Cytoreductive prostatectomy improves survival outcomes in patients with oligometastases: a systematic meta-analysis

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Research Article

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Abstract

Background: At present, controversy remains regarding whether cytoreductive prostatectomy (CRP) should be performed for oligometastatic prostate cancer (OPC). The purpose of this study was to assess the efficacy of CRP for the treatment of OPC by conducting a systematic meta-analysis .

Methods: Design A systematic review and meta-analysis, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.Data sources Publications included in the PubMed, Embase, the Cochrane Library, EBSCO, Web of Science (SCI) databases as of May 2022.Eligibility criteria Prospective studies comparing the efficacy of RP versus no RP in the treatment of OPC.

Results: In total, 11 publications incorporating 888 patients were analyzed. Tumor-reducing prostatectomy was found to have no significant effect on long-term or short-term OS [OR=2.26, 95%CI(0.97,5.28), P=0.06 > 0.05] and [OR=1.73, 95%CI(0.83,3.58), P=0.14 > 0.05], but it significantly improved patient CSS [OR=1.77, 95%CI(1.01,310.), P=0.04 < 0.05]and[OR=2.71, 95%CI(1.72,4.29), P < 0.0001] and PFS [OR=1.93, 95%CI (1.25, 2.97), P=0.003 < 0.05].

Conclusion: These results suggest that cytoreductive prostatectomy can confer survival benefits to OPC patients.

Background

Prostate cancer is the second most prevalent tumor type globally, and the sixth deadliest cancer among males [1]. An estimated 12.76 million and 3.59 million people throughout the world were diagnosed with and died of prostate cancer, respectively, in 2018 [2]. While surgery and radiotherapy can be used to treat early-stage prostate cancer, many patients nonetheless develop metastatic disease [3, 4]. Androgen deprivation therapy (ADT) remains a therapeutic mainstay for advanced metastatic prostate cancer patients, with systemic therapy being critical [5]. However, there is also growing evidence that radical prostatectomy and stereotactic radiotherapy can afford therapeutic benefits to metastatic prostate cancer patients [6].

Hellman and Weichselbaum were the first to propose oligometastatic disease as an intermediate state between localized primary disease and widespread disseminated metastasis during early-stage tumor radiotherapy treatment [7, 8]. However, international definitions of oligometastases remain inconsistent and controversial, with some studies defining this status based on imaging findings of ≤ 5 metastases including the lymph nodes, bones, or vertebrae without visceral organ metastases [9–11]. The value of local treatment in individuals with metastatic disease has historically been limited by difficulties in locating these metastases, with systemic treatment offering an opportunity to slow the progression of disease and thereby prolong the overall survival (OS) of treated patients. However, subsequent research has shown cytoreductive surgery to offer some therapeutic benefit in certain cancer types including ovarian cancer, metastatic renal cell carcinoma, and pancreatic neuroendocrine tumors [12–15]. A mouse model of prostate cancer has also been reported to exhibit reduced metastatic disease progression and prolonged survival following cytoreductive surgery [16]. Recent evidence has further supported the benefit of primary tumor resection in mice with metastatic prostate cancer, with treated animals surviving for longer ($p < 0.001$), exhibiting slower rises in PSA levels ($p < 0.01$), and fewer pulmonary metastases ($p = 0.073$) [17]. Despite such evidence, the value of tumor-reducing surgery in prostate cancer patients remains the subject of controversy.

