

Original Article

Is cytoreductive nephrectomy necessary for metastatic renal cell carcinoma: a systematic review and meta-analysis

Xiaojin Luo¹, Meilian Yi², Qun Hu³, Weihua Yin⁴, Dali Han⁵

Departments of ¹Urology, ²Nursing, ³Anesthesia, ⁴Oncology, The People's Hospital of Yichun City, Jiangxi 336028, China; ⁵Department of Radiation Oncology, Shandong University Affiliated Shandong Cancer Hospital, 440 Jiyuan Road, Jinan 250117, China

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Abstract: Objective: The goal of this study was to explore the necessity of cytoreductive nephrectomy for metastatic renal cell carcinoma. Methods: A systematic search was conducted using PubMed, Cochrane Library, Web of Science, and EMBASE through June 20, 2018 according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines to identify studies reporting on cytoreductive nephrectomy for metastatic renal cell carcinoma. Results: Of a total of 669 studies, 19 were considered for evidence synthesis. A total of 59,915 patients were included, with a median of 3,153 patients per study. Of these, 24,210 patients received cytoreductive nephrectomy and 35,705 patients received other therapy. Patients treated with cytoreductive nephrectomy obtained a reduced risk of death comparing with those treated with other therapies (HR=0.50; 95% CI, 0.45-0.56; P<.001; I²=91.9%). In subgroup analysis, a similar outcome was obtained for targeted therapy as cytoreductive nephrectomy reduced 48% risk of mortality (HR=0.52; 95% CI, 0.46-0.59; P<.001). For cytokine therapy, cytoreductive nephrectomy also contributed to a positive prognosis but not statistically significant (HR=0.67; 95% CI, 0.54-0.82; P=0.423). Conclusion: Targeted therapy or immunotherapy alone was inferior to combine with cytoreductive nephrectomy for metastatic renal-cell carcinoma patients. Cytoreductive nephrectomy combined with targeted therapy was optimal treatment for metastatic renal-cell carcinoma patients.

Keywords: Cytoreductive nephrectomy, metastatic renal cell carcinoma, meta-analyses

Introduction

Approximately 20-30% of patients diagnosed with renal cell carcinoma (RCC) have metastases at presentation [1]. The survival rate for metastatic RCC (mRCC) ranged from 10% to 20% (2-year median survival) [2]. Survival was distinct in different treatment era (cytokine, 1990-2005; targeted therapy, 2006-). Currently, targeted therapy is recommended instead of immunotherapy because of the improved outcomes [3]. Cytoreductive nephrectomy (CN) has been the standard of care in metastatic renal-cell carcinoma, but it has dramatically changed since the emerging of targeted therapies [4].

Several studies investigated the role of CN in treatment of mRCC. In the cytokine era, the 1-,

2-, 5-, and 10-year overall survival rate of the patients treated with CN was 53.6%, 36.3%, 19.4%, and 12.7% compared with 18.5%, 7.4%, 2.3%, and 1.2% for the no-surgery patients, respectively [5]. In the targeted therapy era, CN was independently associated with prolonged overall survival [6-9]. Conflicting data also showed no significant differences in tumor response or survival between the CN and non-CN groups [4, 10]. Petrelli conducted a systematic review and meta-analysis to determine the prognostic role of CN in patients with mRCC. They identified twelve studies involving 39,953 patients and concluded that CN had a reduced risk of death comparing with those treated with targeted therapies alone (hazard ratio, 0.46; 95% confidence interval, 0.32-0.64; P<0.01; I²=99%) [11]. García-Perdomo drew a conclusion from 22,507 patients among seven stud-

ies, where a similar result was obtained showing that CN is effective for improving overall survival in patients with mRCC who undergo targeted therapy compared with no intervention [2].

However, recent studies have not all supported the conclusion [4, 12-15], especially a recent high level research indicated sunitinib alone was not inferior to nephrectomy followed by sunitinib in patients with mRCC [4]. Therefore, it was necessary to reassess the role of CN in mRCC patients according to distinct treatment. Meta-analysis was performed to expound whether CN was necessary. Subgroup analysis was also performed according to therapy strategy.

