Int J Clin Exp Med 2020;13(2):330-339
www.ijcem.com /ISSN:1940-5901/IJCEM0103863

Review Article

A systematic review and meta-analysis of comparative studies on the efficacy of cytoreductive prostatectomy in patients with metastatic prostate cancer

Yan Zhao, Dashuai Peng, Jie Liang, Yingli Lin, Jingguang Qi

Department of Urology, Xuzhou Cancer Hospital, Affiliated Hospital of Jiangsu University, Xuzhou, Jiangsu, China

Received October 22, 2019; Accepted December 14, 2019; Epub February 15, 2020; Published February 28, 2020

Abstract: Background: In several studies, cytoreductive prostatectomy has been performed for the survival benefits in metastatic prostate cancer (mPCa). However, these researches revealed conflicting effects. The present study was designed to determine the relationship between cytoreductive prostatectomy and mPCa. Methods: Original articles concerning cytoreductive prostatectomy published until November 1st, 2018 were searched in PubMed database. The main clinical outcomes included overall mortality (OM), cancer-specific mortality (CSM) and progression-free survival (PFS). Afterwards, meta-analysis was performed. Results: A total of 14 studies were included. Compared with no local therapy (NLT), radical prostatectomy (RP) of mPCa was associated with decreased OM (HR=0.47, 95% CI=0.44 to 0.51, I^2=90.6%) and CSM (HR=0.36, 95% CI=0.31 to 0.43, I^2=28.6%). Subsequent stratified analysis demonstrated that levels below T2a (HR=0.38, 95% CI=0.34 to 0.42, I^2<0.01%) were the possible sources of heterogeneity of OM in RP for mPCa. In detection of the relationship between non-radical prostatectomy (NRP) and mPCa, our results indicated that NRP had beneficial effect on CSM (HR=0.37, 95% CI=0.20 to 0.68, I^2=76.0%) and PFS (HR=0.52, 95% CI=0.33 to 0.482, I^2=0.0%) when compared with NLT. Conclusions: The outcomes demonstrated that cytoreductive prostatectomy including RP and NRP might reveal survival benefits in mPCa patients in comparison with NLT. Additional high-quality trials are still warranted to establish the efficacy of cytoreductive prostatectomy among men with mPCa.

Keywords: Metastasis prostate cancer, prostatectomy, cytoreductive, meta-analysis

Introduction

Prostate cancer is one of the most important cancers, which continues to be a leading cause of cancer-related death in Europe [1]. Survival in males with mPCa is poor with a 5-year overall survival rate of 30% [2]. Therapeutic options in mPCa have still been limited, and androgen deprivation therapy (ADT) with or without chemotherapy remains the traditionally recommended therapy [3]. However, under ADT, progression of mPCa is common and responsible for local complications in most patients [4]. In this setting, new multimodal therapeutic options are being commonly considered and advocated.

Cytoreduction of the primary tumor in the setting of metastatic disease has been an established concept in the survival benefits of solid tumors such as renal and ovarian cancers [5, 6], in which two aspects of the role stood out, interrupting the re-seeding of the primary tumor and reducing the overall tumor burden [7, 8]. According to the aspects of the role, one notion has recently been received attention is cytoreductive prostatectomy, which involves surgical removal of the prostate in the setting of metastatic disease [9]. Such an approach of cytoreductive prostatectomy should include RP and NRP, and NRP should include transurethral resection of the prostate (TURP) and cryosurgery. TURP and cryosurgery have been widely used as mature surgical techniques. Due to the great progress in techniques, RP is becoming safer and more effective in patients with mPCa [10].

Recent studies have shown that RP and NRP successfully delayed the progression among

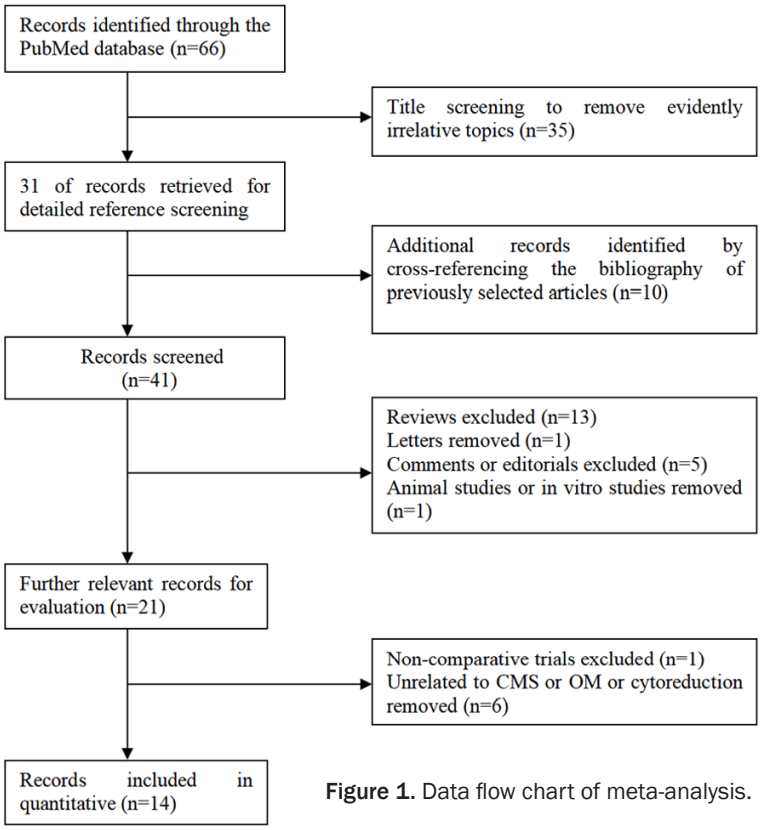

Figure 1. Data flow chart of meta-analysis.