While there is growing consensus among many studies, full consensus regarding the definition of oligometastatic prostate cancer is still lacking. At the 2019 APCCC meeting[18], there was considerable disagreement regarding the location of the metastases, with about 46% of panelists voting for a limited number of synchronous or metachronous metastases in bone or lymph nodes, but not for metastases in internal organs, 33% supported a limited number of synchronous or metachronous metastases, including visceral organ metastases, 8% supported a limited number of bone or lymph node metachronous metastases but not visceral organ metastases,4% supported a limited number of metachronous metastases, and metastatic disease, including visceral organ metastasis, while another 9% believed that oligometastatic prostate cancer was not clinically significant. However, clinical consensus is relatively unified with respect to the number of transfers, with 48% of the members having been in favor of three or fewer transfers, while 41% were in favor of five or fewer transfers. From analyses of the results of the STAMPEDE trial [19], the HORRAD trial [20], and the STOPCAP meta-analysis [21], 98% of the panel members recommended local treatment of the

primary tumor, but cytoreductive surgery was not considered effective in patients with oligometastatic prostate cancer. As such, the overall benefit of such treatment remains highly debated.

The present study was therefore developed to explore the value of cytoreductive surgery in oligometastatic prostate cancer by pooling data from published prospective studies in a comprehensive systematic review and meta-analysis in which patient OS, cancer-specific survival (CSS), and progression-free survival (PFS) could be effectively analyzed to gauge the benefit of this therapeutic approach.

Materials And Methods

Patient and public involvement

Patients and the public had no role in the design or execution of this study.

Study selection

The PubMed, Embase, Cochrane Library, EBSCO, and Web of Science (SCI) databases were searched for all relevant studies published as of May 2021 using MeSH terms and free text terms including the following: prostate cancer, oligometastatic OR oligometastasis OR oligometastases, prostatectomy OR cytoreduction surgical procedures. The references of relevant studies were also manually reviewed to identify other studies of interest. Only studies published in English were included in this meta-analysis, which was conducted in accordance with PRISMA guidelines [22]. Studies eligible for inclusion in this analysis met the following criteria: (1) studies of patients with oligometastatic prostate cancer, as defined by the presence of ≤ 5 metastases; (2) studies examing the clinical outcomes associated with cytoreductive surgery in oligometastatic prostate cancer patients; and (3) studies reporting relevant outcomes following surgery including OS, CSS, and/or PFS.

Two researchers (YM and GW) separately identified relevant studies and extracted data therefrom, with disagreements being resolved through discussion and consensus with MH. The study selection process is outlined in Fig. 1.

Study quality assessment

The Oxford Centre for Evidence-Based Medicine [23] and the Newcastle-Ottawa scale were utilized to examine prospective cohort study quality [24].

Data extraction and statistical analysis

Post-treatment outcomes of interest including OS, CSS, and PFS were extracted from included studies. The pooled data were expressed in the form of risk odds rations (ORs) and 95% confidence intervals (CIs). The I2 statistic was used to assess heterogeneity among studies, with $I2 < 50\%$ being indicative of acceptable heterogeneity. When heterogeneity was acceptable, results were analyzed with a fixed-effects model, whereas a random-effects model was otherwise used. The Z-test was used to analyze pooled effects, with $P < 0.05$ as the significance threshold.

Sensitivity analysis

The reliability of results was assessed through sensitivity analyses of OS, CSS, and PFS outcomes at 3 and 5-year time points. The Review Manager v5.4 software was used for all data analyses.

Results

In total, 11 relevant studies [25-34] incorporating 888 patients were included in the present analysis after having met with study selection criteria (Table 1). All included prospective studies were considered to be of high quality(Table 2.). Ten articles defined metastases in oligometastatic prostate cancer with five or fewer metastases, and all controls were treated with ADT, with no suspicious visceral involvement on pretreatment imaging. One study employed robotic surgery approaches and one study employed cryosurgery approaches.

Overall survival

Of the included studies, 8 reported on patient OS, including 4 that reported 3-year OS outcomes. Data were were analyzed using a fixed-effects model (I^2 = 0%, P = 0.91). As above, there was no significant difference between the experimental and control groups [OR = 1.73, 95%CI(0.83,3.58), P = 0.14 > 0.05](Fig. 2 A). Additionally, 5 studies reported on patient 5-year OS, and the results were analyzed with a random-effects model owing to the presence of heterogeneity (I^2=68%, P=0.01). There were no significant differences between the experimental and control group in this analysis [OR = 2.26, 95%CI(0.97,5.28), P = 0.06 > 0.05](Fig. 2 B).

