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Adjuvant Chemotherapy in High-Risk Prostate Cancer Patients after Primary Local Therapy: Recurrence, Metastasis, and Survival – A Meta-Analysis

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Keywords
Prostate cancer · Docetaxel · Meta-analysis · High risk

Abstract
Context: Several randomized clinical trials (RCTs) have recently tested adjuvant chemotherapy to high-risk prostate cancer patients (PCA) after primary local therapy. ***Objective:*** The aim of the study was to perform a systematic review and meta-analysis of RCTs evaluating the adjuvant chemotherapy in high-risk prostate cancer patients after primary local therapy. The primary endpoint was overall survival (OS). The secondary endpoint was disease-free survival (DFS) and biochemical recurrence-free survival (BRFS). ***Methods:*** A systematic review of PubMed/Medline, Embase, and Cochrane databases was performed to identify relevant studies published in English up to March 2020. Six trials were selected for inclusion. ***Results:*** There were 7 studies included in the present study. The meta-analysis did not show a significant OS benefit from adjuvant chemotherapy in patients with high-risk prostate cancer after primary local therapy (hazard ratio [HR]: 0.87; 95% confidence interval [CI], 0.72–1.05; p = 0.15). But docetaxel in patients with high-risk prostate cancer after primary local therapy was associated with a slightly OS improvement (HR: 0.79; 95% CI, 0.63–0.98; p = 0.03). It also did not show a significant benefit in DFS and BRFS in patients with high-risk prostate cancer (HR: 0.89, 95% CI, 0.75–1.06, p = 0.18; HR: 0.85, 95% CI, 0.69–1.06, p = 0.16). ***Conclusions:*** This meta-analysis shows a slightly OS benefit from docetaxel in patients with high-risk prostate cancer after primary local therapy. It did not show a significant benefit in DFS and BRFS from adjuvant chemotherapy in patients with high-risk prostate cancer.

Introduction

Although the treatment of prostate cancer has improved significantly, it still ranks the second in American men's malignant tumors, resulting in 29,430 deaths in 2018 [1]. About 15–30% of prostate cancer patients after primary local therapy are at risk of PSA recurrence [2, 3]. Patients with an increased PSA level after prostate cancer surgery face greater risk of metastasis [4]. The definition

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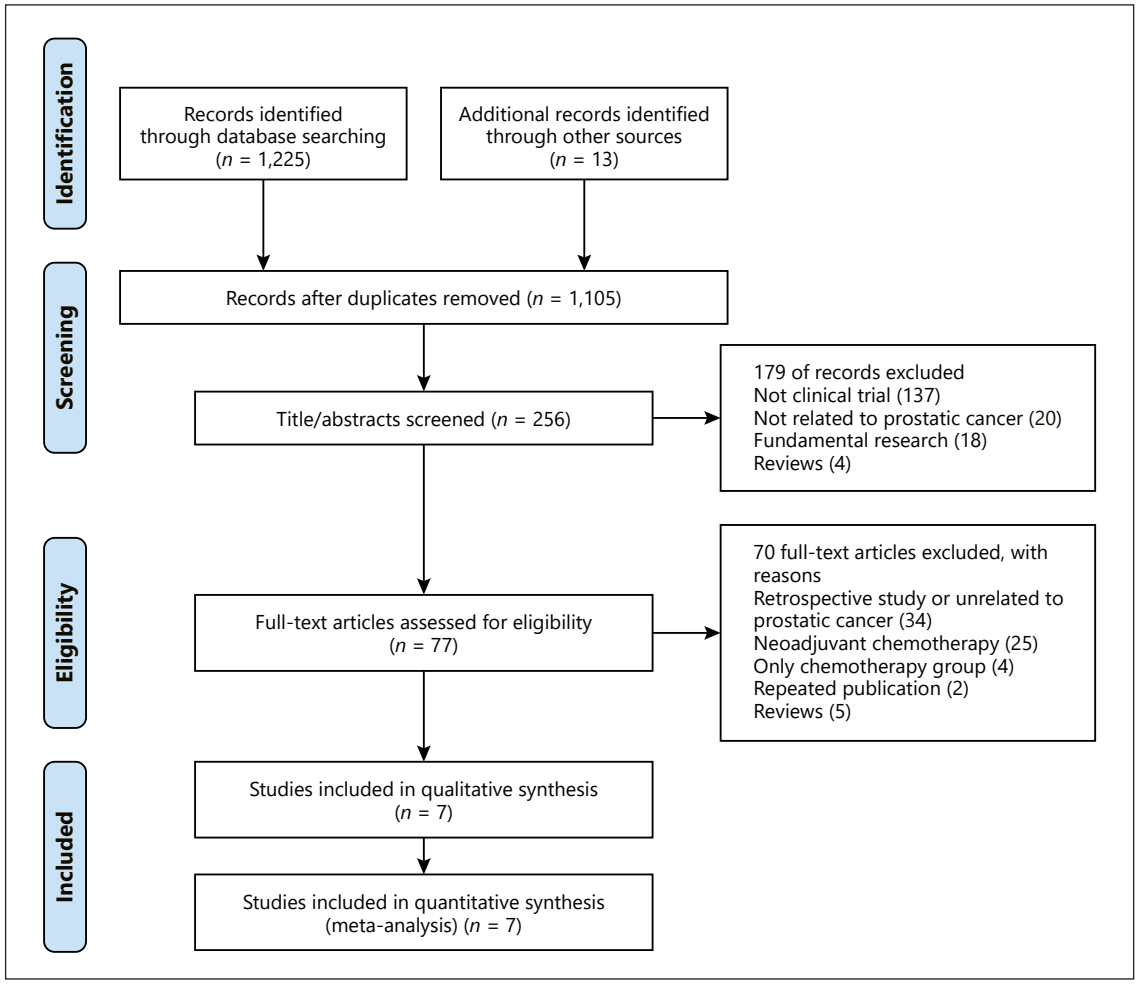