Methods

Evidence acquisition

Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Meta-analysis of Observational Studies in Epidemiology guidelines were used to conduct this systematic review and meta-analysis [16].

Search strategy

The review was performed by searching the PubMed, Cochrane Library, Web of Science, and EMBASE through June 20, 2018. Additional records identified through other sources. Searches included the terms “cytoreductive nephrectomy” [All Fields] AND “renal cell carcinoma” [All Fields]. Citation of retrieved articles was analyzed to identify other potentially relevant reports.

Inclusion and exclusion criteria

Studies included in this meta-analysis should meet the following criteria: (1) all patients were diagnosed with tumor metastasis by B-ultrasound or CT, pathologically diagnosed as renal cell carcinoma except for non-CN patients; (2) patients were regular treated and follow up; (3) sufficient data for examining overall survival and hazard ratio (HR) with 95% confidence interval (95% CI). Major reasons for exclusion of studies were as follows: (1) incomplete data for the analysis; (2) letters to editors/commentaries/editorials, reviews, conference abstracts, and articles published in a language could not be translated into English; (3) duplicate data. Two authors (XJ L, ML Y) conducted the search

and identification independently, and the selection of an article was reached by consensus with a third author.

Risk of bias

Assessment for the risk of bias was performed in accordance with the guidelines outlined in the Cochrane handbook for systematic reviews of interventions [17]. Two independent researchers objectively reviewed all studies and assigned a value of “high risk”, “low risk” or “unclear risk” to the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other biases [18].