mPCa patients in comparison with patients undergoing NLT [11, 12], suggesting that cytoreductive prostatectomy might have advantages over NLT. By contrast, Moschini's research showed no survival benefits using such a surgical approach [13]. Thus, the benefits of cytoreductive prostatectomy in mPCa patients remain inconsistent. Hence, the objective of this current meta-analysis was to examine the available evidence and to further assess the potential effect on mPCa by using such an approach of cytoreductive prostatectomy.

Materials and methods

Search strategy

We performed a systematic PubMed literature search with the terms "metastatic prostate cancer", "metastatic cancer of the prostate", "mPCa" and "cytoreduction", "cytoreductive", "debulking". Only English language literature for studies were enrolled and searched up to November 1st, 2018. By cross-referencing the bibliography of previously selected articles, additional relevant articles were collected. The major inclusion criteria were listed in the following: (1) Patients with mPCa; (2) Focused on the relationship between cytoreductive prostatectomy and mPCa; (3) Prospective randomized clinical trials (RCTs) (single-blinded, double-blinded or cross-over) and observational (case-control or cohort) studies; (4) Patients in the control group were treated with NLT only. The major exclusion criteria were as follows: (1) Unrelated to CSM or OM or PFS or cytoreduction; (2) Reviews or comments or letters or editorials; (3) Patients in the control group were not treated with NLT; (4) In vitro studies or animal studies.

Data extraction

Data were investigated by two independent reviewers (Y. Z and DS. P). If there was some disagreement of the two reviewers, a consensus would be reached after a consultation with a third reviewer (J. L). In studies where patients were divided into more than two groups, only comparisons between cytoreductive prostatectomy and NLT were extracted to keep the baselines as similar as possible.

Outcomes

The primary outcome was survival analysis, including CSM, OM and PFS, which was shown as HR and 95% confidence interval (CI). The following data were retrieved from relevant studies, including publication year, first author's name, mean age, months of follow-up, dominant ethnicity, number of patients, treatment, *P* value, most Gleason score, most PSA and most tumor stage. If the data of HRs with 95% CIs could not be directly obtained, it would be extracted from Kaplan-Meier curves [14, 15].

Quality assessment

We used Newcastle-Ottawa scale (NOS) tool to evaluate the risk of bias in these studies. A score of 1-9 stars was allocated to all cohort

Table 1. Characteristics of included studies in the systematic review and meta-analysis

Study	Year	Mean age (year)	Dominant ethnicity	Median follow-up (months)	Survival analysis	Number of patients	Treatment	Control	HR (95% CI)	*P* value	most Gleason score	most PSA (ng/ml)	most Tumor stage			Quality score
													T	N	M	
Lppenberg	2017	65	American	39	OM	15501	RP	NLT	0.37 (0.32-0.44)[a]	NA	≥8	10-20	≤T2a	N0	M1b	★★★★★★★
Moschini	2017	61	American	38.8	CSM	47	RP	NLT	0.24 (0.05-1.23)[a]	0.3	≥8	≥20	≥T2c	NA	M1a	★★★★★★★
Parikh	2017	72	American	22	OM	5846	RP	NLT	0.39 (0.34-0.45)	<0.01	≥8	≥20	≤T2a	N0	M1b	★★★★★★★★
Leyh-Bannurah	2017	64	NA	NA	CSM	2209	RP	NLT	0.35 (0.26-0.46)	<0.001	≥8	≥20	≤T2a	NA	M1b	★★★★★★★★
Steuber	2017	65	European	32.7	OM PFS	83	RP	NLT	1.56 (0.30-8.16)[a] 1.49 (0.67-3.30)[a]	0.25 0.92	7	NA	≥T2c	NA	NA	★★★★★
Sheng	2017	68	Asian	37	CSM PFS	49	NRP	NLT	0.21 (0.09-0.46) 0.54 (0.29-0.99)[a]	0.0027 0.0011	≥8	NA	NA	N0	NA	★★★★★★★★
Rusthoven	2016	61	American	61.2	OM	5913	RP	NLT	0.38 (0.25-0.58)	<0.001	≥8	NA	NA	N0	NA	★★★★★★★
Satkunasivam	2015	73	American	20	CSM	3874	RP	NLT	0.58 (0.35-0.95)	0.03	7	<10	≥T2c	N0	M1b	★★★★★★
Heidenreich	2015	61	European	34.5	CSM PFS	61	RP	NLT	0.50 (0.26-0.97)[a] 1.21 (0.69-2.11)[a]	NA NA	≥8	NA	≥T2c	NA	NA	★★★★★★★
Fossati	2015	65	American	36	CSM	NA	RP	NLT	NA	NA	NA	NA	NA	NA	NA	★★★★★★
Culp	2014	62	American	16	OM CSM	8056	RP	NLT	0.67 (0.59-0.75) 0.38 (0.27-0.53)	<0.001 <0.001	≥8	<10	NA	N0	M1b	★★★★★★
Bryan	2014	NA	American	NA	OM	709	RP	NLT	0.48 (0.34-0.68)[a]	NA	NA	NA	NA	NA	NA	★★★★★
Antwi	2014	65	American	NA	OM CSM	7738	RP	NLT	0.27 (0.20-0.38) 0.28 (0.20-0.39)	<0.0001 <0.0001	NA	NA	NA	NA	M1b	★★★★★★
Qin	2012	69	Asian	15	PFS CSM OM	146	NRP	NLT	0.50 (0.26-0.97)[a] 0.77 (0.30-1.98)[a] 0.69 (0.27-1.73)[a]	0.007 0.198 0.071	NA	NA	NA	NA	NA	★★★★