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Fig. 1. PRISMA flowchart for study selection. RCT, randomized controlled trial. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

of high-risk prostate cancer is that the Gleason score is between 8 and 10, with positive surgical margin, and PSA >20 ng/mL; the tumor stage is pT3b or pT4; or pathological node positive [5]. In previous studies, androgen deprivation therapy by medical or surgical castration is a treatment for advanced or metastatic prostate cancer because the androgen receptors play an important role in the development of prostate cancer [6]. Endocrine therapy can improve the endpoint of high-risk prostate cancer, but it seems that radiotherapy (RT) and chemotherapy can enable a further improvement of the risk/benefit ratio [7].

Several recent phase III clinical trials have shown that docetaxel for the treatment of metastatic castration-sensitive and castration-resistant prostate cancer has demonstrated survival benefits [8, 9]. But the study of high-risk patients after primary local therapy has yielded conflicting results [10]. Is adjuvant chemotherapy available for high-risk prostate cancer patients after primary local therapy? There is no specific guideline recommendation and clinical consensus [11]. It is hoped that this meta-analysis can clarify whether adjuvant chemotherapy can improve the prognosis of the patients [12].

Methods

Literature Search and Study Selection

The identification and selection of the studies were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [13] criteria and the Population, Intervention, Comparator, Outcomes (PICO) methodology. The PICO was defined as follows: prostate cancer population (P); ad-

Table 1. Demographics and baseline characteristics

Author	Study	Publishing time	Country	Study type	Follow-up time	Control	Treatment	Primary endpoints (HR, 95% CI)	OS, number of events		PFS/DFS, number of events	
									Intervention	Control	Intervention	Control
Hussain et al. [11]	SWOG S9921	2018	America	RCT	1999–2007	RP + ATD	SOC + mitoxantrone	OS (1.06, 0.79–1.43)	91/480	85/481	*150/480	148/481
James et al. [10]	STAMPEDE	2016	America	RCT	2005–2013	RT + ATD	SOC + docetaxel	OS (1.11, 0.67–1.85)	24/168	44/130	–	–
Lin et al. [18]	#553	2019	America	RCT	2006–2011	RP + observation	SOC + docetaxel	PFS (0.80, 0.58–1.11)	11/140	17/157	#66/140	84/157
Ahlgren et al. [19]	SPCG-12	2018	Northern Europe	RCT	2005–2010	RP + observation	SOC + docetaxel	PSA PFSI	–	–	–	–
Oudard et al. [12]	–	2019	France	RCT	2003–2007	RP/RT + ATD	SOC + docetaxel	PSA PFS (0.85, 0.62–1.16)	40/125	46/125	#79/125	81/125
Rosenthal et al. [15]	RTOG 0521	2019	America	RCT	2005–2009	RT + ATD	SOC + docetaxel	OS (0.69, 0.49–0.97)	43/282	59/281	*99/282	123/281
Carles et al. [16]	–	2018	Spanish	RCT	2008–2012	RT + ATD	SOC + docetaxel	OS (0.80, 0.21–2.96)	–	–	*12/65	7/64