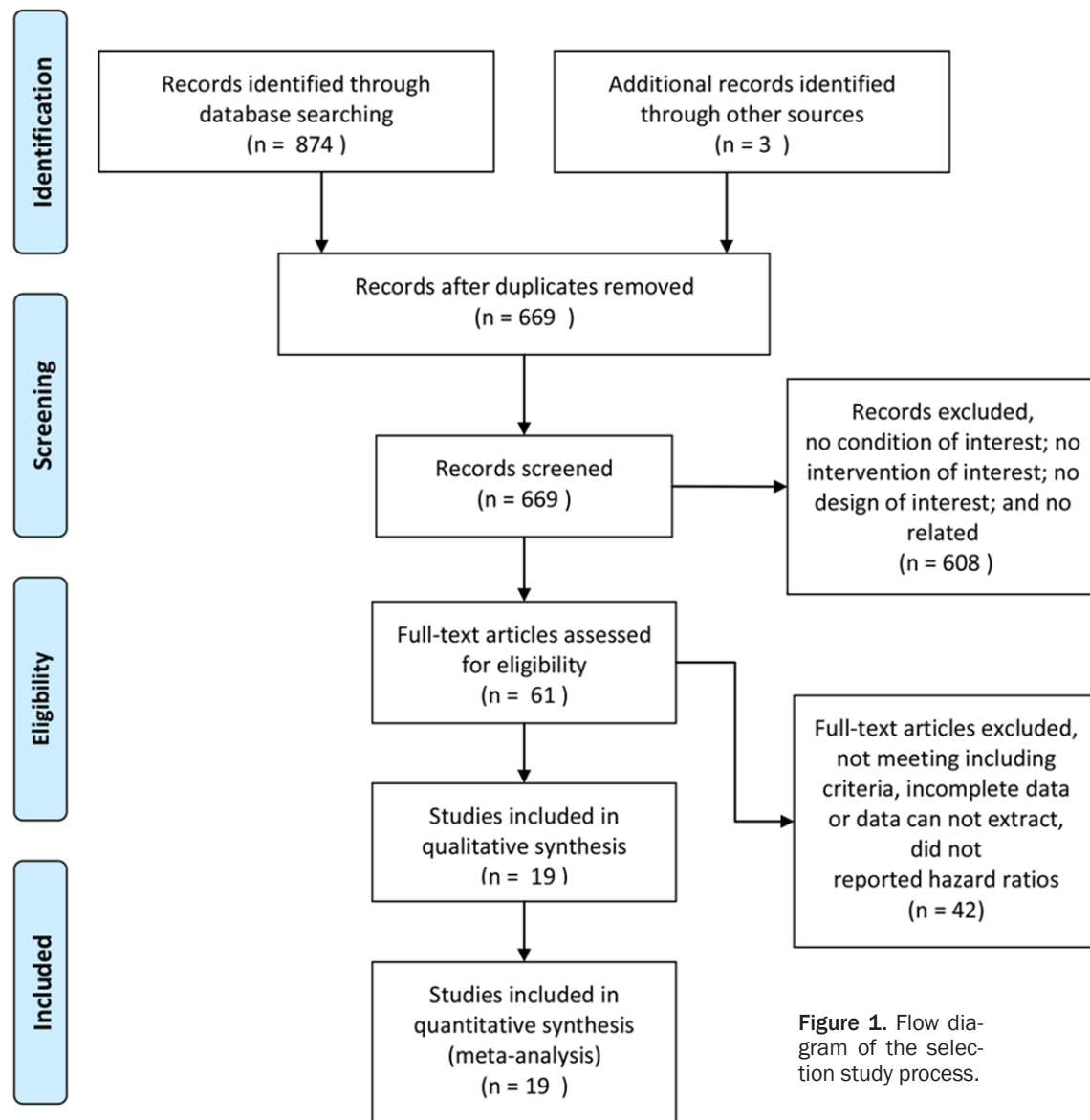
Data analysis and synthesis of results

The hazard ratio (HR) was estimated with 95% confidence interval (CI) for dichotomous outcomes, and the weighted mean difference (WMD) with 95% CI for continuous outcomes. Statistical heterogeneity among studies was evaluated utilizing I^2 statistics (ranges from 0 to 100%), λ^2 test, and P values [19]. Information was pooled with a fixed effect meta-analysis according to the heterogeneity expected. The fixed effects model method (Mantel-Haenszel) was used, except in the case where a significant Q test ($P < 0.05$) or $I^2 > 50\%$ indicated the existence of heterogeneity among studies. When the existence of heterogeneity was indicated, the random effects model (DerSimonian-Laird method) was instead applied [20]. The presence of publication bias was also evaluated using Begg and Egger tests. Sensitivity analysis was performed to assess the stability of the results. Funnel plots were drawn to estimate any potential publication bias, where the standard error of log (HR) of each study was plotted against its log (HR). Whether the funnel plot was symmetrical was assessed with the Egger's test [21, 22]. When using Egger's test to assess the publication bias, $P < 0.05$ was considered statistically significant. The statistical analysis was performed by using STATA 12.0 (StataCorp., College Station, TX, USA).

Results

Study selection

The work flow chart for this study is shown in **Figure 1**. A total of 874 records were identified



through database searching, and 3 additional records were identified through reference screening. A total of 669 relative references were identified after a comprehensive search and duplicated records removed. After full-text review of 61 manuscripts, 19 were selected in the meta-analysis [4-10, 12, 13, 23-32].

Characteristic of included studies

The nineteen included studies were published between 2001 and 2018. A total of 59,915 patients were included, the sample size ranged from 78 to 20,104 patients, with a median of 3,153 patients per study. Of these, 24,210 patients received CN and 35705 patients re-

ceived other therapy. Two studies evaluated the role of CN in the immunotherapy era [31, 32], five studies researched in mixed therapy [5, 8, 26, 27, 29], and twelve studies included 28,327 patients researched the role of CN in the targeted therapy era [4, 6, 7, 9, 10, 12, 13, 23-25, 28, 30]. The follow up were 12-50.9 months, overall survival were 4-25.6 months (Table 1).

