	CSS	OS	CSS	NA	NA
Hypothesis	An early combination of RT and HT might improve long-term outcomes	Combination of RT plus HT might improve the CSS and OS of patients with LNI	NA	NA	NA
Patient enrollment and follow-up					
Accrual start	January 1988	September 1988	1988	2004	2004
Accrual stop	December 2007	January 2003	2010	2015	2013
No. of patients	250	364	1338	5498	8074
ADT alone	121	247	676	3200	2065
ADT plus RT	129	117	325	2298	1520
Median follow-up	91.2 mo	95.1 mo	69 mo	49 mo	48 mo

ADT = androgen deprivation therapy, BCR = biochemical recurrence, CSS = cancer-specific survival, ePLND = extended pelvic lymph node dissection, HT = hormonal therapy, LHRH = luteinizing hormone-releasing hormone, LNI = lymph node invasion, LNM = lymph node metastasis, NA = no available, OS = overall survival, PCa = prostate cancer, RP = radical prostatectomy, RT = radiotherapy.

Table 2

Main characteristics of enrolled patients.

Da PLF 2009	Briganti A 2011	Touijer KA 2018	Abdollah F 2018	Gupta M 2018
Age (yr)				
ADT alone:	ADT alone:	ADT alone:	ADT alone:	ADT alone:
Median 67.6 yr	Median 66.7 yr	Median 66 yr	Median 63.0 yr	Median 62.01 yr
(Range: 51–80)	(Range: 47–80)	(IQR: 60–70)	(IQR: 57.0–68.0)	(IQR: 57–67)
ADT and RT:	ADT and RT:	ADT and RT:	ADT and RT:	ADT and RT:
Median 65 yr	Median 65 yr	Median 65 yr	Median 61.0 yr	Median 60.08 yr
(Range: 47–80)	(Range: 48–72)	(IQR: 59–69)	(IQR: 56.0–66.0)	(IQR: 55–65)
Gleason score				
ADT alone:	ADT alone:	ADT alone:	ADT alone:	ADT alone:
Gleason $\leq$6 26.4%	Gleason $\leq$6 9.3%	Gleason6 18%	Gleason2–6 0.5%	Gleason 6 0.9%
Gleason 3+4 27.3%	Gleason 7 58.3%	Gleason7 50%	Gleason7 32%	Gleason 3+4 13.6%
Gleason 4 + 3 19.0%	Gleason 8–10 32.4%	Gleason 8–10 33%	Gleason 8–10 67%	Gleason 4 + 3 20.1%
Gleason 8–10 29.8%				Gleason 8 17.3%
				Gleason 9–10 44.5%
				Missing 3.6%
ADT and RT:	ADT and RT:	ADT and RT:	ADT and RT:	ADT and RT:
Gleason $\leq$6 16.3%	Gleason $\leq$6 9.4%	Gleason6 10%	Gleason2–6 0.3%	Gleason 6 0.5%
Gleason 3 + 4 23.2%	Gleason 7 53.8%	Gleason 7 43%	Gleason7 37%	Gleason 3 + 4 14.9%
Gleason 4+ 3 21.7%	Gleason 8–10 36.8%	Gleason 8–10 47%	Gleason 8–10 62%	Gleason 4 + 3 20.8%
Gleason 8–10 36.4%				Gleason 8 16.4%
				Gleason 9–10 43.6%
				Missing 3.9%
Preoperative PSA				
ADT alone:	ADT alone:	ADT alone:	ADT alone:	ADT alone:
Median 15	Median 18.5	Median 14	Median 11.2	$<$4 8.7%
(range: 4.9–103)	(range: 1.6–616)	(IQR: 8–27)	(IQR: 6.6–24.0)	4–10 36.0%
				10–20 24.9%
				20+ 25.4%
				Missing 5.1%
ADT and RT:	ADT and RT:	ADT and RT:	ADT and RT:	ADT and RT:
Median 16	Median 19.5	Median 15	Median 10.2	$<$4 9.9%
(range: 2.8–148)	(range: 2.8–321)	(IQR: 8–31)	(IQR: 6.0–20.4)	4–10 39.2%
				10–20 23.0%
				20+ 24.5%
				Missing 3.4%
Stage				
ADT alone:	ADT alone:	ADT alone:	ADT alone:	ADT alone:
pT2 a/b/c 13.2%	pT2 a/b/c 1.6%	pT2/pT3a 37%	pT2/pT3a 36%	pT2 12.7%
pT3a 19.8%	pT3a 8.5%	pT3b 59%	pT3b 59%	pT3 81.9%
pT3b 57.0%	pT3b 84.6%	pT4 4.0%	pT4 5.3%	pT4 5.4%
pT4 9.9%	pT4 5.3%			
ADT and RT:	ADT and RT:	ADT and RT:	ADT and RT:	ADT and RT:
pT2 a/b/c 3.9%	pT2 a/b/c 2.6%	pT2/pT3a 22%	pT2/pT3a 32%	pT2 8.9%
pT3a 10.9%	pT3a 8.5%	pT3b 63%	pT3b 63%	pT3 84.9%
pT3b 64.3%	pT3b 79.5%	pT4 14%	pT4 4.8%	pT4 6.3%
pT4 20.9%	pT4 9.4%			
Number of lymph nodes removed and examined				
ADT alone:	ADT alone:	ADT alone:	ADT alone:	NA
Median 15	Median 13	Median 12	Median 10.0	
(range: 3–44)	(range: 2–33)	(IQR: 9–17)	(IQR: 6.0–16.0)	
ADT and RT:	ADT and RT	ADT and RT	ADT and RT	NA
Median 16	Median 14	Median 17	Median 9.0	
(range: 5–52)	(range: 2–32)	(IQR: 12–22)	(IQR: 5.0–15.0)	
Number of positive lymph nodes				
ADT alone:	ADT alone:	ADT alone:	ADT alone:	ADT alone:
Median 1	Median 2	1 54%	Median 1.0	1 49.6%
(range: 1–31)	(Range: 1–19)	2 21%	(IQR: 1.0–3.0)	2 22.2%
		3+ 24%		3+ 26.7%
				Unknown 1.4%
ADT and RT:	ADT and RT:	ADT and RT:	ADT and RT:	ADT and RT:
Median 2	Median 2	1 43%	Median 1.0	1 60.5%
(range: 1–14)	(range: 1–10)	2 25%	(IQR: 1.0–2.0)	2 18.4%
		3+ 32%		3+ 18.9%
				Unknown 2.2%