RCT, randomized controlled trial; OS, overall survival; PFS, progression-free survival; SOC, standard of care; RP, radical prostatectomy; RT, radiotherapy; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval. * Endpoint was DFS. # Endpoint was PFS.

juvant chemotherapy or docetaxel (I); standard of treatment (C); and overall survival (OS), disease-free survival (DFS), progression-free survival (PFS) (O). This meta-analysis database mainly consists of PubMed, Embase, and Cochrane Library. The database was searched until March 01, 2020. The retrieval strategy is free word and subject word method. The specific search terms are "chemotherapy," "Docetaxel," "prostatic cancer," "High-risk." The supplementary literature mainly comes from the references after the literature. The original text cannot be retrieved from the database. (Contact the author by e-mail to obtain the data.) The meta-analysis is based on the analysis and evaluation of previous published articles, so it does not involve medical ethical approval.

Data Extraction and Study Quality

This meta-analysis has the following criteria: (1) the risk point estimate was reported as a hazard ratio (HR) with the 95% confidence interval (CI), or the survival curve and related data can be used to calculate HR indirectly; (2) type of study: randomized controlled trials (RCTs); (3) the study evaluated chemotherapy with prostate cancer; and (4) the initial treatment of prostate cancer is radical prostatectomy (RP) or RT. Radiologic PFS is defined as time from randomization to the first detection of distant metastasis or death from any cause, whichever came first. OS is defined as time from randomization to death from any cause. DFS is defined as consisting of the first occurrence of biochemical (PSA-based) failure local or distant failure, or death resulting from any cause. For each selected study, the following items were recorded in an Excel: primary endpoints, secondary endpoints, treatment, subgroup source, follow-up time, and average age. The RCT mainly used Cochrane Collaboration Network bias risk assessment criteria.

Statistical Analysis

The meta-analysis method mainly relies on Review 5.3 software systems. Meta-analyses were performed for primary and secondary outcome parameters: OS, DFS, and radiologic PFS. Heterogeneity was assessed using Cochran Q statistic and quantified using the I^2 statistic. The heterogeneity was classified as low ($I^2 \leq 50\%$) and high ($I^2 > 50\%$). If the heterogeneity is high, a random-effect model is used. If the heterogeneity is low, a fixed effects model is used [14]. If the heterogeneity is high, subgroup analysis and sensitivity analysis are used to find the reason of high heterogeneity.

Results

Characteristics of Studies

A total of 1,238 documents were included in the selection. After gradual screening, 7 documents were finally included in this meta-analysis. The process of the literature search and screening are detailed in Figure 1. Basic information of finally documents included in Table 1.

Overall Survival

For this study, 6 RCTs were included. The meta-analysis did not show a significant OS benefit from adjuvant chemotherapy in patients with high-risk prostate cancer after primary local therapy (HR: 0.87; 95% CI, 0.72–1.05;