Risk of bias

An evaluation of the risk of bias was performed with a Cochrane Collaboration tool (Figure 2). Most studies had a low risk of bias for almost all items except for blinding of participants and

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Table 1. Characteristics of included studies

Study and year	Country	Study design	Case number			HR	Lower CI	Upper CI	Treatment	Follow up (months)	OS (months)	
			Total	CN	non-CN						CN	non-CN
Abern 2014	U.S.A.	Retrospective Study	7143	2629	4514	0.4	0.37	0.43	Targeted	13	NA	NA
Bamias 2014	Greece	Retrospective Study	186	150	36	0.35	0.23	0.53	Targeted	34	23.9	9
Choueiri 2011	U.S.A.	Retrospective Study	314	201	113	0.68	0.46	0.99	Targeted	16.3	19.8	9.4
de Groot 2016	Netherlands	Retrospective Study	227	74	153	0.61	0.41	0.92	Targeted	NA	17.9	8.8
Flanigan 2004	U.S.A.	Randomized Controlled Trial	324	161	163	0.69	0.55	0.87	Cytokine	NA	13.6	7.8
Hanna 2016	U.S.A.	Retrospective Study	12995	4559	8436	0.49	0.46	0.52	Targeted	NA	17.1	7.7
Heng 2014	Canada	Retrospective Study	1658	982	676	0.6	0.52	0.69	Targeted	39.1	20.6	9.6
Klatle 2018	UK	Retrospective Study	261	97	164	0.63	0.46	0.83	Targeted	14.6	25.6	12.4
Mejean 2018	France	Randomized Controlled Trial	450	226	224	0.89	0.71	1.1	Targeted	50.9	13.9	18.4
Mickisch 2001	Netherlands	Randomized Controlled Trial	75	34	41	0.54	0.31	0.94	Cytokine	NA	17	7
Tatsugai 2015	Japan	Retrospective Study	330	254	76	0.4	0.29	0.57	Mixed	NA	15.5	4.4
Upreti 2018	U.S.A.	Retrospective Study	3376	1110	2266	0.43	0.39	0.47	Targeted	NA	18	4
Warren 2009	Canada	Retrospective Study	134	101	33	0.38	0.19	0.74	Targeted	24.9	NA	NA
Xiao 2015	China	Retrospective Study	1505	1045	460	0.42	0.34	0.52	Targeted	NA	NA	NA
Zini 2009	Canada	Retrospective Study	5372	2447	2925	0.62	0.58	0.65	Mixed	NA	NA	NA
Aben 2011	Netherlands	Retrospective Study	328	123	205	0.31	0.24	0.4	Mixed	NA	NA	NA
Aizer 2014	U.S.A.	Retrospective Study	5055	3057	1998	0.45	0.37	0.55	Mixed	20	14	6
Conti 2014	U.S.A.	Retrospective Study	20104	6915	13189	0.41	0.39	0.43	Mixed	12	19	4
You 2011	Korea	Retrospective Study	78	45	33	0.63	0.32	1.11	Targeted	NA	21.6	13.9

CN: cytoreductive nephrectomy; non-CN: non cytoreductive nephrectomy; NA: not available.