ADT = androgen deprivation therapy, IQR = interquartile range, NA = no available, PSA = prostate specific antigen, RT = radiotherapy.

Table 3

Cancer-specific and overall survival data reported in each single trial.

	Da PLF 2009[19]	Briganti A 2011[20]	Touijer KA 2018[21]	Abdollah F 2018[22]	Gupta M 2018[23]
No. of patients					
ADT alone	121	247	676	3200	2065
ADT plus RT	129	117	325	2298	1520
No. of events					
ADT alone	37 (both arms)	NA	NA	NA	363
ADT plus RT		NA	NA	NA	184
Survival rates					
ADT alone	CSS 5 yr 81.4% 8 yr 73.5% 10 yr 71.8%	CSS 5 yr 88% 8 yr 78% 10 yr 70%	NA	OS 8 yr Low risk 83% Intermediate risk 64% High risk 49% Very high risk 55%	OS 5 yr 88.1% 10 yr 67.5%
ADT plus RT	CSS 5 yr 88.4% 8 yr 85.2% 10 yr 70.3%	CSS 5 yr 95% 8 yr 91% 10 yr 86%	NA	OS 8 yr Low risk 75% Intermediate risk 71% High risk 70% Very high risk 56%	OS 5 yr 90.8% 10 yr 74.0%
Median survival, mo					
ADT alone	Not reached	Not reached	NA or not reached	NA or not reached	Not reached
ADT plus RT	Not reached	Not reached	Not reached	Not reached	Not reached
HR (95%CI)					
ADT plus RT vs ADT only	CSS: 0.38 (0.18–0.79)	CSS: 0.4 (0.21–0.75)	OS: 0.46 (0.32–0.66) CSS: 0.41 (0.21–0.79)	OS: Low risk 1.37 (0.84–2.25) Intermediate risk 0.75 (0.62–0.91) High risk 0.57 (0.38–0.86) Very high risk 0.92 (0.61–1.41)	OS: 0.76 (0.63–0.93)

ADT = androgen deprivation therapy, CSS = cancer-specific survival, NA = no available, OS = overall survival, RT = radiotherapy.

effects and *P*-values, but do not give CIs.[20,21] Thus, we used the method of Altman et al[26] to obtain the CIs.