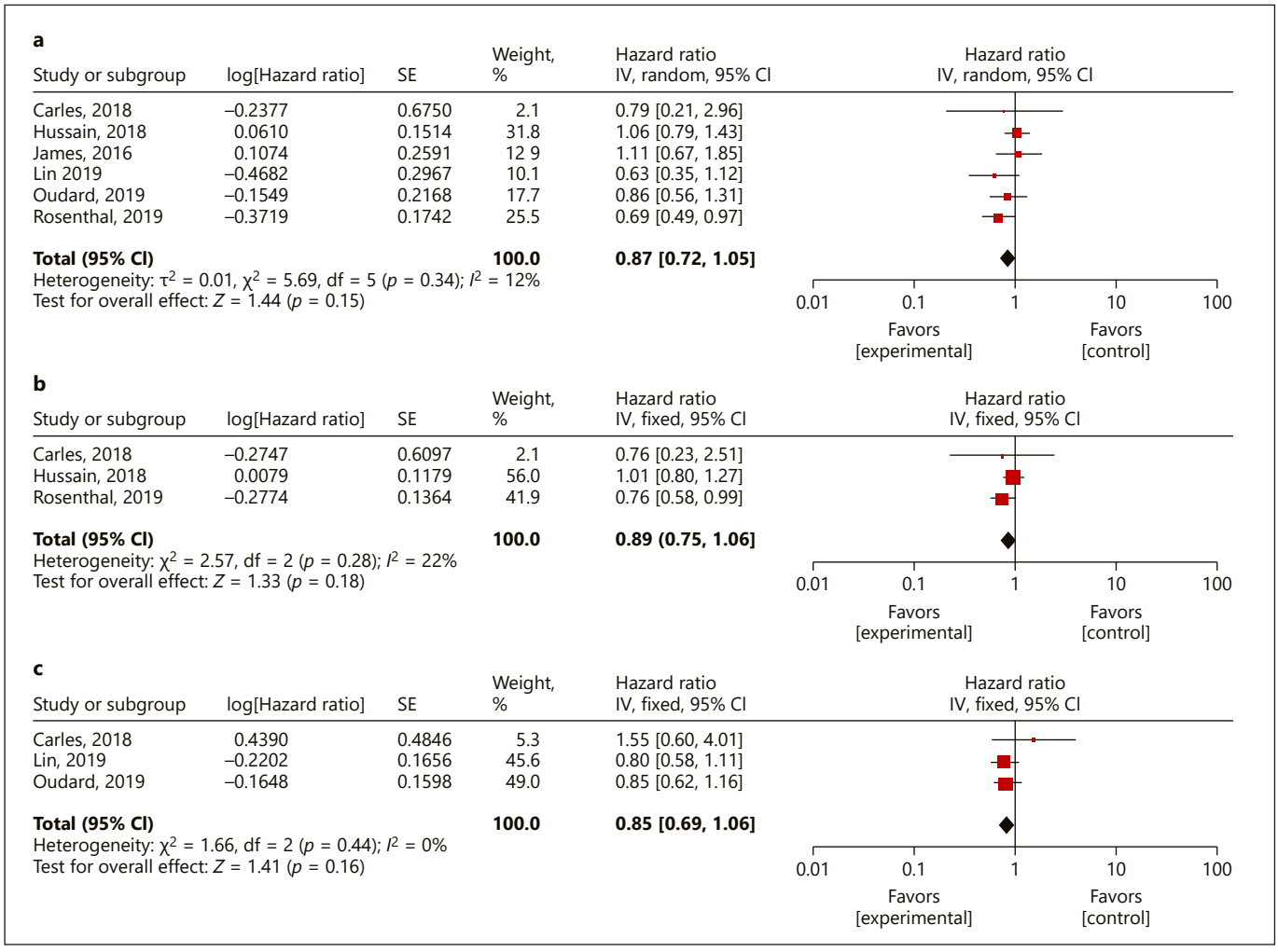

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Fig. 2. Forest plots of the effect of adjuvant chemotherapy on the OS (**a**) and DFS (**b**) and BRFS (**c**) of high-risk prostate cancer. OS, overall survival; DFS, disease-free survival; BRFS, biochemical recurrence-free survival.

$p = 0.15$). There was no significant heterogeneity between studies ($I^2 = 12\%$) (Fig. 2a). But docetaxel in patients with high-risk prostate cancer after primary local therapy was associated with a slightly OS improvement (HR: 0.79; 95% CI, 0.63–0.98; $p = 0.03$) (Fig. 3a). For the initial treatment of chemotherapy and surgery, no significant OS benefit was observed (HR: 0.80, 95% CI, 0.61–1.06, $p = 0.11$; HR: 0.95; 95% CI, 0.73–1.24, $p = 0.72$) (Fig. 3b).

DFS and Biochemical Recurrence-Free Survival

The second endpoint is DFS. A total of 3 documents reported on the DFS indicator in detail. Adjuvant chemotherapy to high-risk prostate cancer patients after primary local therapy cannot extend the time of DFS (HR: 0.89; 95% CI, 0.75–1.06; $p = 0.18$). There was no significant heterogeneity between studies ($I^2 = 22\%$) (Fig. 2b). Adjuvant chemotherapy to high-risk prostate cancer patients after primary local therapy extend the time of biochemical recurrence-free survival (BRFS; HR: 0.85; 95% CI, 0.68–1.06; $p = 0.16$) (Fig. 2c).

