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ORIGINAL ARTICLE

Comparison of radical prostatectomy versus conservative treatment in localized prostate cancer: systematic review and meta-analysis

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Summary

Purpose: *To evaluate the effects of radical prostatectomy (RP) and conservative treatment (CT) on the survival of localized prostate cancer by conducting a systematic review and meta-analysis.*

Methods: *We searched for all studies about RP and CT for localized prostate cancer in PubMed and Web of Science up to December 2017. A systematic review and meta-analysis was performed.*

Results: *There were 4 randomized clinical trials (RCTs) and 12 cohort studies including 69871 patients treated with RP and 65765 patients treated with CT. There was a significantly reduced all-cause mortality (HR:0.575;95%CI:0.487 to 0.678;p<0.001) along with a reduced risk of prostate cancer mortality in patients treated with RP compared to those treated with CT (HR:0.408;95%CI:0.313 to 0.533;p<0.001). RP was effective with a lower all-cause mortality and prostate cancer mortality for patients with intermediate risk disease (HR:0.774;95%CI:0.664 to 0.902,p=0.001; HR:0.428;95%CI:0.286 to 0.641, p=0.001, respectively). However, for low risk (HR:0.774;95%CI:0.505 to 1.187, p=0.241; HR:0.603;95%CI:0.332 to 1.097, p=0.098, respectively) and high risk (HR:0.662;95%CI:0.376 to 1.164, p=0.152; HR:0.584;95%CI:0.315 to 1.084, p=0.089, respectively) prostate cancer patients, there was no significant difference between RP and CT. In the subgroup analysis according to the age and follow-up time, the results favored the RP and there was no specific factor affecting the outcomes.*

Conclusions: *RP offers a better survival rate than CT in patients with localized prostate cancer. For some patients with localized prostate cancer, treatment should be chosen very carefully.*

Key words: *conservative treatment, localized prostate cancer, radical prostatectomy*

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer in men. With the widespread use of prostate specific antigen (PSA), the spike of detecting asymptomatic PCa had been in the late 1980s and early 1990s [1]. A stage migration towards the detection of earlier disease occurred through the emergence of PSA testing [2]. In 2016, it was estimated that 180,890 new cases of PCa would be diagnosed in the United States [3].

However, given that the vast majority of cases are of indolent nature, most patients die of competing risks other than the disease itself [4,5], bringing the dilemma of overtreatment in the treatment of PCa. This dilemma will have negative impact on patients, clinicians, and ultimately for the health care systems. Treatment guidelines recommend conservative treatment with either watchful waiting or active surveillance as an appropriate option

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for patients with localized PCa [6]. Meanwhile, radical prostatectomy (RP) is also the primary choice of treatment in clinical practice. Since the outcomes of three main studies (SPCG-4, PIVOT and PROTECT) are different, the optimal extent regarding which treatment should be performed is a long-standing debate. In SPCG-4, during 23.2 years of follow-up, a substantial reduction in mortality was observed after RP compared to CT [7]. However, in PIVOT study, RP was not associated with significant lower all-cause and PCa mortality, compared with CT [8]. PROTECT trial also showed no mortality decrease of surgery as compared with observation.

The optimal treatment for localized PCa is one of the highest priority clinical questions. In this study, we conducted a systematic review and a quantitative meta-analysis of the available literature, with the goal of obtaining more definitive results in patients with localized PCa treated with different therapies.

Methods

Search strategy

A systematically literature search was performed with the keywords as follows: [Title/Abstract]: radical prostatectomy AND (conservative treatment OR watchful waiting OR active surveillance OR monitor OR expectant management) AND (localized prostate cancer OR early prostate cancer OR low risk prostate cancer). There was no language restriction. The search was updated to December 2017. The primary sources were the electronic databases of PubMed and Web of Science. This systematic review was done according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses statement [9]. The details of the full search strategy are shown in Figure 1.

Inclusion and exclusion criteria of trials

All available randomized controlled trials and cohort studies comparing RP to CT for patients with localized PCa were included. Eligible trials had to fulfill the following criteria: localized PCa patients should be diagnosed pathologically; the articles should contain the clinical data of RP and CT; outcomes should include all-cause mortality or PCa mortality; Life expectancy should be more than 10 years. For studies with multiple publications, only the most updateed were utilized.

The studies including advanced PCa were excluded. Repeated published data were excluded. Editorials, letters to the editor, review articles, unpublished articles were excluded.