In assessing heterogeneity among studies, we used the Cochran *Q* test and I^2 statistics. For the Q statistic, a *P*-value of less than .10 was used as an indication of the presence of heterogeneity; for I^2, a value >50% was considered a measure of severe heterogeneity. All statistical analyses were performed using STATA, version 11.0 (STATA, College Station, TX,). A 2-tailed *P*-value of less than .05 was considered to be statistically significant.

3. Results

We conducted the meta-analysis following the PRISMA statement guidelines.[27] The selection process of studies eligible for the meta-analysis is reported in Figure 1. Our literature search identified 579 unique references. After a full text review of 12 manuscripts, we identified 5 relevant studies.

3.1. Characteristics and quality of the studies

Table 1 lists the main characteristics of the 5 studies included in the meta-analysis. ADT in both arms consisted of orchiectomy, luteinizing hormone releasing hormone agonist, and/or androgen blockade. RT consisted of local radiation to the prostatic bed, pelvic lymph nodes area or whole-pelvis. Adjuvant ADT and RT were usually started immediately after RP or within 3 to 12 month after surgery. The protocols and methods of all included studies were reviewed and generally deemed to be low risk of bias with adequate randomization.

3.2. Patient characteristics

Overall, there were 15,524 patients included in the 5 studies. This included 6309 (40.6%) patients receiving ADT, 4389 (28.3%) patients receiving ADT plus RT, and 4826 (31.1%) patients receiving observation. Patients were enrolled in these studies between 1988 and 2015 (Table 1). The main characteristics of these patients receiving ADT or ADT plus RT are described in Table 2. The median age ranged from 60.08 to 67.6 years, and men in the adjuvant ADT group were older. There were several differences between the 5 studies. Touijer et al reported that men receiving ADT + RT had higher rates of Gleason score (8–10) and higher pathologic state than men receiving ADT only.[22] However, Briganti et al observed no significant differences in terms of pre- and postoperative characteristics between patients receiving ADT or ADT plus RT.[21] The 2 groups of patients were comparable with regard to number of lymph nodes removed and number of positive lymph nodes.

Table 3 summarizes the number of patients and survival data reported in each study. Overall, 10,698 patients were included for the main comparison (ADT vs ADT plus RT). However, only 1 study provided number of deaths in each group,[24] and most patients who received ADT or ADT plus RT have not reached median survival.

3.3. Overall survival

As shown in Figure 2A, the addition of RT to ADT in node-positive PCa patients was associated with a statistically significant OS benefit (HR: 0.74; 95% CI, 0.59–0.92; $P = .008$). There was significant heterogeneity among the 3 studies ($P = .009$, $I^2 = 67.4\%$) (Fig. 2A).

3.4. Cancer specific survival

As shown in Figure 2B, the addition of RT to ADT in node-positive PCa patients was associated with a statistically significant benefit in CSS (HR: 0.40; 95% CI, 0.27–0.59;