Discussion

This meta-analysis is the first report on adjuvant chemotherapy for high-risk patients after primary local therapy. It is also the most detailed meta-analysis with 2,498 participants. Among men with high-risk prostate cancer after RP or RT, we found that adjuvant chemotherapy using docetaxel lead to a slightly improvement in OS. How-

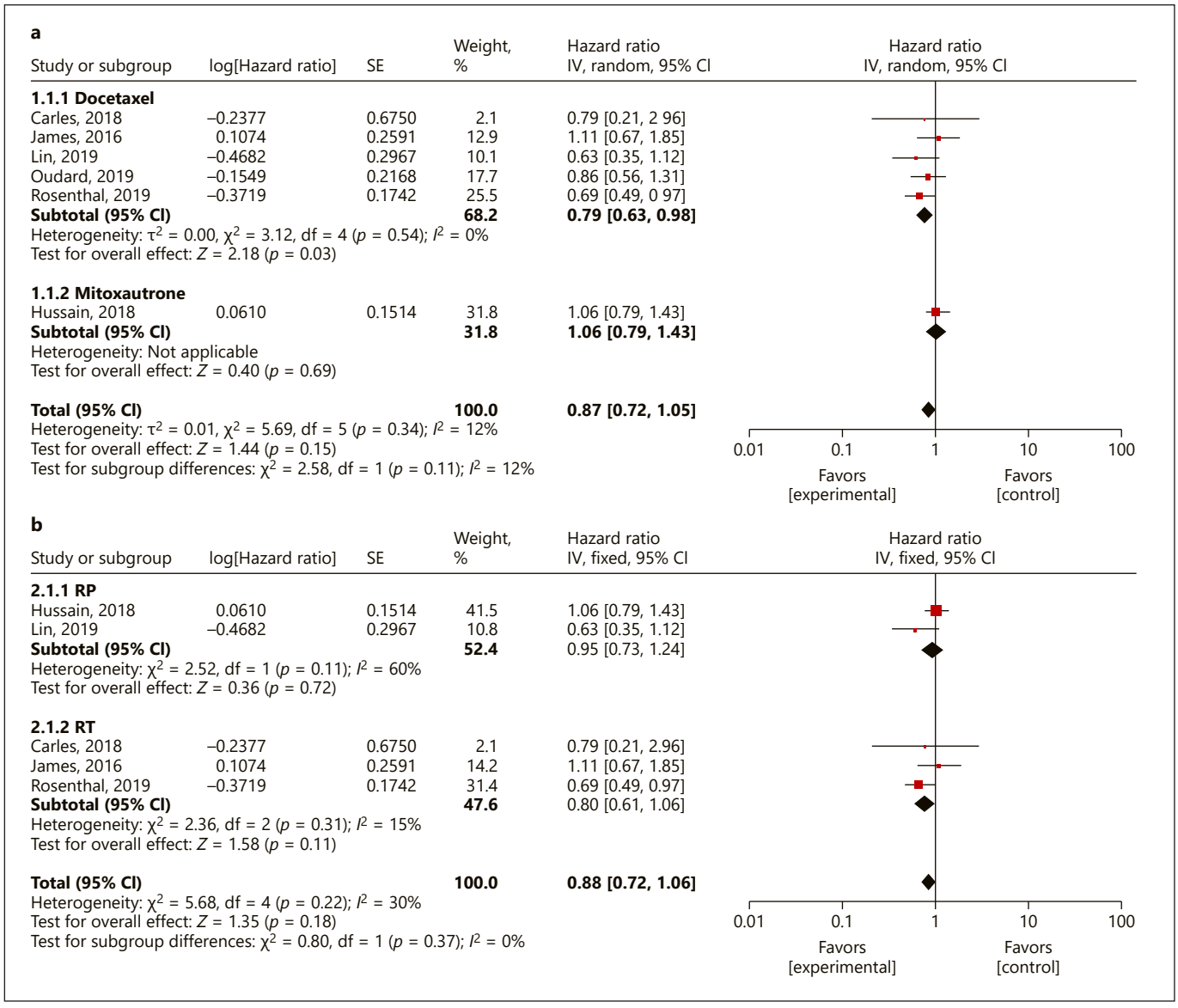

Fig. 3. Forest plots of the effect of adjuvant chemotherapy on the OS of high-risk prostate cancer. Subgroup analysis: docetaxel and mitoxantrone (**a**); RP and RT (**b**). OS, overall survival; RP, radical prostatectomy; RT, radiotherapy; CI, confidence interval; HR, hazard ratio; SE, standard error.