Tumor-specific survival

Just 8 of the included studies reported on patient CSS, of which 5 reported on 3-year CSS outcome data. Results were analyzed with a fixed-effects model (I^2 = 0%, P = 0.84), revealing a significant difference between the surgery and non-surgery groups [OR = 1.77, 95%CI(1.01,3.10), P = 0.04 < 0.05](Fig. 3 A). Moreover, 6 studies reported on patient 5-year CSS. There was significant heterogeneity associated with this endpoint (I^2 = 70%, P = 0.005), with results thus being analyzed using a random-effects model .There were no significant differences between the experimental and control group in this analysis [OR = 2.71, 95%CI(0.98,4.63), P = 0.06> 0.05](Fig. 3 B).

Progression-free survival

In total, 5 studies reported on 5-year PFS outcomes for included patients, with data being analyzed with a fixed-effects model (I^2 = 40%, P = 0.16). A significant difference in 5-year PFS was observed between the surgery and non-surgery groups [OR = 1.93, 95%CI(1.25, 2.97), P = 0.003 < 0.05](Fig. 4), suggesting that beneficial improvements in PFS were associated with cytoreductive surgery.

Sensitivity analyses

Sensitivity analyses were performed for each of the five outcomes. For these analyses, individual studies were iteratively excluded from the corresponding outcome assessments to examine the effect of the absence of a given study on overall result stability. The results pertaining to 3y-OS, 3y-CSS, and 5yPFS outcomes remained consistent in these sensitivity analyses, indicating the reliability of the results. However, the results of 5y-CSS and 5y-OS outcomes were altered when xx and xx were excluded, respectively, indicating heterogeneity that affected the above results. However, as no more than ten studies were included in these analyses, these skewed results may have been inaccurate and were reported as a potential source of publication bias.

Discussion

Some prior reports have indicated that cytoreductive surgical treatment of primary tumors can afford benefits to the survival and quality of life of patients with certain cancer types, leading some researchers to propose a ‘seed and soil’ theory in which primary tumor cells can be regarded as circulating tumor cells that can seed both local and distal metastatic tumor growth. As such, prolonged primary tumor survival may increase the odds of further disease metastasis [35–39].

In certain diseases including ovarian cancer, metastatic renal cell carcinoma, and pancreatic neuroendocrine tumors, the benefits of primary tumor cytoreductive surgery have been confirmed. There is also further evidence that tumor reduction can improve the quality of life in oligometastatic prostate cancer patients [40, 41]. Importantly, this surgical intervention is feasible and safe in individuals with metastatic prostate cancer. However, as randomized controlled trials focused on this surgical intervention in oligometastatic prostate cancer patients are lacking, its purported survival benefits remain controversial.

The meta-analysis published by Cheng et al.[42] demonstrated that cytoreductive surgery offered obvious advantages in terms of overall survival, tumor-specific survival, and progression-free survival. In contrast, our included studies were more recent (after 2000), and includedmore comprehensive and updated data. In addition, instead of assessing at OS, CSS, and PFS, we examined 3-year and 5-year OS, CSS, and PFS in patients, which may have led to distinct study findings. Our analysis revealed that cytoreductive surgery can effectively improve the 3-year CSS and 5-year-PFS of patients, it cannot improve the overall survival rate and 5-year CSS of patients in the short- and medium-term. Multiple reports have similarly demonstrated the benefits of