Data extraction

For each eligible study, we retrieved the information including the year of publication, study type, number of patients, mean or median age, follow-up time, and the

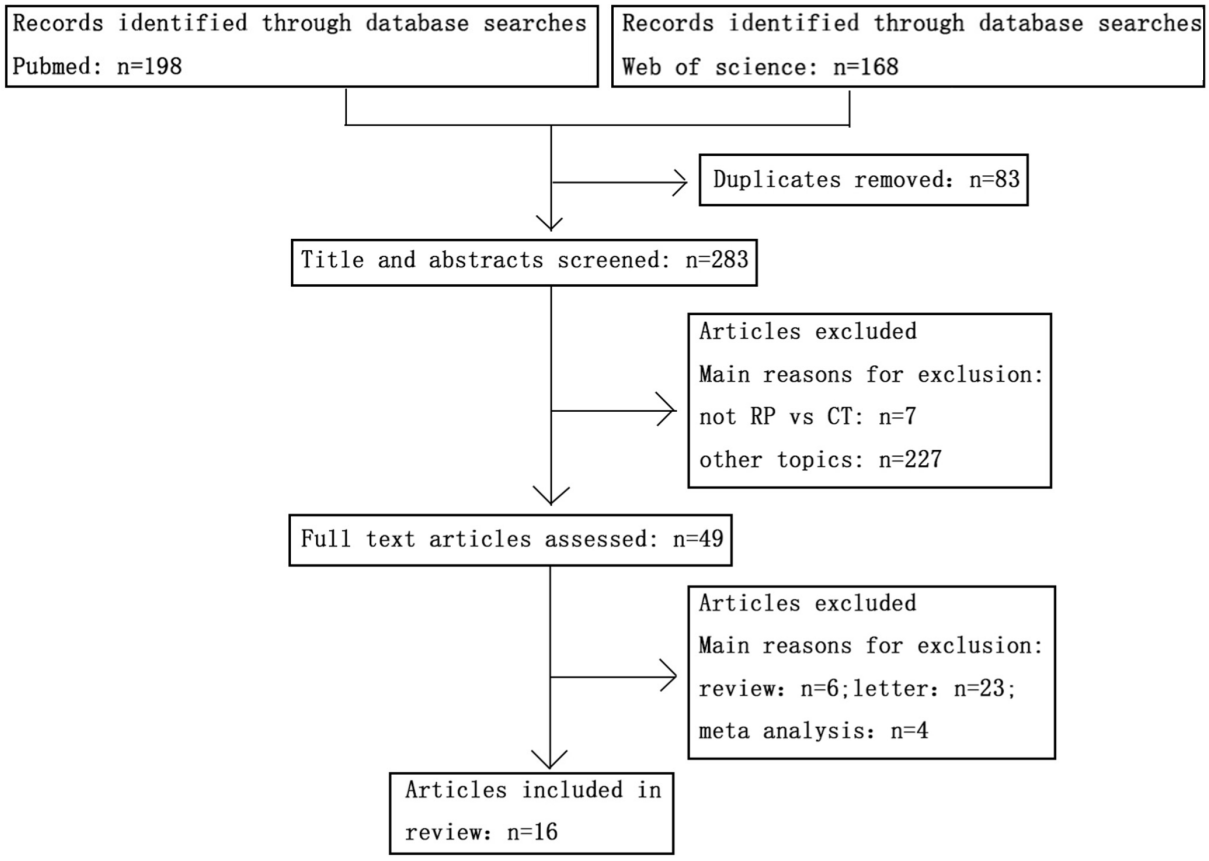


Figure 1. Details of the full search strategy.

quality of study (Table 1). The primary outcome of the meta-analysis was all-cause mortality and the secondary outcome was PCa mortality.

Quality assessment and statistical analysis

Two reviewers independently assessed the eligibility of all identified citations and extracted data from original trial reports. Disagreements or uncertainties were resolved by consensus with an additional investigator. Data extraction was based on the original data of the literature. When the data was incomplete or not described in detail, the following two methods were used to obtain the data: 1) E-mail to contact the authors to obtain the original data; 2) the data extraction methods proposed by Tierney [10] could be used for the literature without explicit data. Meta-analysis was performed in line with recommendations from the Cochrane Collaboration and the Quality of Reporting Meta analyses (QUORUM) guidelines [11,12]. Study quality was assigned by two reviewers using the methodology and categories described in the Cochrane Collaboration Handbook [13].