ever, only 3 studies were included in the subgroup analysis, and the sample size was small. Whether docetaxel combined with endocrine therapy is beneficial to the survival time of patients remains to be further determined in large sample clinical research. For secondary endpoints, it did not show a significant benefit in DFS and BRFS in patients with high-risk prostate cancer. According to the Cochrane Collaboration Network bias risk assessment criteria, the 7 RCTs included in this study are of high quality (Fig. 4).

High-risk patients and the best treatment plan are not clear. After the initial treatment, the adjuvant antiandrogen and estrogen or abiolone showed different degrees of prolongation of survival time [17–19]. However, single drug faces serious side effects. With the prolongation of medication time, drug resistance, or drug sensitivity will decrease. The combination of drugs has become a new research field.

Several recent studies have reported in detail the adjuvant treatment of high-risk prostate cancer. Lin et al. [20]

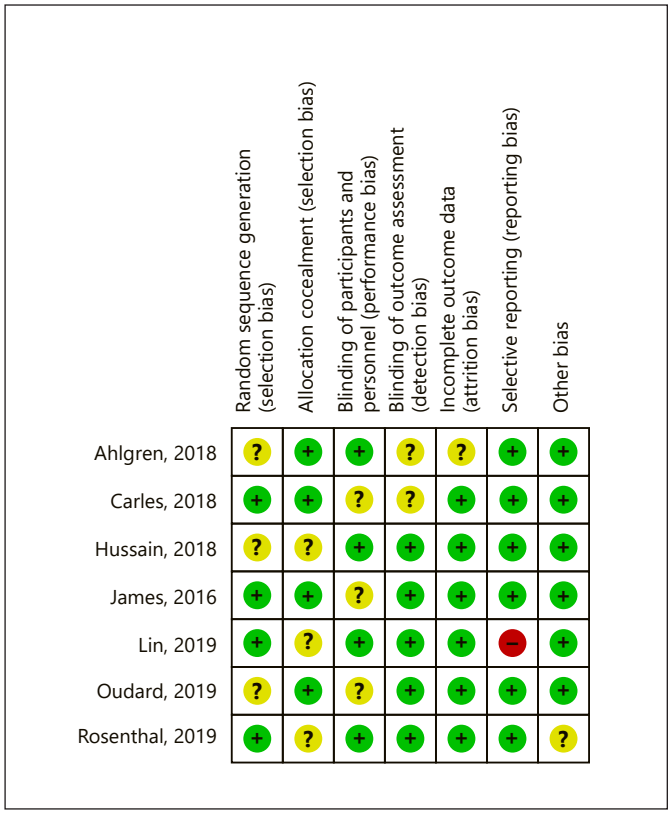

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Fig. 4. Cochrane Collaboration's tool for assessing risk of bias.

reported that docetaxel had no significant improvement in biochemical DFS at high risk of prostate cancer after RP in the absence of endocrine therapy. Due to the early termination of the treatment population, longer follow-up data were not obtained [20]. In the study of another similar conclusion, one-third of the patients in the study did not have lymphadenectomy, but no specific subgroup analysis was performed for lymphadenectomy in this study [21]. The results of these 2 studies are different from those of this meta-analysis. It was found that the 2 reports were only for docetaxel alone. In this meta-analysis, we included the effect of docetaxel combined with endocrine therapy on the survival of prostate cancer. And a more detailed subgroup analysis is carried out, hoping to get a more objective and comprehensive conclusion.