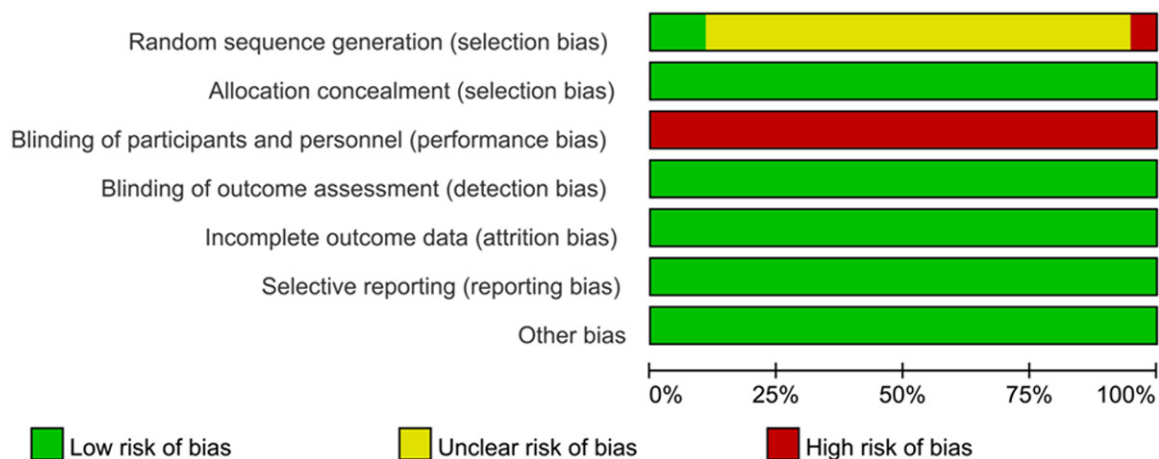


Figure 2. Risk of bias graph.

personnel (performance bias). One study had a high risk of bias for the random sequence generation (selection bias) [7]. However, those studies performed a multivariate and adjusted analysis or a propensity score analysis.

Overall survival

Most studies indicated a higher survival rate for the CN group except for one high quality study [4] (**Table 1**). Pooled data showed patients treated with CN had a reduced risk of death comparing with those treated with other therapies (HR, 0.50; 95% CI, 0.45-0.56; $P < .001$; $I^2 =$

91.9%; **Figure 3**). Heterogeneity existed between studies, so the random-effects model was used. Two studies published between 2001 and 2004 explored the role of CN combined with cytokine therapy (**Table 1**). Subgroup analyses were performed to detect the potential heterogeneity. High heterogeneity still existed in target therapy and thus the random-effects model was used. Similar outcome was obtained in targeted therapy era as CN reduced 48% risk of death (HR, 0.52; 95% CI, 0.46-0.59; $P < .001$; $I^2 = 86.3\%$; **Figure 4**). For cytokine therapy, CN also contributed to a positive prognosis but not statistically significant (HR, 0.67; 95% CI, 0.54-

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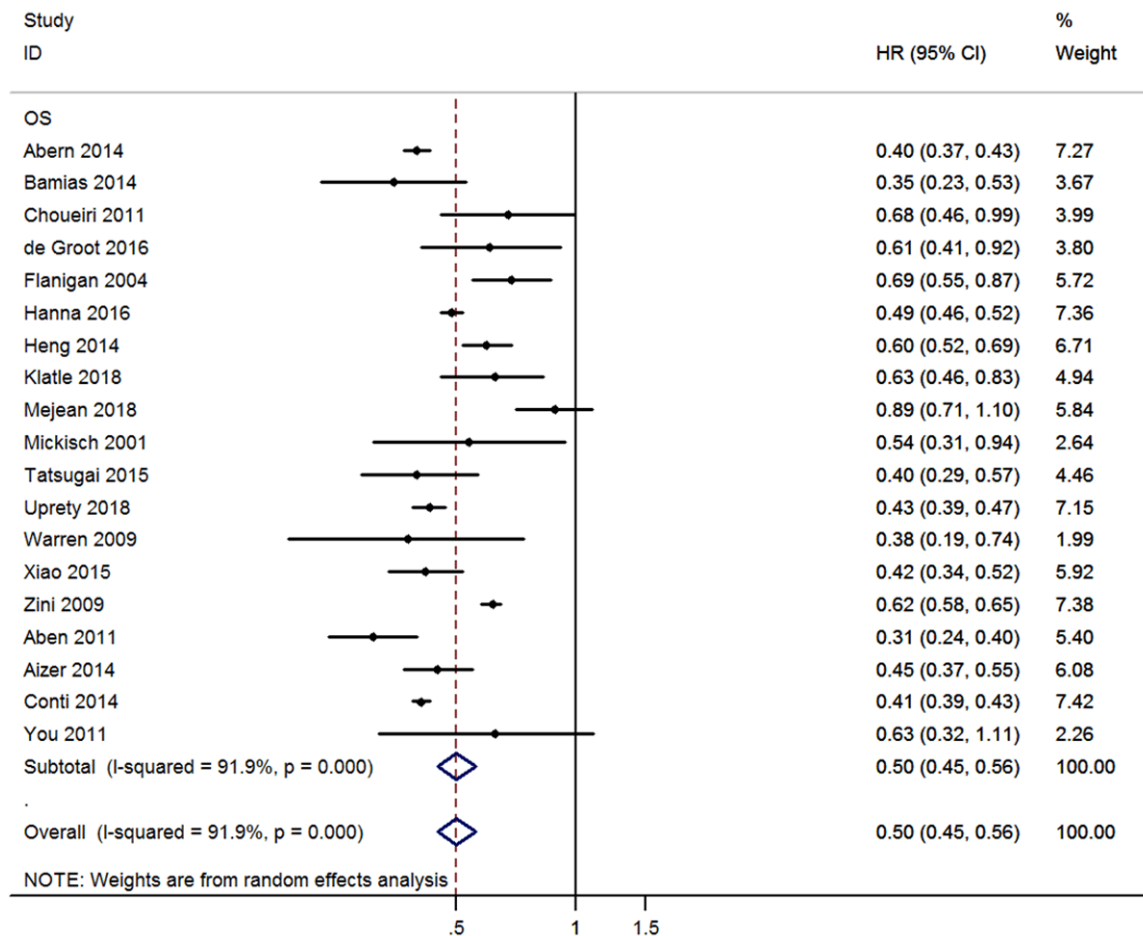