cytoreductive surgery in metastatic prostate cancer, as in a study performed by Cul et al. [43] assessing 8185 patients with IV (M1a–c) PCa (NSR (n = 7811), RP (n = 245)), which found debulking surgery to significantly improve both 5-year OS (67.4% vs 22.5%) and 5-year CSS (75.8% vs 48.7%) in these patients ($p < 0.01$). Gratzke et al. [44] also recently analyzed the Munich Cancer Registry dataset and found that of the 1538 newly diagnosed prostate cancer patients, 74 who had undergone RP exhibited significantly higher 5-year survival outcomes as compared to patients that did not (55% vs. 21%) ($p < 0.01$). Heidenreich et al. [45]further analyzed 113 metastatic prostate cancer patients from 4 institutions who had undergone surgical treatment, and observed respective 3- and 5-year OS rates of 87.6%, and 79.6%, with 3- and 5-year CSS rates of 89.3% and 80.5%, respectively. As such, cytoreductive debulking therapy offers benefits to the CSS and OS of metastatic prostate cancer patients. However, whether cytoreductive surgery also has an overall benefit for oligometastatic prostate cancer remains to be confirmed. Using prospective institutional data, Steuber et al. [46]compared 43 patients with oligometastatic prostate cancer treated with CRP and 40 patients with optimal systemic therapy and found that at a median follow-up of 82.2 months, there were no significant differences in CSS ($p = 0.92$) or OS ($p = 0.25$). The findings of this study are consistent with our results suggesting that debulking surgery did not improve the overall survival rate of patients.

In one single-institution long-term analysis of 11 oligometastatic prostate cancer patients, Gandaglia et al. [47] reported 7-year clinical progression and cancer-specific mortality (CSM)-free survival rates of 45% (95% CI, 30–85%) and 82% (95% CI, 62–99%), respectively, with long-term rates of CSM-free survival being higher than those for ADT only (48%-55%) [43, 47]. This is inconsistent with the results of our analysis, which may also be due to the short follow-up time of the included studies. However, Battaglia et al. [48] further conducted metastatic surgical treatment in 17 oligometastatic prostate cancer patients, and observed a 4-year OS of 66%, with three patients dying of prostate cancer. These results and those of our analysis suggest that cytoreductive surgery can significantly improve short-term oligometastatic prostate cancer patient CSS.

Overall, the results of this meta-analysis suggest that cytoreductive surgery does not improve the OS of prostate cancer patients. This may be attributable to the limited number of included studies and limited overall sample size, or may suggest that the side effects associated with cytoreductive surgery may contribute to a lack of overall benefit to patient OS.

There are several limitations to this analysis. For one, as randomized clinical trials on this therapeutic approach are lacking, the majority of included studies were retrospective in nature and of varying quality levels. There were also inconsistencies among studies with respect to the standards used for patient inclusion, and parameters such as PSA levels or age cannot be controlled for in our pooled analyses. Moreover, our results are inevitably affected by the short follow-up period and limited number of included patients. There was also substantial heterogeneity among the stage of metastatic prostate cancer patients included in the analyzed studies, further complicating the interpretation of these results and underscoring directions for further study.

Conclusion

The results of this meta-analysis suggest that cytoreductive surgery may confer certain survival benefits to prostate cancer patients with oligometastatic disease. However, additional large-scale prospective randomized controlled trials will be critical to validating these results and establishing the overall benefit of such treatment to the quality of life of patients suffering from this form of cancer.

Abbreviations

Cytoreductive prostatectomy	CRP
Oligometastatic prostate cancer	OPC
Androgen deprivation therapy	ADT
Overall survival	OS
Cancer-specific survival	CSS
Progression-free survival	PFS
Web of Science	SCI
Confidence intervals	CIs
Cancer-specific mortality	CSM

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and material

Not Applicable

Competing interests

The authors have no conflicts of interest to declare.

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Authors' contributions

Yifeng Mao contributions:data collection, drafting and critical revision of the manuscript.Mingqiu Hu contributions:drafting and critical revision of the manuscript.