Abbreviations: NA, not available; OM, overall mortality; CSM, cancer-specific mortality; PFS, progression-free (from mHSPC to HRPC) survival; RP, radical prostatectomy; NRP, non-radical prostatectomy; NLT, no local therapy. [a]Data was extracted from Kaplan-Meier curves.

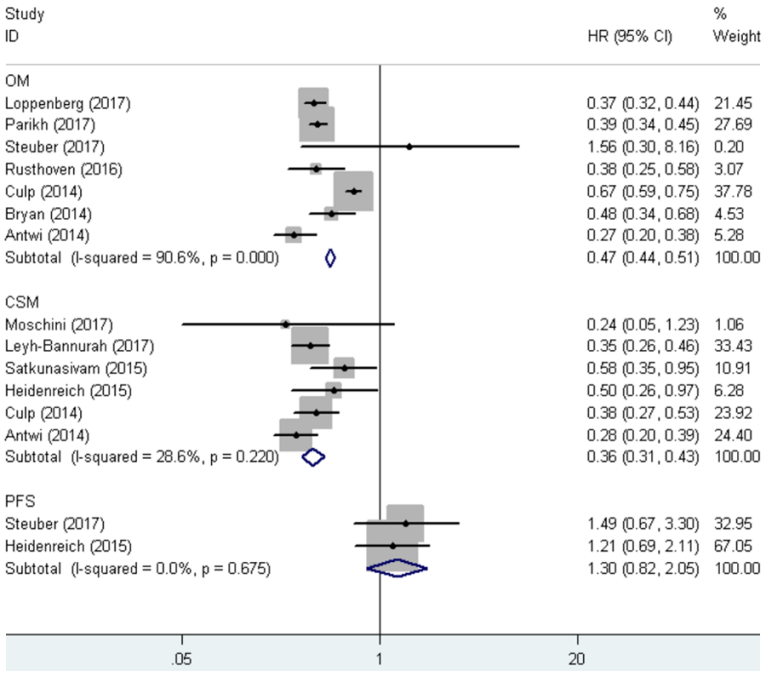

Figure 2. Forest plots of overall mortality (OM), cancer-specific mortality (CSM) and progression free survival (PFS) in association with RP for mPCa.

and case-control studies in the Newcastle-Ottawa scale [16].

Statistical analysis

A pooled hazard ratio (HR) with 95% CI was computed for all clinical outcomes reported in the enrolled studies by use of Stata software (version 11.0; StataCorp LP, College Station, TX). We employed Cochrane Chi-square χ^2 (Cochran Q) statistic and the I^2 test to analyze heterogeneity [17]. I^2>50% or Chi-square test P<0.1 indicated significant heterogeneity. Meta-analysis was performed using the fixed-effects method (Mantel-Haenszel method) or the random-effects method (DerSimonian-Laird method) when significant heterogeneity was not identified [18]. According to treatment, different levels of Gleason score, PSA, T-stage, M-stage or ethnicity, the patients were divided into several groups, and subgroup analyses were further performed to explore possible heterogeneity then. Moreover, we explored the existence of publication bias in included studies by use of a contour-enhanced funnel plot and Egger's method to determine other causes of publication bias through the way of examining the symmetry of the plot [19, 20], where P<0.05 indicated the presence of publication bias. Further, sensitivity analyses were performed to assess the robustness of pooled estimates.

Results

Characteristics of enrolled studies

We retrieved a total of 66 articles. The study selection process was shown in **Figure 1**. We excluded the following studies: letters, reviews, comments or editorials, animal studies or *in vitro* studies, articles unrelated to CMS or OM or cytoreduction and non-comparative trials. Finally, 14 studies [8, 11-13, 21-30] with a total of 50,232 patients were included in this meta-analysis.

Characteristics of all the 14 studies were presented in **Table 1**. All the studies were observational cohort studies published between 2012 and 2017. Of the 14 included studies, 12 articles with 50,037 patients focused on RP vs. NLT and the remaining two with 195 patients focused on NRP vs. NLT. In the 12 studies comparing RP and NLT, most of them focused on one or both of the OM and the CSM, except for Steuber et al. and Heidenreich et al. who concentrated on not only OM or CSM, but also PFS [8, 29]. In the two studies focusing on NRP vs. NLT, one adopted TURP and the other one adopted cryosurgery when taking the survival analysis item into account. Qin et al. focused on OM, CSM and PFS, while Sheng et al. focused on CSM and PFS [12, 21].