To assess the quality of RCT evidence, we used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach that classifies evidence as high, moderate, low, or very low quality based on considerations of risk of bias, consistency, directness, precision, and publication bias [14].

The methodological quality of cohort studies was assessed by the modified Newcastle Ottawa scale [15] which consists of three factors: patient selection, comparability of the study groups, and assessment of outcome. A score of 0-9 (allocated as stars) was allocated to each study and only the study achieving 6 or more stars was considered to be of high quality.

For dichotomous outcomes, the hazard ratios and the corresponding 95% confidence interval calculated the variance between studies. The random effects model was used to calculate the data, considering P interaction<0.05 as statistically significant. We evaluated statistical heterogeneity using x^2 test and I^2 statistic [16].

Clinical heterogeneity was investigated by prespecified subgroup analysis. For subgroup analysis, we tested for interaction using x^2 significance test. Sensitivity analysis was performed at the same time.

Publication bias was examined by using funnel plots. Data were analyzed with STATA software (version 12.0, TX, USA).

Results

Study and patient characteristics

After screening abstracts and full text articles, 16 studies (4 RCTs and 12 cohort studies) including 69871 patients treated with RP and 65765 patients treated with CT fulfilled the predefined inclusion criteria and included in the final analysis. Table 1 shows the main characteristics of the selected studies.

Outcomes

Pooling the data from 4 RCTs and 8 cohort studies that assessed all-cause mortality showed significant difference between the RP and CT (Figure 2). Compared to CT, RP significantly reduced all-cause mortality (HR:0.575;95%CI:0.487 to 0.678; p<0.001).

Table 1. Characteristics of included studies and the main characteristics

Study	*Year*	*Design*	*RP*	*CT*	*Age*(years)*	*Follow up*	*Quality***
Wilt,T.J [8]	2017	RCT	364	367	67	12.7y	moderate risk
Hamdy,F.C [17]	2016	RCT	553	545	50-69	10y	moderate risk
Bill Axelson,A [7]	2014	RCT	347	348	65	13.4y	low risk
Iversen [18]	1995	RCT	61	50	62.7/66.0	23m	high risk
Sun,M [19]	2014	Retro	15 532	17 942	70/73	NA	5
Rice,K.R [20]	2013	Retro	194	324	72.2/75.3	6.4y	6
Abdollah,F [21]	2011	Retro	22 244	22450	69.8/73.5	7.1y	7
Stattin,P [4]	2010	Retro	3399	2021	61.2/64.7	8.2y	7
Hadley,J [22]	2010	Retro	11936	5879	66-74	12y	7
Schymura,M.J [23]	2010	Retro	1321	619	NA	5y	6
Liu,L [24]	2008	Retro	2567	970	65-74	11.8y	7
Tewari,A [25]	2007	Retro	119	197	60.0/62.9	68m	7
Merglen,A [26]	2007	Retro	158	378	71	6.7y	6
Albertsen,P.C [27]	2007	Retro	802	114	65/70	13.3y	7
Wong,Y.N [28]	2006	Retro	13292	12608	65-80	12y	7
Tward,J.D [29]	2006	Retro	34758	18895	NA	3.8y	6

*Mean/median age of RP/CT or overall age. RCT: randomized controlled trial; Retro:retrospective study(cohort study). **The number represents NOS;≥6 consider high quality; NA: not available. RP: radical prostatectomy; CT: conservative treatment.