Figure 3. Meta-analysis of included studies for overall survival.

0.82; $P=0.423$; **Figure 4**). For mixed therapy, patients received CN obtained better overall survival (HR, 0.67; 95% CI, 0.54-0.82; $P=0.423$; **Figure 4**).

Sensitivity analysis and publication bias

One-way sensitivity analyses were performed to assess the stability of the pooled results. In the sensitivity analysis, each single study included in the meta-analysis was deleted each time to observe the influence of the data on the pooled HRs. Publication bias was not found through use of the Begg's and Egger's statistics as p -values = 0.944 and 0.573, respectively (**Figure 5**).

Discussion

The treatment of metastatic RCC has changed dramatically in the past decade, switching from cytokine therapy to targeted therapy. Cytore-

ductive nephrectomy has been the standard of care in metastatic renal-cell carcinoma, supported by randomized trials and large retrospective studies [4]. Since the appliances of targeted therapy, it was debated that whether targeted therapy could substitute CN. Targeted therapies aimed to target the molecular mechanisms underlying renal-cancer carcinogenesis. Ten novel agents targeting the vascular endothelial growth factor (VEGF) or the mammalian target of rapamycin pathways, or inhibiting the interaction of the programmed death 1 receptor with its ligand, have been approved since 2006 and have dramatically improved the prognosis of mRCC [33].

In this meta-analysis, CN improved patients overall survival by reducing 50% risk of mortality compared with those who were non-CN. Among 19 included studies, only two studies indicated no significant difference in OS between the CN and non-CN groups [4, 10]. You