OM, CSM and PFS associated with RP for mPCa

The forest plots on the OM, CSM and PFS associated with RP for mPCa were shown in **Figure 2**. Overall, RP was associated with reduction in OM using fixed-effects model (pooled HR=0.47, 95% CI=0.44 to 0.51, P<0.001, I^2=90.6%). Meanwhile, these included studies revealed a prognostic role of RP for mPCa on CSM by fixed-effects model based on moderate

Table 2. Subgroup analysis of OM and CSM comparisons of RP versus NLT

Outcomes of interest	Studies (no.)	X^2	I^2 (%)	OM		Studies (no.)	X^2	I^2 (%)	CSM	
				P value	HR (95% CI)				*P* value	HR (95% CI)
Gleason										
7	1					1				
≥8	4	49.54	93.9	<0.001*	0.48 (0.45-0.52)	4	1.25	0.0	0.740	0.37 (0.30-0.46)
PSA (ng/ml)										
≤10	1					1				
10-20	1					0				
≥20	1					2	0.21	0.0	0.649	0.35 (0.26-0.46)
T										
≤T2a	2	0.24	0.0	0.627	0.38 (0.34-0.42)	1				
≥T2c	1					3	1.09	0.0	0.579	0.52 (0.36-0.77)
M										
M1a	0					1				
M1b	4	60.49	95.0	<0.001*	0.47 (0.44-0.51)	2	2.96	66.3	0.085	0.39 (0.31-0.51)
Ethnicity										
American	6	61.47	91.9	<0.001*	0.47 (0.44-0.51)	4	6.03	50.2	0.110	0.36 (0.29-0.45)
European	1					1				

Abbreviations: RP, radical prostatectomy; NLT, non-local treatment; OM, overall mortality; CSM, cancer-specific mortality. *Statistically significant.

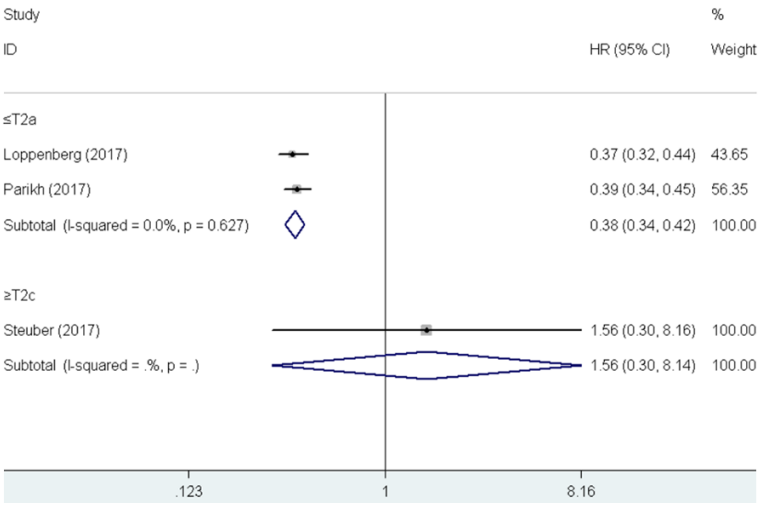

Figure 3. Forest plots of T subgroup analysis of OM in RP versus NLT.

heterogeneity (P=0.220, I^2=28.6%). RP for mPCa was associated with decreased CSM (pooled HR=0.36, 95% CI=0.31 to 0.43). Nevertheless, in comparison with NLT, RP did not show any superiority in decreasing PFS using fixed-effects model (pooled HR=1.30, 95% CI=0.82 to 2.05, P=0.675, I^2<0.01%). Overall estimates on OM were significantly heterogeneous (P<0.001, I^2=90.6%). Subgroup analyses were carried out by multiple factors, which contained Gleason score, PSA, ethnicity and tumor stage, to explore the possible reasons for the heterogeneity. As a result, levels below T2a (pooled HR=0.38, 95% CI=0.34 to 0.42, P=0.627, I^2<0.01%) were the possible sources of heterogeneity of OM in RP for mPCa (**Table 2** and **Figure 3**).

CSM and PFS associated with NRP for mPCa

Only two studies reported CSM and PFS in the comparison of NRP and NLT. Overall, NRP was associated with reduced risk of CSM using fixed-effects model (pooled HR=0.37, 95% CI=0.20 to 0.68). Meanwhile, overall estimates on CSM showed a significant heterogeneity (P=0.041, I^2=76.0%). Moreover, in a pooled analysis of these two studies, NRP use was associated with increased risk of PFS among patients with mPCa (pooled HR=0.52, 95% CI=0.33 to 0.82, P=0.867, I^2<0.01%) (**Figure 4**).

Publication bias

The combined application of Begg's and Egger's test was utilized to evaluate the publication bias. The results of publication bias based on the Egger's test of RP versus NLT and NRP versus NLT were shown in **Table 3**. In the pooled analysis of OM associated with RP for mPCa, the *p* value of Egger's test was 0.62. Moreover, in the pooled analysis of CSM associated with