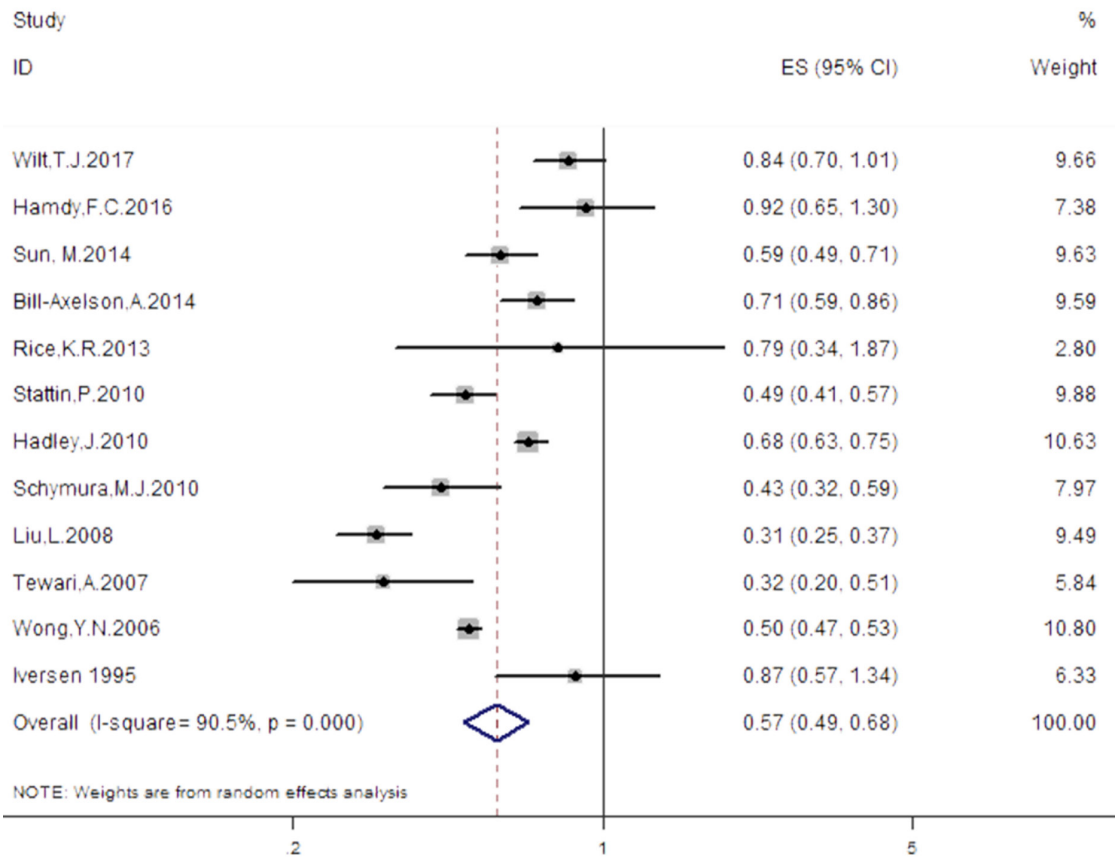


Figure 2. All cause mortality: RP vs CT.