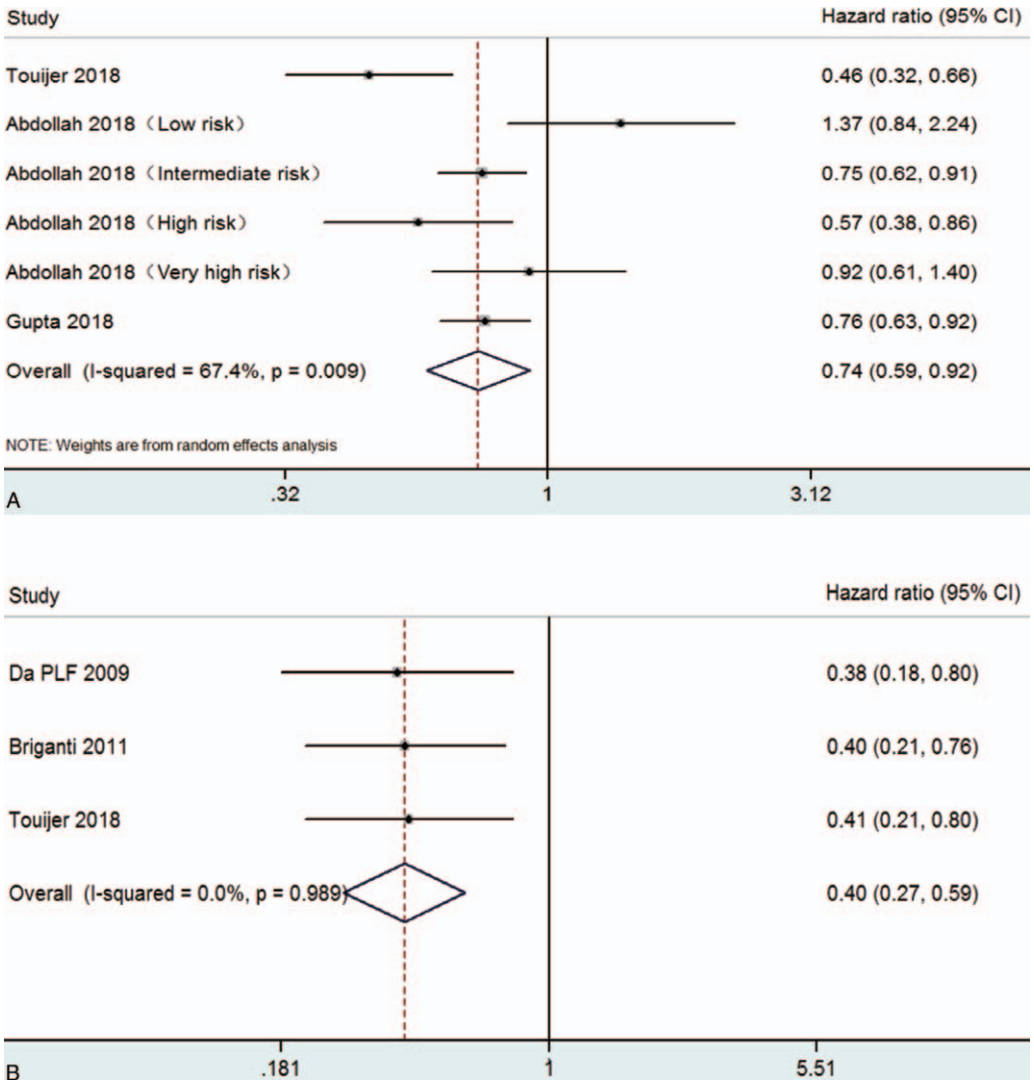

Figure 2. Forest plot for meta-analysis of combination of radiotherapy (RT) with androgen deprivation therapy (ADT) versus ADT alone in men with node-positive prostate cancer after radical prostatectomy: (A) Overall survival; (B) Cancer-specific survival.

$P = .000$) without significant heterogeneity among the 3 studies ($P = .989$; $I^2 = 0.0\%$) (Fig. 2B).

4. Discussion

Although the diagnosis of PCa has shifted to early clinical stages in the PSA era, lymph node metastases are indeed still diagnosed in a wide range of patients.[19,28–30] Controversy exists regarding the optimal treatment for patients with node-positive PCa after RP, and most patients are typically treated according to their physician's preferences or institutional practice patterns.

This meta-analysis shows that the addition of adjuvant RT to ADT in patients with lymph node-positive PCa contributes to a dramatic improvement in OS and CSS. A quantitative synthesis of the available evidence on this treatment strategy can be really helpful for clinical decisions. To the best of our knowledge, this meta-analysis represents the first synthesis of all the evidence produced to date.