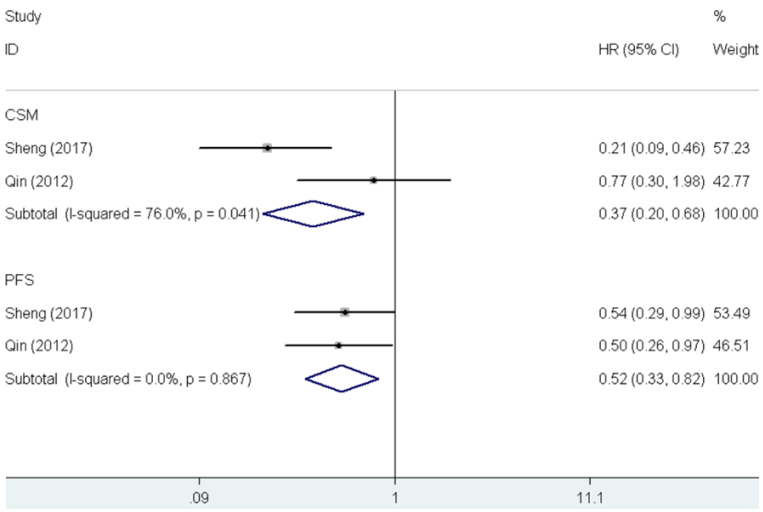

Figure 4. Forest plots of cancer-specific mortality (CSM) and progression free survival (PFS) in association with NRP for mPCa.

Table 3. Publication bias based on the Egger's test of RP versus NLT and NRP versus NLT

Outcomes of interest	Studies (no.)	Patients no.	Coef.	SE	*P* value	95% CI
RP versus NLT						
OM	7	42846	-1.35	2.54	0.62	-7.88-5.19
CSM	6	21985	0.75	1.29	0.59	-2.86-4.35
PFS	2	144	1.71			
NRP versus NLT						
CSM	2	195	19.92			
PFS	2	195	-3.39			

Abbreviations: RP, radical prostatectomy; NLT, non-local treatment; OM, overall mortality; CSM, cancer-specific mortality; NRP, non-radical prostatectomy; PFS, progression free survival.

RP for mPCa, the *p* value of Egger's test was 0.59. There was no significant publication bias. The funnel figures of OM and CSM for RP versus NLT were shown in **Figure 5**.

Sensitivity analysis

By sequentially deleting one single study each time to reflect the impact of the individual to overall, sensitivity analysis was performed to access the stability of results. No significant differences were detected for any parameters. The robust results of sensitivity analysis of OM and CSM for RP versus NLT were shown in **Figure 6**.

Discussion

Prostate cancer continues to be the important cause of death among men each year [31]. The high-risk patients with PCa are those likely to benefit from multidisciplinary interventions as they are more likely to have biochemical recurrence after initial treatment [32]. Patients with mPCa have a poor survival rate compared to men with non-metastatic PCa [33]. ADT with or without chemotherapy is traditionally recommended by EAU guidelines for mPCa. However, no sign of the survival benefit has been definitely demonstrated by use of ADT. Clearly, additional therapies for mPCa are urgently needed. There has been strong evidence showing improved survival rate in patients undergoing cytoreductive surgery in examining other malignancies with metastasis [5, 6]. Therefore, interest in the role of cytoreductive prostatectomy for mPCa has been rising. In recent years, some retrospective data have suggested survival benefits for such an approach in patients with mPCa.

The potential mechanisms by which cytoreduction in mPCa can improve survival has been explored. Tumor self-seeding theory suggested that increased circulating tumor cells portended a worse overall survival in mPCa, which were the intermediaries between primary tumors and metastases [34, 35]. It might be appropriate to reduce overall tumor volume or remove the primary tumor for reducing effects to fatal circulating tumor cells burden in mPCa. Moreover, suppression of androgen activity by use of ADT might lead to a dramatically increased sensitivity of tumor cells to androgens, which renders PCa cells survival in a low androgen environment in primary tumor [36]. These hypersensitive PCa cells would be the sources of recurrence and metastasis. Removal of primary tumor could eliminate these PCa cells, leading to improved outcomes. In addition, the tumor microenvironment is a source of continued androgen production, which has the potential