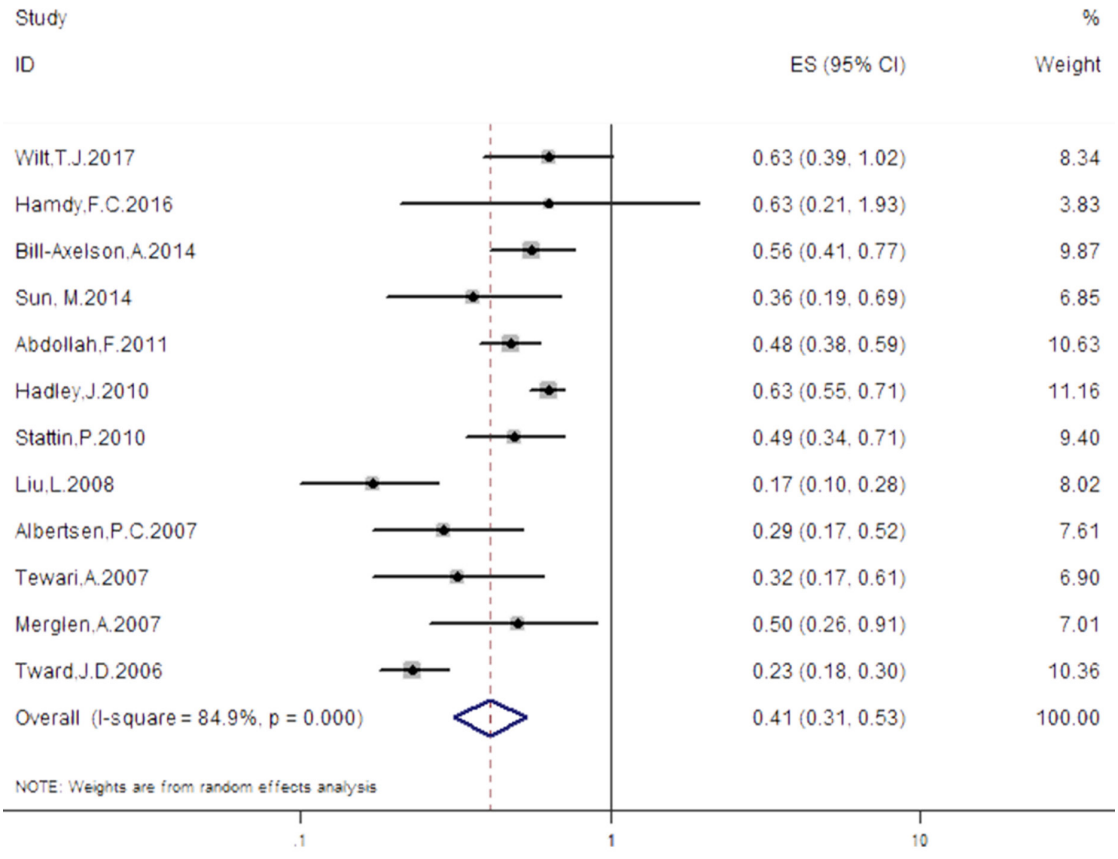


Figure 3. Prostate cancer and mortality: RP vs CT.

In our meta-analysis, 3 RCTs and 9 cohort studies reported the outcome of PCa mortality (Figure 3). Compared to CT, RP showed a reduced risk of PCa mortality (HR: 0.408; 95%CI: 0.313 to 0.533; p<0.001).

Subgroup analysis

Age

Seven studies reported all-cause mortality in patients over 65 years of age, 2 studies reported all-cause mortality in patients less than 65 years of age and 3 studies did not report the mean age. In patients over 65 years of age, the outcome showed significant difference between RP and CT (HR:0.587; 95%CI:0.474 to 0.726; p<0.001). All-cause mortality in patients less than 65 years of age group also showed statistically significance (HR:0.42; 95%CI:0.281 to 0.627; p<0.001) (Table 2).

Eight studies reported PCa mortality in patients over 65 years of age, 2 studies reported PCa mortality in patients less than 65 years of age and 2 studies did not report the mean age. Pooling the data of these 8 studies showed that RP significantly decreased the risk, compared with CT (HR: 0.441; 95%CI: 0.338 to 0.575; p<0.001). Meanwhile, in the group of less than 65 years of age, the outcomes showed that the difference between the two groups was statistically significant (HR: 0.430; 95%CI: 0.293 to 0.632; p<0.001) (Table 3).

Follow-up time

Eight studies reported all-cause mortality in a follow-up time ≥10 years, 3 studies reported all-cause mortality in a follow up-time <10 years. All groups showed significant difference between the RP and CT (HR:0.613; 95%CI:0.501 to 0.749; p<0.001; HR: 0.425; 95%CI: 0.295 to 0.613; p<0.001, respectively) (Table 2).

Six studies reported a PCa mortality in a follow-up time ≥10 years, 5 studies reported PCa mortality in a follow-up time <10 years. Our pooled analysis showed a reduced risk of PCa mortality in the RP group (HR:0.439; 95%CI:0.297 to 0.649, p<0.001; HR: 0.383; 95%CI: 0.262 to 0.560, p<0.001, respectively) (Table 3).

Risk classification

Three studies reported all-cause mortality in the low risk group, 2 studies reported all-cause mortality in the intermediate risk group, and 3 studies reported all-cause mortality in the high risk group. The survival benefit of RP was limited to men with intermediate risk disease (HR: 0.774; 95%CI: 0.664 to 0.902; p=0.001). For men with low risk or high risk disease, the difference did not reach statistical significance (HR:0.774; 95%CI:0.505 to 1.187, p=0.241; HR:0.662; 95%CI:0.376 to 1.164, p=0.152, respectively) (Table 2).

Table 2. Subgroup analysis: all cause mortality (RP vs CT)

Outcomes of interest	*HR*	*95% CI*	*df*	I^2,%	*p value*	*z*
≥65 years	0.587	0.474 to 0.726	6	93.60	<0.001	4.92
<65 years	0.42	0.281 to 0.627	1	64.70	<0.001	4.24
Follow up time≥10y	0.613	0.501 to 0.749	7	93.50	<0.001	4.77
Follow up time<10y	0.425	0.295 to 0.613	2	41.60	<0.001	4.58
Low risk	0.774	0.505 to 1.187	2	72.00	0.241	1.17
Intermediate risk	0.774	0.664 to 0.902	1	0	0.001	3.28
High risk	0.662	0.376 to 1.164	2	89.20	0.152	1.43

df= degrees of freedom; CI= confidence interval;Statistically significant results are shown in bold