Gaowei Yangc, Erke Gaoc, Wangwang Xu contributions: study design and conception, drafting and critical revision of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. The characteristics of included studies for meta-analysis

Authors and year	Patients	Group	No of patients	Ag□range□ (years)	Follow-up □range) □mo□	CPFS	CSS	OS
Tian Lan al. 2019[21]	111	ADT	76	71.17 ±7.73	35□22-41□	27.0%□3years□ 21.0%□5years□	87.9%□3years□ 74.9%□5years□	85.5%(3-y)
		CRP+ADT	35	67.83± 7.19	35□25-45□	42.7%□3years□ 19.0%□5years□	90.8%□3years□ 63.6%□5years□	88.6%(3-y)
Won Sik Jang al. 2018[22]	79	ADT	41	71 (67–76)	40(25-48)	41/41(1-y) 17/41(3-y) 4/41(5-y)	40/41(1-y) 16/41(3-y) 6/41(5-y)	
		RARP	38	65 (62–69)	40(25-48)	37/38(1-y) 24/38(3-y) 14/38(5-y)	38/38(1-y) 31/38(3-y) 14/38(5-y)	
Axel Heidenreich al. 2015[23]	61	ADT	38	63.9(47-83)	44.0 (24-96)		84.2%(3-y)	78.9%(3-y)
		CRP	23	61(42-69)	40.6 (3-71)		95.6%(3-y)	91.3%(3-y)
Thomas Steuber al. 2010[24]	158	RP-	50	62(49-70)	98(88-113)	61%(5-y) 31%(10-y)	81%(5-y) 46%(10-y)	80%(5-y) 42%(10-y)
		RP+	108	64(46-76)	98(88-113)	77%(5-y) 61%(10-y)	84%(5-y) 76%(10-y)	79%(5-y) 69%(10-y)
Nasser Simforoosh al. 2019[25]	49	ST	23		22.8(14-43)		65.2%(3-y)	65.2%(3-y)
		CRP	26		19.2(9-42)		76.9%(3-y)	76.9%(3-y)
M Moschini al. 2016[31]	61	Surgery	31	62 (56–66)	38.8		100%(1-y) 91.3%(3-y) 61.9%(5-y)	
		ADT	16	59 (54–59)			93.8%(1-y) 76.9%(3-y) 46.2%(5-y)	
Ming-Xiong Sheng al 2017[27]	49	Surgery	23	68.1 ± 9.9 □57–83□	37□19-53□	86.96(5-y)		86.96%(5-y)
		ADT	26	72.0 ± 4.7 □63–84□	41□24-56□	92.31%(5-y)		73.08%□5-y□
Grimm MO al. 2002[30]	82	RP	50			53%(5-y) 36%(10-y)	90%□5-y□ 47%□10-y□	86%(5-y) 34%(10-y)
		ADP	32			31%(5-y)10	53%□5-y□	39%(5-y)

					15%(10-y)	32%（10-y）	17%10-y)
Shubin Si al. 2021[28]	84	RP	27	76.67 ± 9.66			96.2%(3-y) 76.0%(5-y)
		-RP	57	76.42 ± 9.69			94.7%(3-y) 74.9%(5-y)
Bimal Bhindi al. 2017[29]		RRP	34			79%(5-y)	77%
		-RRP	34			55%(5-y)	55%

Continuous variables were expressed as (mean±SD), mean (range) or median (IQR). PSA：The nadir of prostate-specific antigen ,CSS：Cancer-specific survival,OS：overall surviva,RP radical retropubic prostatectomy, CRP cytoreductive prostatectomy, RARP robot-assisted radical prostatectomy, ADT androgen deprivation therapy