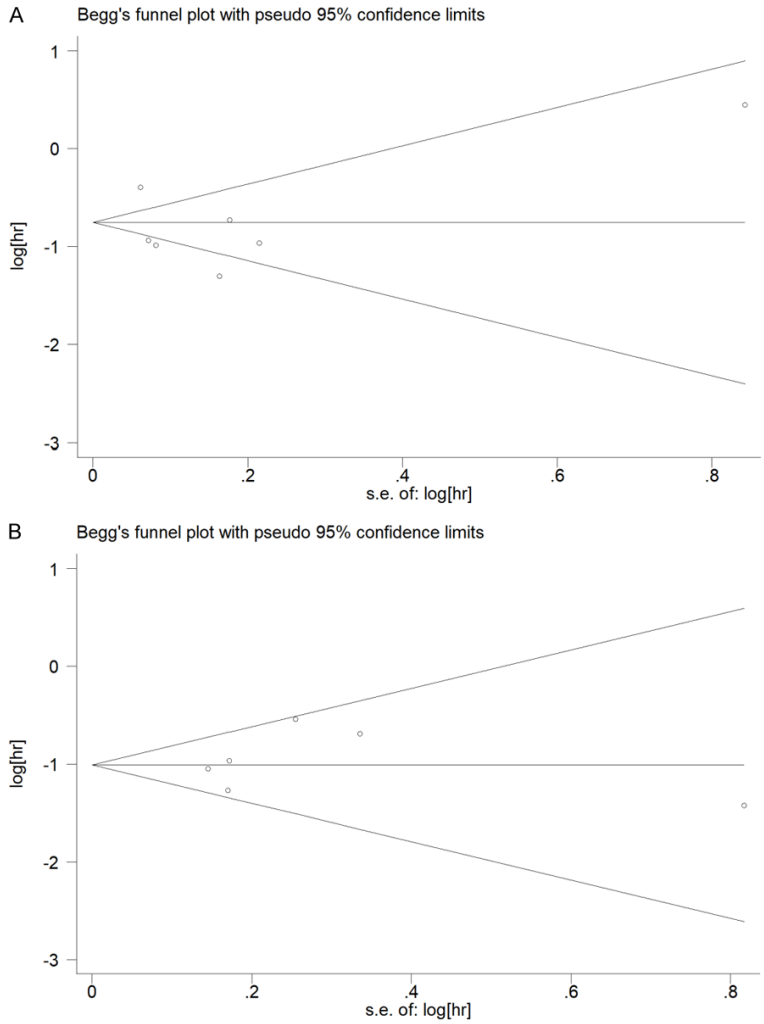

Figure 5. Funnel figures of included studies. A. Overall mortality for radical prostatectomy versus non-local treatment. B. Cancer-specific mortality for radical prostatectomy versus non-local treatment.

function of driving tumor cells to grow and spread [37]. Removing the primary tumor could mitigate this function.

Local complications are important considerations in patients with mPCa. Prevention of local complications should be taken seriously before determining suitable therapeutic approaches. A previous study showed that mPCa patients treated with RP experienced a low complication rate of 0%, while the mPCa patients treated with ADT alone experienced a higher local progression related complication rate of 33% [8]. In addition, Won's research retrospectively compared complication rates of patients with mPCa treated by RP plus ADT and ADT alone [38]. The findings indicated that the complication rate was significantly lower in patients who initially received RP. These evidences demonstrated the feasibility of RP for mPCa. Another form of cytoreductive prostatectomy is NRP, including TURP and cryosurgery. These two traditional approaches were safe and effective, which have been important surgical options to relieve complications in patients with prostate cancer [39, 40]. Hence, cytoreductive prostatectomy as an approach of local surgery could mitigate the related complications and be feasible in patients with mPCa.

In recent years, some retrospective data have suggested a possible role for cytoreductive prostatectomy in patients with mPCa. However, such an approach has not been rigorously evaluated, with controversial survival benefits on it. Hence, we carried out a meta-analysis to clarify the merits of cytoreductive prostatectomy. Our results successfully shed light on the relationship that RP for mPCa was associated with decreased OM and CSM in comparison with NLT. In detection of the relationship between NRP and survival in patients with mPCa, our results revealed that NRP had beneficial effect on CSM and PFS when compared with NLT. In other words, cytoreductive prostatectomy could significantly reveal survival benefits in mPCa patients. Subsequent publication bias and sensitivity analysis manifested the robustness of our study.

It is critical to identify appropriate candidates for cytoreductive prostatectomy in mPCa. Fossati's study [25] demonstrated that the potential benefits of RP among mPCa patients greatly depended on baseline characteristics and patient selection. Furthermore, Heidenreich's study [8] only considered RP in mPCa

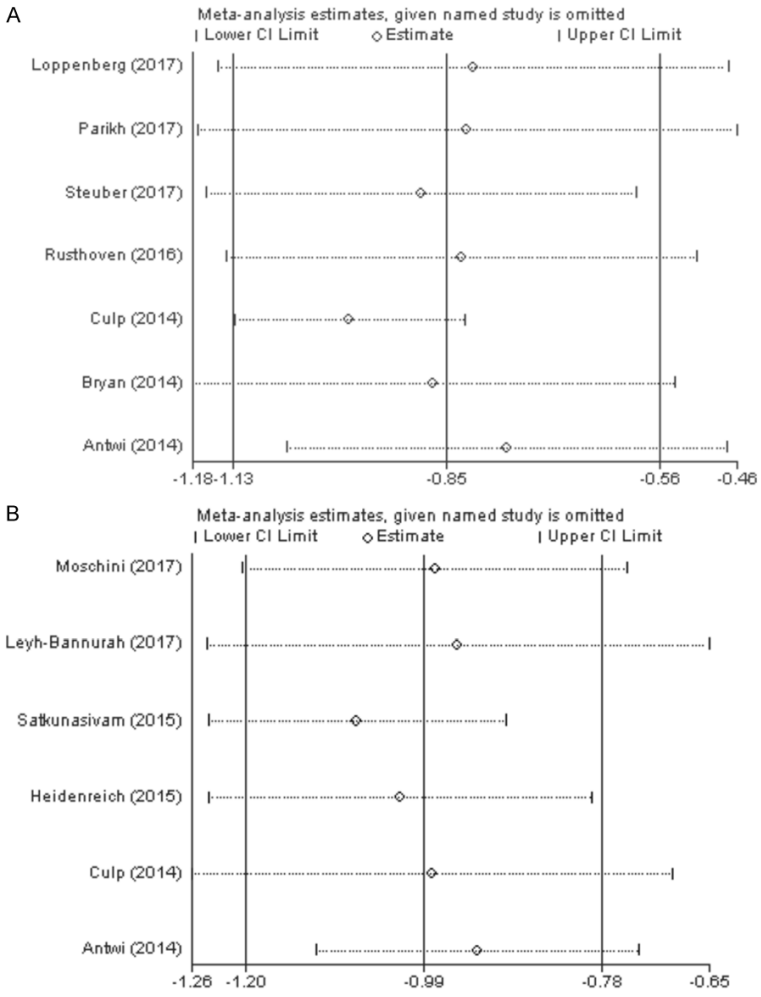

Figure 6. Sensitivity analysis of included studies. A. Overall mortality for radical prostatectomy versus non-local treatment. B. Cancer-specific mortality for radical prostatectomy versus non-local treatment.