Table 3. Subgroup analysis: PCa mortality (RP vs CT)

Outcomes of interest	*HR*	*95% CI*	*df*	I^2,%	*p value*	*z*
≥65 years	0.441	0.338 to 0.575	7	78.70	**<0.001**	6.04
<65 years	0.43	0.293 to 0.632	1	22.00	**<0.001**	4.3
Follow up≥10y	0.439	0.297 to 0.649	5	83.50	**<0.001**	4.12
Follow up<10y	0.383	0.262 to 0.560	4	81.80	**<0.001**	4.96
Low risk	0.603	0.332 to 1.097	1	0	0.098	1.66
Intermediate risk	0.428	0.286 to 0.641	1	0	**<0.001**	4.12
High risk	0.584	0.315 to 1.084	2	65.8	0.089	1.7

df= degrees of freedom; CI= confidence interval;Statistically significant results are shown in bold

Two studies reported PCa mortality in the low risk group, 2 studies reported PCa mortality in the intermediate risk group and 3 studies reported PCa mortality in the high risk group. RP exhibited improved survival compared to CT in the intermediate risk group (HR:0.428; 95%CI:0.286 to 0.641; p=0.001). However, in the low risk and high risk group, RP showed no statistically significant difference compared to CT (HR:0.603; 95%CI:0.332 to 1.097, p=0.098; HR:0.584; 95%CI:0.315 to 1.084, p=0.089, respectively) (Table 3).

Sensitivity analysis and publication bias

Sensitivity analysis of RCT was conducted. All-cause mortality and PCa mortality in RCT also showed statistically significance (HR:0.797; 95%CI:0.708 to 0.896, p<0.001; HR:0.583; 95%CI:0.451 to 0.753, p<0.001, respectively). The statistical heterogeneity decreased after sensitivity analysis.

For possible publication bias, Begg's and Egger's tests were used. All studies indicating no publication bias are given in Supplementary Tables 1 and 2. Supplementary Figure 1 shows a funnel plot of the studies included in this meta-analysis.

Discussion

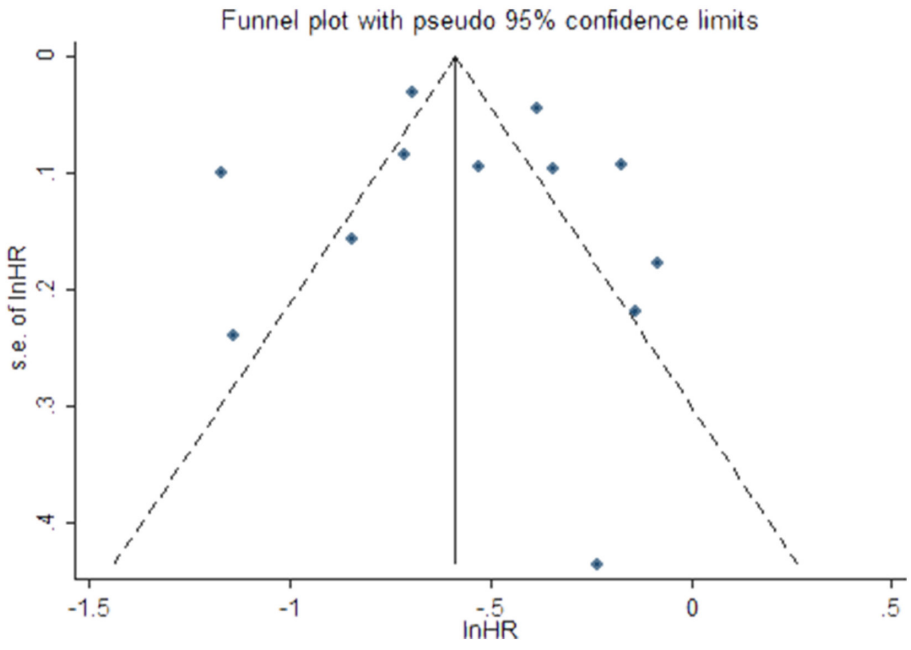
Nowadays, overtreatment of PCa is recognized by urologists and oncologists. Thus, how to reduce unnecessary treatment of men with localized PCa has become an important issue. But, the optimal treatment for localized PCa is still uncertain, because the published results comparing RP versus CT are different. After searching the literature, only one meta-analysis [30] reported the efficacy of RP