Our meta-analysis shows an OS and CSS improvement that are not only statistically significant but also clinically relevant. The addition of adjuvant RT to ADT is associated with a 26% reduction in the risk of death from all causes (HR: 0.74), and the reduction in the risk of death from PCa is 60% (HR: 0.40). The efficacy demonstrated by adjuvant RT plus ADT in patients with lymph node-positive PCa is not surprising. Previous randomized studies have observed a positive impact of adjuvant RT in patients with locally advanced PCa.[31–33] Thompson et al reported that RT resulted in significantly reduced risk of PSA relapse and disease recurrence in men who had undergone RP for pathologically advanced PCa.[32] Bolla and colleagues found that immediate external irradiation after RP improves biochemical progression-free survival and local control in patients with positive surgical margins or pT3 PCa who are at high risk of progression.[31] Therefore, adjuvant RT would contribute to optimizing local control and preventing distant metastases and death.[31–34]

Noteworthy, details of the RT treatment were different among the 5 studies.[20–24] Da Pozzo LF stated that 34 patients received irradiation of the prostatic bed only (median dose: 66.6 Gy), while the other 95 patients also received pelvis irradiation

(median dose 66.6 Gy). The template of adjuvant RT was generally determined by the treating radiotherapist, and a 3-dimensional conformal RT (3D-CRT) approach was used in 55.8% of the patients.[20] In another study, adjuvant RT consisted of local radiation to the prostatic seminal vesicle bed and pelvic lymph nodes area (whole-pelvis RT) with a median dose of 68 Gy. All patients were treated with a 3D-CRT approach or intensity-modulated RT.[22] Despite the differences in RT techniques, combination of adjuvant RT and ADT significantly improved OS and CSS, reinforcing the need for a multimodal approach in PCa patients with LNI.

It has been widely accepted that not all PCa patients with LNI are at a uniform risk of cancer recurrence and death. Cheng reported that patients with a single nodal metastasis appeared to have long-term outcomes as favorable as those without nodal involvement.[35] Noteworthy, patients with high-volume nodal disease have significantly inferior survival rates compared to patients with lower volume of LNI, regardless of adjuvant treatment administration.[12,14,15,35,36] However, whether adjuvant RT + ADT was effective in preventing progression and recurrence according to the extent of nodal invasion was not available in the present meta-analysis.

Using a previously developed algorithm,[37] Touijer et al divided PCa patients into 5 groups and found that around 25% of the patients treated with RT + ADT would not benefit from adjuvant RT. These consisted of either patients who have locally limited disease (<pT3a disease with negative margins and less than or equal to 2 positive nodes) and thus have a good disease control with surgery alone or those with extensive LNI disease (more than 4 positive nodes) who probably harbor a systemic disease beyond the reach of local control at the time of surgery.[22] In another recent study, Gupta M also observed that the use of adjuvant RT + ADT did not confer significant OS benefit in up to 30% of patients without high-risk features, who may be managed with observation and forego the morbidity associated with immediate ADT or radiation.[24] The identification of important risk factors for disease progression may help risk-stratify and individualize treatments for this heterogeneous group of node-positive PCa patients and warrants further investigation in prospective randomized controlled studies.[14]

There are some limitations in our meta-analysis and some important caveats have to be stressed for data interpretation. First, the included studies were retrospective in nature, and there might be partial overlapping of the study populations. Synthesizing data from predominantly retrospective studies may overestimate the pooled estimates. However, prospective randomized data which investigates the impact of adjuvant RT in node-positive PCa patients are not available. Second, the use of published aggregate data compared with individual patient data meta-analysis limits the ability to perform meaningful analysis of subgroup effects or of effect modification. Third, no standardized template and doses of adjuvant RT were used for all patients. Fourth, the type of adjuvant ADT was not standardized, and its duration was extremely heterogeneous among different studies. Finally, inherent in any meta-analysis of published data is the possibility of publication bias, that is small studies with null results tend not to be published.

5. Conclusions

Our meta-analysis clearly shows a significant impact on OS and CSS with the concomitant administration of adjuvant RT and ADT in patients with lymph node-positive PCa. These findings may provide guidance to patients and clinicians when making treatment decisions and may help inform the design of future comparative studies. Future work should focus on risk stratification and identifying which patients are most likely to benefit from combination treatment.

Author contributions

The research project was designed by Zhaowei Zhu and Xuepei Zhang; organized and executed by Lijuan Guo and Zhaowei Zhu. The first draft of the manuscript was written by Lijuan Guo, and the manuscript was reviewed and critiqued by Zhaowei Zhu and Xuepei Zhang. All authors read and approved the final manuscript.

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