patients with three or less bone metastases and no bulky lymphadenopathy, indicating that patients with less extent of metastatic disease appeared to benefit most. However, population-based studies reported a survival benefit of RP regardless of tumor metastasis extent [22, 24]. Hence, it is of great significance to identify appropriate candidates for RP in mPCa. In selecting the appropriate NRP patients in mPCa, Sheng's research [12] identified lower PSA at diagnosis and lower biopsy Gleason score as independent predictive factors of longer PFS.

Importantly, there are several limitations of our meta-analysis. First, in the group of NRP vs. NLT, the fewer studies could be a potential cause for the heterogeneity of CSM in the pooled study estimates. Second, there was a relative high heterogeneity of OM in the group of RP vs. NLT. Several studies included failed to perform a regression or propensity analysis, therefore, the group of treated and the NLT group perhaps were statistically different in several categories such as levels below T2a, performance status of patients, comorbidities, dosage of NLT and exclusion of patients because of missing data. Third, the two approaches of cytoreductive prostatectomy might vary in the enrolled studies, which could not be identified in this meta-analysis. In addition, the included researches were all cohort studies derived from retrospective data, which could not have a clear impact on group baseline features as RCTs.

To sum up, it is a systematic review and meta-analysis to demonstrate that RP for mPCa was associated with decreased OM and CSM when compared with NLT. Our results also revealed that NRP had beneficial effect on CSM and PFS in comparison with NLT. We successfully demonstrated the feasibility and survival benefits of cytoreductive prostatectomy for mPCa. In addition, well-designed RCTs and comparative studies with long-term follow-up results should be further conducted to elaborate the efficacy in the future.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yingli Lin, Department of Urology, Xuzhou Cancer Hospital, Affiliated Hospital of Jiangsu University, Xuzhou, Jiangsu, China. Tel: +86-15996959302; Fax: +86-85528553; E-mail: 529735655@qq.com

References

[1] Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, Mottet N, Schmid HP,

van der Kwast T, Wiegel T and Zattoni F; European Association of Urology. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011; 59: 61-71.

[2] Wu JN, Fish KM, Evans CP, Devere White RW and Dall'Era MA. No improvement noted in overall or cause-specific survival for men presenting with metastatic prostate cancer over a 20-year period. Cancer 2014; 120: 818-823.

[3] Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F and Mottet N; European Association of Urology. EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014; 65: 467-479.

[4] Wiegand LR, Hernandez M, Pisters LL and Spiess PE. Surgical management of lymph-node-positive prostate cancer: improves symptomatic control. BJU Int 2011; 107: 1238-1242.

[5] Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H and Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004; 171: 1071-1076.

[6] Bookman MA. Optimal primary therapy of ovarian cancer. Ann Oncol 2016; 27 Suppl 1: i58-i62.

[7] Kim MY, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L and Massague J. Tumor self-seeding by circulating cancer cells. Cell 2009; 139: 1315-1326.

[8] Heidenreich A, Pfister D and Porres D. Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. J Urol 2015; 193: 832-838.

[9] Faiena I, Singer EA, Pumill C and Kim IY. Cytoreductive prostatectomy: evidence in support of a new surgical paradigm (Review). Int J Oncol 2014; 45: 2193-2198.

[10] Mathieu R, Korn SM, Bensalah K, Kramer G and Shariat SF. Cytoreductive radical prostatectomy in metastatic prostate cancer: does it really make sense? World J Urol 2017; 35: 567-577.

[11] Loppenberg B, Dalela D, Karabon P, Sood A, Sammon JD, Meyer CP, Sun M, Noldus J, Peabody JO, Trinh QD, Menon M and Abdollah F. The impact of local treatment on overall survival in patients with metastatic prostate cancer on diagnosis: a national cancer data base analysis. Eur Urol 2017; 72: 14-19.

[12] Sheng MX, Wan LL, Liu CM, Liu CX and Chen SS. Cytoreductive cryosurgery in patients with bone metastatic prostate cancer: a retrospective analysis. Kaohsiung J Med Sci 2017; 33: 609-615.

[13] Moschini M, Morlacco A, Kwon E, Rangel LJ and Karnes RJ. Treatment of M1a/M1b prostate cancer with or without radical prostatectomy at diagnosis. Prostate Cancer Prostatic Dis 2017; 20: 117-121.

[14] Williamson PR, Smith CT, Hutton JL and Marson AG. Aggregate data meta-analysis with time-to-event outcomes. Stat Med 2002; 21: 3337-3351.

[15] Tierney JF, Stewart LA, Ghersi D, Burdett S and Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16.

[16] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 1999.

[17] Van Houwelingen HC, Arends LR and Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med 2002; 21: 589-624.

[18] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

[19] Deeks JJ, Macaskill P and Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005; 58: 882-893.

[20] Peters JL, Sutton AJ, Jones DR, Abrams KR and Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008; 61: 991-996.