Supplementary Table 1. Publication bias: Begg's (RP vs CT)

Outcomes of interest	*z (continuity corrected)*	*Pr>z (continuity corrected)*
All cause mortality	0.34	0.732
PCa mortality	0.21	0.837

Supplementary Table 2. Publication bias: Egger's (RP vs CT)

Outcomes of interest	*Std_Eff*	*Coef.*	*Std.Error*	*t*	*p>t*	*95% CI*
All cause mortality	slope	-0.6282017	0.1182574	5.31	0	-0.8916957 to -0.3647078
	bias	0.7054865	1.623805	0.43	0.673	-2.912577 to 4.32355
PCa mortality	slope	-0.4672193	0.194239	-2.41	0.037	-0.9000108 to -0.0344279
	bias	-2.007864	1.273662	1.58	0.146	-4.845759 to 0.8300317



Supplementary Figure 1. Funnel plot.

and CT in localized PCa; however, this article did not have subgroup analysis. Our meta-analysis aimed to find a better treatment for localized PCa.

According to the results of our study, RP was superior to CT in either all-cause mortality or PCa mortality, similar to the results of a previous meta-analysis [30]. A total of 4 randomized controlled trials were conducted to compare the efficacy of RP and CT. After extending the follow-up time, SPCG-4 [7] also reported a difference favoring RP in all-cause and PCa mortality. In this study, 695 patients with localized PCa were randomized to receive either RP or CT. As a result, after 23.2 years of follow-up, a significant absolute reduction in the rate of death from all-cause and the rate of death from PCa in the RP group was observed. However, in the VACURG study [18], after a median follow-up of 23 years, the median overall survival was 10.6 years for the RP group and 8 years for the CT group. The results were not statistically significant. However, this study had limitations since it included only 142 patients and was judged to be of poor quality. After a median of 10 years follow-up, Hamdy et al. [17] showed that RP did not significantly reduce all-cause mortality and PCa mortality. Similarly, in the latest publication, Wilt et al. reported the updated results from the PIVOT trial [8]. All-cause mortality rate was 61.3% in the RP group and 66.8% in the CT group. PCa mortality occurred in 7.4% of patients in the RP group and 11.4% in the CT group, indicating no improvement in disease specific or overall survival through 19.5 years of follow-up. The difference may be due to the following reasons: 1) SPCG-4 was conducted between 1989 and 1999; this study was conducted before the development of the PSA blood test, with only 5.2% of patients being assessed by PSA. PIVOT, which was conducted in the early era of PSA test between 1994 and 2002 after the rapid adoption of PSA screening in the United States 75% of the cases were assessed by PSA screening. The PROTECT trial was the product of the later era of PSA testing. 2) Compared to SPCG-4, the patients in PIVOT and PROTECT trials had earlier stage of disease. The rates of T1c patients in PIVOT, PROTECT, and SPCG-4 were 50.3, 76 and 11.7%, respectively. In SPCG-4, T1c tumors were only included after 1994 and the majority were diagnosed based on abnormal rectal examination (25%) or symptoms (43%) [31]. 3) Furthermore, the use of the PSA test was associated with significant lead time effect and overdiagnosis. According to Xia et al. [32] hypothesis, lead time effect and overdiagnosis may largely explain the difference among the trails. In the absence of PSA screening era, PCa diagnosed by overdiagnosis would not have been detected in the patients' lifetimes. 4) The duration of follow-up may influence the outcomes. The follow-up time of SPCG-4 study (13.4y) was longer than that of PIVOT (12.7y) and PROTECT study (10y).

Other reasons may still lead to differences in the results of the cohort studies. First, treatments, and diagnostic techniques for PCa have evolved, such as laparoscopic RP and Da Vinci robotic surgery. The progressing androgen deprivation therapy, bone-targeting agents, and immunotherapy also impact the effect. Second, some studies have shown that black men with PC have higher comorbidities than whites [3,33,34] and this gap may be widening [35]. Underwood et al. [36] indicated that, compared to whites, hispanics and blacks were less likely to receive definitive therapy. Black patients were less likely to undergo lymph node dissection at the time of surgery. The article pointed out that the blacks were discriminated against the use of new technology [37]. On the other hand, Schmid et al. [38] indicated that blacks had a longer treatment delay and more likely to experience adverse events than non-hispanic whites, but the outcome failed to show a significant difference in all-cause mortality [38]. Thus, the real reason for the difference needs to be discussed. Third, underlying diseases in patients can also affect mortality; however, few studies report this information.