Tab. 2 Literature quality evaluation table

Study	selection				comparability	Exposure			scores
	Adequate Definition of cases	representativeness of the cases	selection of controls	definition of controls	control for important factor	Ascertainment of exposure	Same method of ascertainment for cases andcontrols	Non-reponse rate	
Tian Lan al. 2019[21]	☆	/	☆	☆	☆	☆	/	☆	6
Won Sik Jang al. 2018[22]	☆	☆	☆	☆	☆	☆	/	☆	7
Axel Heidenreich al. 2015[23]	/	☆	☆	☆	☆	☆	/	☆	6
Thomas Steuber al. 2010[24]	☆	☆	☆	☆	/	☆	☆	☆	7
Nasser Simforoosh al. 2019[25]	☆	/	☆	☆	/	☆	☆	☆	6
M Moschini al. 2016[31]	☆	☆	☆	☆	☆☆	☆	/	☆	8
Ming-Xiong Sheng al 2017[27]	/	☆	☆	☆	/	☆	☆	☆	6
Grimm MO al. 2002[30]	☆	☆	☆	☆	/	☆	☆	☆	7
Shubin Si al. 2021[28]	☆	☆	☆	☆	☆☆	☆	/	☆	8
Bimal Bhindi al.	/	☆	☆	☆	☆	☆	☆	☆	7