There are also several studies on prostate RT and adjuvant chemotherapy. Two RCTs of docetaxel combined with endocrinotherapy after prostate RT have different conclusions on the OS and the other endpoints. James et al. [10] reported a study of 2,463 participants that docetaxel could improve the OS for high-risk patients, but there was no significant benefit in the RT participants (HR: 1.11, 95% CI, 0.67–1.85). In our meta-analysis, there was only 1 study in which the initial treatment was radical RT, and there was no subgroup analysis of radical RT. As the initial treatment is surgery or RT, whether there are differences in the results of the study remains to be further studied.

Postoperative adjuvant chemotherapy did not bring significant survival advantage. How about the outcome of preoperative neoadjuvant chemotherapy? In recent years, some scholars have proposed that neoadjuvant chemotherapy before the operation of local high-risk prostate cancer can reduce PSA, tumor stage, hormone level, delay the progress of disease, and improve the quality of life. In 2004, 2 US clinical studies on prostate cancer chemotherapy showed that docetaxel had a significant survival advantage for advanced prostate cancer. Febbo et al. [22] used docetaxel alone to treat 19 patients with high risk of prostate cancer. The single dose was 36 mg/m^2, once a week, and the course of treatment was 6 months. The results showed that 58% of the patients had a decrease in PSA >50%, 21% of the patients had a reduction of tumor volume at least 50%, but there was no pathologic complete response [22]. Recently, Bergstrom et al. [23] combined with docetaxel and mitoxantrone for new adjuvant therapy in 57 cases of high-risk prostate cancer before operation and followed up for 10 years. It was found that 53% of the patients had a biochemical relapse of PSA, the 2-year relapse-free survival rate was 63%, the 5-year relapse-free survival rate was 46%, and the 10-year relapse-free survival rate was 29%. The therapeutic effect of neoadjuvant chemotherapy for solid tumors in other parts of human body has been recognized, but its application in prostate cancer is still in the exploratory stage. Although many combined chemotherapy schemes at present mostly suggest that neoadjuvant chemotherapy can improve some indexes of high-risk patients, such as focus volume, positive rate of cutting edge, and PSA. But whether it can improve the pathological stage and the OS rate requires more RCTs. Fortunately, in order to compare the benefits of docetaxel and androgen deprivation therapy in patients with high-risk prostate cancer, a third phase of RCTs is under way [24].

Docetaxel is the first drug to prolong the OS of patients with metastatic castration-resistant prostate cancer. The choice of docetaxel was based on 2 RCTs comparing mitoxantrone and prednisone with docetaxel and either prednisone or estramustine [9, 25]. The median lifetime benefit is about 3 mouths (HR, 0.76, 95% CI, 0.62–0.94) for docetaxel compared with mitoxantrone. The main

mechanism of docetaxel is to disturb the normal physiological function of microtubules during mitosis, which leads to cell cycle arrest. In addition, docetaxel can also phosphorylate Bcl-2 protein, cause the deactivation of Bcl-2 protein, and finally lead to apoptosis [26]. In the field of basic research on docetaxel, it was found that 2 antiandrogen drugs, bicalutamide and enzalutamide, can inhibit the activity of ABCD-1 and ATPase and increase the sensitivity of prostate cancer cells to docetaxel [27]. It seems to provide a theoretical basis for docetaxel combined with antiandrogen therapy. Although we also found that the level of androgen receptor expression is related to the drug sensitivity of docetaxel [28], but how the 2 interact is not clear.

There are still many limitations in this meta-analysis. First, this literature search is limited to articles published in English, so there may be publication bias. Second, the number of literature studies included in this meta-analysis is small, and the total number of samples included is only 4,275, which affects the promotion of the results. Third, the endpoint is scattered in the original literature, so it is not very well to analyze the important outcome indicators, such as the quality of life of patients and the recurrence of PSA.

Conclusion

This meta-analysis shows a slightly OS benefit from docetaxel in patients with high-risk prostate cancer after primary local therapy. It did not show a significant benefit in DFS and BRFS in patients with high-risk prostate cancer. Due to the limitation of original literature, the results of meta-analysis in this study need to be further verified and improved by large sample and high-quality RCTs.

Statement of Ethics

This meta-analysis is based on published literature and does not involve original research. So the study is exempt from ethical committee approval.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Qiang Zhang is responsible for the methodology and project administration. Jing Huang is responsible for the software and supervision and validation. Chaofan Xie is responsible for the writing the original draft. Tao Wu is responsible for the data curation and funding acquisition and writing review and editing.

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