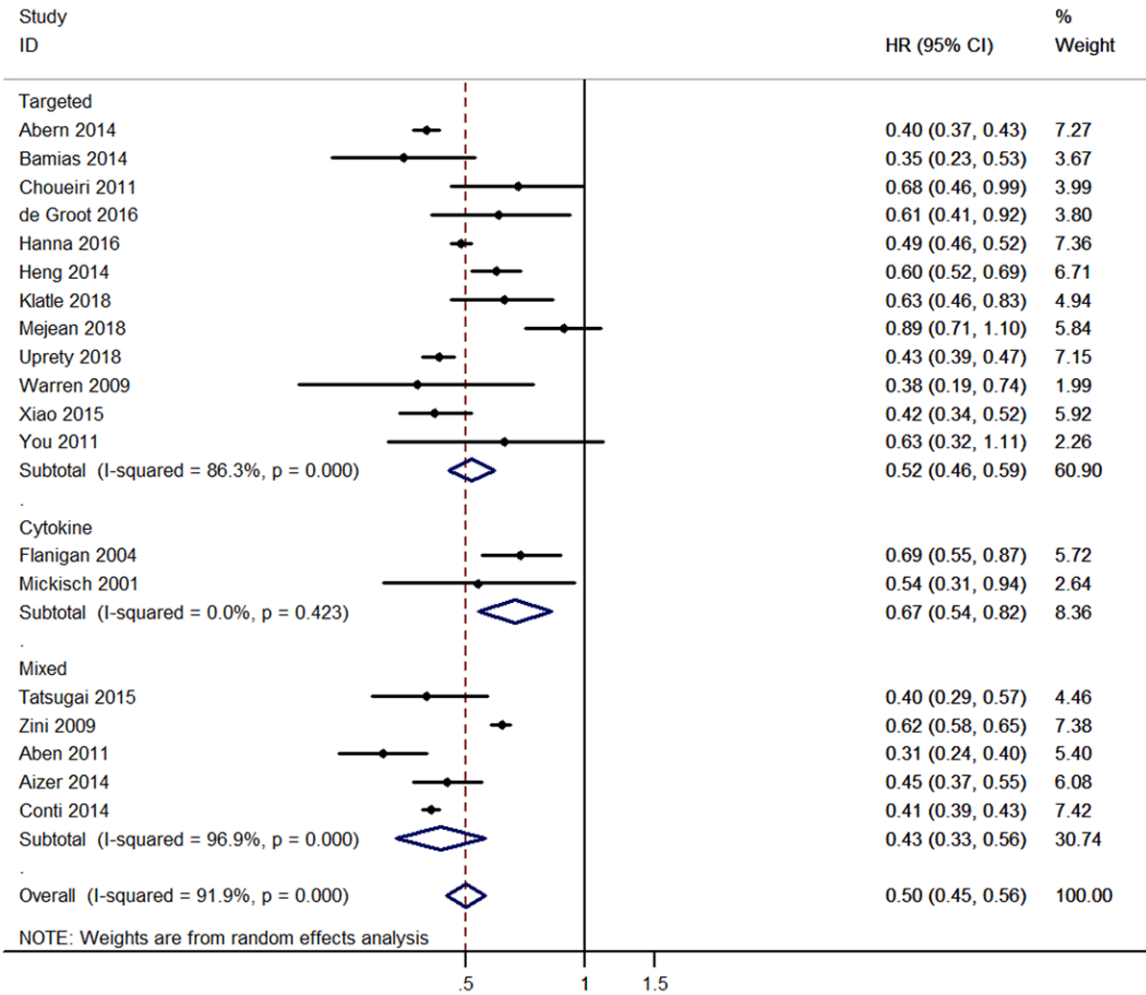


Figure 4. Subgroup analysis for treatment.

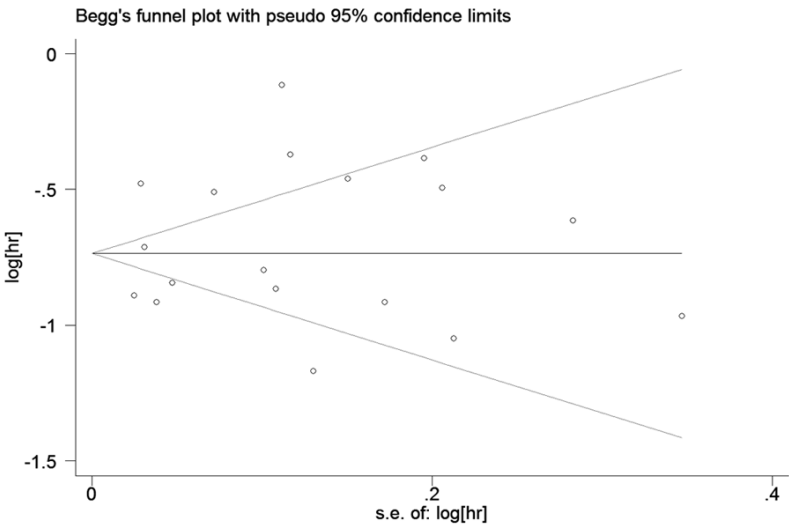


Figure 5. Funnel plot for publication bias.