[21] Qin XJ, Ma CG, Ye DW, Yao XD, Zhang SL, Dai B, Zhang HL, Shen YJ, Zhu Y, Zhu YP, Shi GH, Xiao WJ, Lin GW and Swanson GP. Tumor cytoreduction results in better response to androgen ablation--a preliminary report of palliative transurethral resection of the prostate in metastatic hormone sensitive prostate cancer. Urol Oncol 2012; 30: 145-149.

[22] Antwi S and Everson TM. Prognostic impact of definitive local therapy of the primary tumor in men with metastatic prostate cancer at diagnosis: a population-based, propensity score analysis. Cancer Epidemiol 2014; 38: 435-441.

[23] Bryan RT, Kirby R and Mostafid H. Does the nonurologic scientific community understand urothelial bladder cancer? Eur Urol 2014; 66: 601-602.

[24] Culp SH, Schellhammer PF and Williams MB. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. Eur Urol 2014; 65: 1058-1066.

[25] Fossati N, Trinh QD, Sammon J, Sood A, Larcher A, Sun M, Karakiewicz P, Guazzoni G,

Montorsi F, Briganti A, Menon M and Abdollah F. Identifying optimal candidates for local treatment of the primary tumor among patients diagnosed with metastatic prostate cancer: a SEER-based study. Eur Urol 2015; 67: 3-6.

[26] Satkunasivam R, Kim AE, Desai M, Nguyen MM, Quinn DI, Ballas L, Lewinger JP, Stern MC, Hamilton AS, Aron M and Gill IS. Radical prostatectomy or external beam radiation therapy vs no local therapy for survival benefit in metastatic prostate cancer: a SEER-medicare analysis. J Urol 2015; 194: 378-385.

[27] Rusthoven CG, Jones BL, Flaig TW, Crawford ED, Koshy M, Sher DJ, Mahmood U, Chen RC, Chapin BF, Kavanagh BD and Pugh TJ. Improved survival with prostate radiation in addition to androgen deprivation therapy for men with newly diagnosed metastatic prostate cancer. J Clin Oncol 2016; 34: 2835-2842.

[28] Parikh RR, Byun J, Goyal S and Kim IY. Local therapy improves overall survival in patients with newly diagnosed metastatic prostate cancer. Prostate 2017; 77: 559-572.

[29] Steuber T, Berg KD, Roder MA, Brasso K, Iversen P, Huland H, Tiebel A, Schlomm T, Haese A, Salomon G, Budaus L, Tilki D, Heinzer H, Graefen M and Mandel P. Does cytoreductive prostatectomy really have an impact on prognosis in prostate cancer patients with low-volume bone metastasis? Results from a prospective case-control study. Eur Urol Focus 2017; 3: 646-649.

[30] Leyh-Bannurah SR, Gazdovich S, Budaus L, Zaffuto E, Briganti A, Abdollah F, Montorsi F, Schiffmann J, Menon M, Shariat SF, Fisch M, Chun F, Steuber T, Huland H, Graefen M and Karakiewicz PI. Local therapy improves survival in metastatic prostate cancer. Eur Urol 2017; 72: 118-124.

[31] Siegel R, Ma J, Zou Z and Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64: 9-29.

[32] Bremer M. Radical prostatectomy versus observation for localized prostate cancer. Strahlenther Onkol 2012; 188: 1159-1160.

[33] SEER Cancer Statistics Review, 1975-2010. National Cancer Institute. Bethesda; 2013.

[34] Shao YH, Kim S, Moore DF, Shih W, Lin Y, Stein M, Kim IY and Lu-Yao GL. Cancer-specific survival after metastasis following primary radical prostatectomy compared with radiation therapy in prostate cancer patients: results of a population-based, propensity score-matched analysis. Eur Urol 2014; 65: 693-700.

[35] Goldkorn A, Ely B, Quinn DI, Tangen CM, Fink LM, Xu T, Twardowski P, Van Veldhuizen PJ, Agarwal N, Carducci MA, Monk JP 3rd, Datar RH, Garzotto M, Mack PC, Lara P Jr, Higano CS, Hussain M, Thompson IM Jr, Cote RJ and Vogelzang NJ. Circulating tumor cell counts are prognostic of overall survival in SWOG S0421: a phase III trial of docetaxel with or without atrasentan for metastatic castration-resistant prostate cancer. J Clin Oncol 2014; 32: 1136-1142.

[36] Mostaghel EA, Page ST, Lin DW, Fazli L, Coleman IM, True LD, Knudsen B, Hess DL, Nelson CC, Matsumoto AM, Bremner WJ, Gleave ME and Nelson PS. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. Cancer Res 2007; 67: 5033-5041.

[37] Negri-Cesi P and Motta M. Androgen metabolism in the human prostatic cancer cell line LNCaP. J Steroid Biochem Mol Biol 1994; 51: 89-96.

[38] Won AC, Gurney H, Marx G, De Souza P and Patel MI. Primary treatment of the prostate improves local palliation in men who ultimately develop castrate-resistant prostate cancer. BJU Int 2013; 112: E250-255.

[39] Nguyen HD, Allen BJ and Pow-Sang JM. Focal cryotherapy in the treatment of localized prostate cancer. Cancer Control 2013; 20: 177-180.

[40] Pelletier J, Cyr SJ, Julien AS, Fradet Y, Lacombe L and Toren P. Contemporary outcomes of palliative transurethral resection of the prostate in patients with locally advanced prostate cancer. Urol Oncol 2018; 36: 363.e7-363.e11.