Since PCa is an indolent cancer, the majority of patients often have an extended life expectancy and die of competing causes [7,8,17], hence the quality of life is important in determining whether surgery is the most appropriate treatment option. Level 1 evidence [8,39] indicated that RP was associated with sexual dysfunction and urinary incontinence. A systematic review [40] also suggested that men were distressed by their poor urinary and sexual side effects more often when assigned to RP than CT. Erectile dysfunction may not profoundly affect quality of life in older men; this may be because older men start with lower sexual function and have lower recovery expectations than younger patients [41-43]. PROTECT study [39] reported that the negative effect of RP on urinary continence and sexual function was worst at the 6th month. Although there was some recovery, these outcomes over 6 years remained worse in the RP than CT. At the same time, sexual and urinary function declined gradually in the CT, and this may be because of aging, tumor growth, or castration [44]. Quality of life is an important end point in PCa treatment. Some studies [8,39,44] demonstrated no significant difference between the RP and CT. Punnen et al. [45] reported that the difference in quality of life among treatments attenuated over time. The different side effect profiles of these options are crucial factors

for patients and clinicians before deciding on selecting treatment strategy. Therefore, each patient must be informed of the physical side effects and potential influences.

Unlike another meta-analysis [30], our work was based on the age of patient, duration of follow-up, and the risk of PCa to analyze the result of subgroups. In subgroup analysis, the benefit for all-cause mortality and PCa mortality did not differ by age. According to the different follow-up times, the groups were divided into 2 groups i.e. follow-up period of more than 10 years and less than 10 years. The results showed that RP can reduce the risk of all-cause mortality and PCa mortality better than CT. Of the included studies, only three studies included subgroup analysis based on the risk of PCa. Interestingly, RP has only been associated with lower all-cause mortality and PCa mortality than CT among men with intermediate risk disease, but not among those with low risk and high risk disease.

PCa is a significantly heterogeneous tumor. Different clinical and pathological features of PCa have different biological behaviors. Low risk PCa is almost non-fatal because of its inertia, hence the result of the RP and CT are the same. However, high risk PCa is easy to relapse and metastasize because of its high aggressiveness. After RP, adjuvant radiotherapy or endocrine therapy is needed to prolong the survival of patients. The 3 included studies about the high risk subgroup analysis of PCa were published relatively early. At that time, the limited level of radiotherapy and endocrine therapy may not be enough to control disease progression and this may be due to the reason that RP is not superior to the CT. It is worth noting that we still need to pay attention to the risk of PCa and the choice of treatment may have an impact on prognosis. Further studies should focus on more accurate tests for diagnosis and grading of PCa.

To the best of our knowledge, compared to another meta-analysis [30], this meta-analysis is the largest one powered with subgroup analysis. Subgroup analysis may have more details to observe the special population. Despite this, there were limitations in this meta-analysis. First, only 4 RCTs were brought into the study, the rest were retrospective cohort studies. Thus, this may give rise to bias. Second, all the studies included were relatively early studies. Current surgery, chemotherapy, radiotherapy and endocrine therapy have been improved significantly compared to the past years, thus the result may not be fully applicable to the present. Third, the sample size for subgroup analysis was relatively small and we look forward to articles that include more detailed data. The heterogeneity of pooling data was significant, but this was minimized with sensitivity analysis. No publication bias was found in Egger's and Begg's tests.

Nevertheless, this meta-analysis was conducted at an appropriate time, because enough data have accumulated for the first time. We applied multiple strategies to identify studies and also used strict criteria to include and evaluate the methodological quality of the studies. Therefore, we believe that our outcomes are reliable. Nevertheless, despite our rigorous methodology, the inherent limitations of included studies prevent us from reaching definitive conclusions. Future large-scale, high quality, and multi institutional trials are needed for confirming and updating the findings of this meta-analysis.

Conclusions

Radical prostatectomy has a significant advantage over conservative treatment for both all-cause and PCa mortality. Urinary incontinence and sexual dysfunction were greater with RP than CT. For quality of life, no significant differences were found between the two groups. For some patients with localized prostate cancer, the choice of treatment should be done be very carefully and should be considered in combination with other factors of patients.

Conflict of interests

The authors declare no conflict of interests.

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