[10] investigated 78 patients showed that CN and non-CN groups had a similar response rate

(23.1% and 30.3%) and median PFS (11.7 and 9.0 months, respectively). Although median OS was longer in the CN than in the non-CN group (21.6 VS 13.9 months), differences were not statistically significant (P=0.128). Mejean [4] conducted a phase 3 trial. They randomly assigned, in a 1:1 ratio, 450 patients with confirmed mRCC at presentation who were suitable candidates for nephrectomy to undergo nephrectomy and then receive sunitinib (standard therapy) or to receive sunitinib alone. After 50.9 months follow up, the results showed non-CN group were equal to those in the CN group with regard to

overall survival (stratified hazard ratio for death, 0.89; 95% CI, 0.71 to 1.10). The sample size was relative small in the You' research [10], Mejean' study was a high quality research that it was prospective, multicenter, open-label, randomized, phase 3 trial. More large and high quality studies were needed to assess the role of CN. Despite these two negative results, our subgroup analysis of CN in the targeted therapy era received similar outcome, twelve studies included 28,327 patients identified a 48% reduced risk of mortality for patients treated with CN (**Figure 4**). To the best of our knowledge, this is the most comprehensive and up-to-date review of this issue, our study confirms the positive role of CN in mRCC patients.

In the subgroup analysis, patients were received better outcome when combined CN with targeted therapy. Cytokine therapy plus CN seems to be benefit for patients but not statistically significant compared with cytokine alone. Currently, cytokine therapy is being replaced by targeted therapy because of its worse outcomes [3]. So far, CN combined with targeted therapy was optimal treatment for mRCC patients.

A potential limitation of this meta-analysis is that most studies were retrospective analysis (**Table 1**), the non-CN group patients may with a poorer performance status, more primary tumor burden, and high volumes of metastatic disease, the two groups may have a poor comparability. In addition, the pathology of RCC in studies may be different, as study suggested sarcomatoid differentiation was independently associated with progression-free survival [34], and molecular intra-tumour heterogeneity in clear cell renal carcinomas led to distinct targeted responses [35]. Further, our meta-analysis did not discriminate targeted drug in studies, axitinib, cabozantinib, everolimus, nivolumab, or sunitinib may have received dissimilar outcomes [36]. Additionally, the included studies did not evaluate the difference between nephrectomy-targeted therapy group and targeted therapy-nephrectomy group. Delayed cytoreductive nephrectomy following targeted therapy shrink tumor burden may reduce the complication of surgery [37]. Finally, cancer specific survival were not evaluated in our meta-analysis due to lack of sufficient data, studies were suggested to determine whether any benefit exists on quality of life when performing CN

or targeted therapy. Thus, more high quality studies are expected to update this meta-analysis in the future.

Conclusions

In conclusion, meta-analysis indicated that targeted therapy or immunotherapy alone was inferior to combine with CN for mRCC patients. CN combined with targeted therapy was optimal treatment for mRCC patients.

Disclosure of conflict of interest

None.

Abbreviations

RCC, renal cell carcinoma; mRCC, metastatic RCC; CN, cytoreductive nephrectomy; CI, confidence interval; WMD, weighted mean difference; HR, hazard ratio; VEGF, vascular endothelial growth factor.

Address correspondence to: Dali Han, Department of Radiation Oncology, Shandong University Affiliated Shandong Cancer Hospital, 440 Jiyan Road, Jinan 250117, China. E-mail: dalihan_sdch@163.com

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