Figures

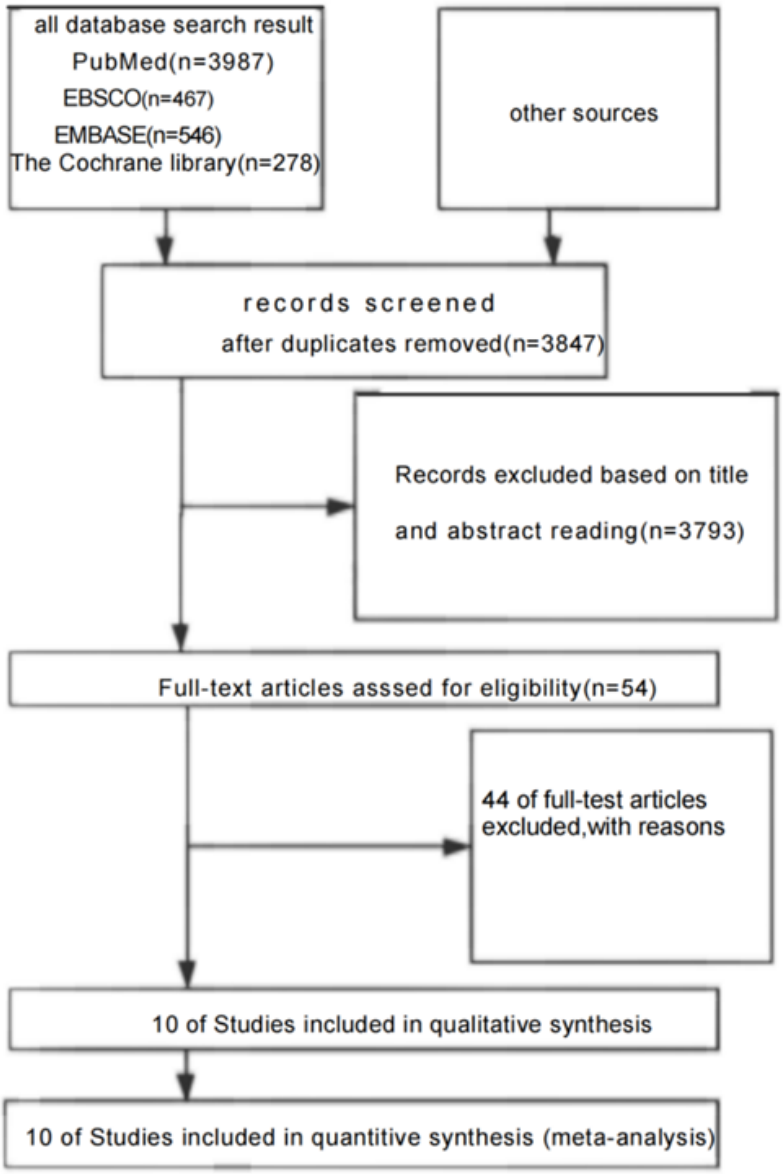

Figure 1

Flow diagram of the search strategy

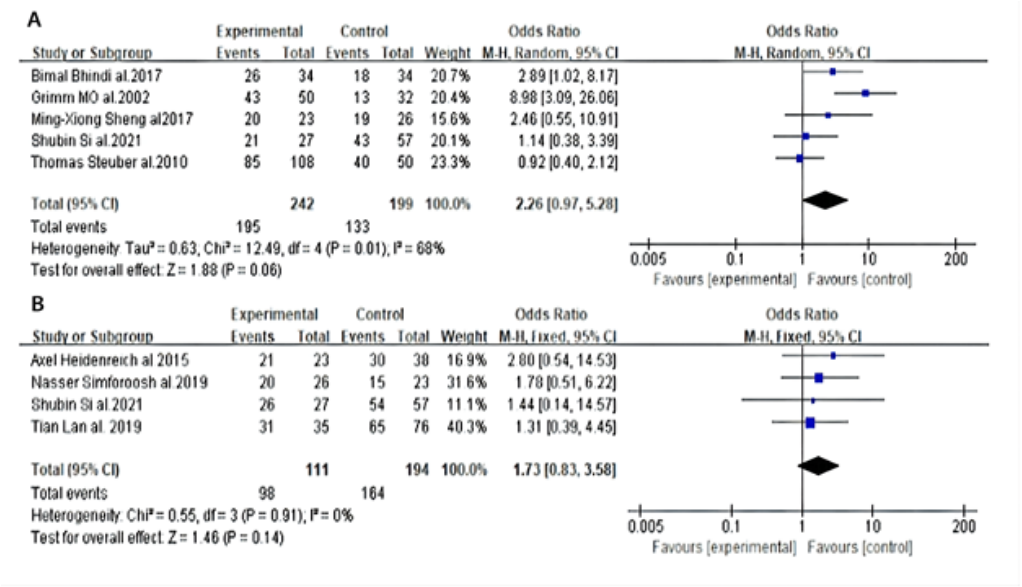

Figure 2

Forest plot of overall survival at 3 years (A) and 5years (B) in cytoreductive prostatectomy group and androgen deprivation therapy group.OS has not difference at 3years(A[OR = 1.73, 95%CI(0.83,3.58), P = 0.14 > 0.05] and 5 years(B) [OR = 2.26, 95%CI(0.97,5.28), P = 0.06 > 0.05].

Figure 3

Forest plot of CSS at 3-years(A) and 5-years(B1),Sensitivity analysis of 5-years CSS(B2) in cytoreductive prostatectomy group and androgen deprivation therapy group.The operating group has higher CSS at 3-years(A) [OR = 1.77, 95%CI(1.01,3.10), P = 0.04 < 0.05] .CSS at 5-years(B1) has no difference[OR = 2.71, 95%CI(0.98,4.63), P = 0.06> 0.05]

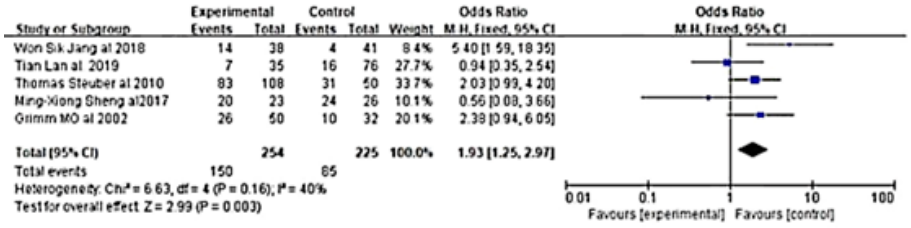

Figure 4

Forest plot of PFS at 5-years in cytoreductive prostatectomy group and androgen deprivation therapy group. A significant difference in 5-year PFS was observed between the surgery and non-surgery groups,sutgery group is higher[OR = 1.93, 95%CI(1.25, 2.97), P = 0.003 < 0.05].