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Prognostic value of cytoreductive nephrectomy combined with targeted therapy for metastatic renal cell carcinoma: a meta-analysis

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Abstract
Purpose The role of cytoreductive nephrectomy (CN) has been controversial with the advent of targeted therapy. Our study was to identify the prognostic value of CN combined with targeted therapy for treatment of metastatic renal cell carcinoma (mRCC) by conducting a meta-analysis based on the existing population-based studies.
Methods Research articles published up to September 2015 were searched through PubMed and Embase. A meta-analysis was performed to assess the overall survival (OS) and progression-free survival (PFS) of patients with mRCC undergoing CN combined with targeted therapy compared with targeted therapy alone. Furthermore, analysis was made to evaluate some potential prognostic factors predicting survival.
Results Eight studies were included in our analysis with 2688 mRCC patients. A fixed-effect model was performed and found the pooled HR of OS was 0.60 (95 % CI 0.53–0.67, $p < 0.0001$). Furthermore, the pooled median survival ratio was elevated (HR 2.11, 95 % CI 1.78–2.49, $p < 0.0001$), indicating that patients who received CN combined with targeted therapy yielded a more than twofold prolonged OS compared with those who received targeted therapy alone. Moreover, no significant difference was observed in PFS in the patients undergoing CN combined with targeted therapy (HR 0.82, 95 % CI 0.57–1.19, $p = 0.30$).
Conclusions Current evidence suggests that CN combined with targeted therapy has a significant OS advantage in patients with mRCC. However, the results should be evaluated in the context of the potential selection biases of the existing evidence. Large prospective cohort studies are required to confirm these findings.

Keywords Renal cell carcinoma · Nephrectomy · Molecular targeted therapy · Prognosis · Meta-analysis

Introduction

Renal cell carcinoma (RCC) is the most common neoplasm of the kidney and accounts for approximately 90 % of all renal malignancies [1]. Currently, the mortality as a result of RCC exceeds 100,000 patients each year. Because of high rate of metastasis and recurrence, the incidence and mortality rate of RCC increase by 2–3 % per decade [2]. About 25–30 % of patients have metastatic disease at the time of diagnosis. In addition, another 20 % of patients undergoing nephrectomy will have a relapse and develop into metastatic renal cell carcinoma (mRCC) during follow-up [3]. The prognosis of RCC is closely related to the stage of disease or degree of tumor dissemination. For those with metastases, the prognosis is extremely poor. The invasion and spread of cancer cells to surrounding and remote organ is the principal cause of death in patients diagnosed with RCC [4].

Cytoreductive nephrectomy (CN) is often indicated as part of an integrated management strategy for mRCC. It is largely considered as a palliative measure for control of hemorrhage, pain, paraneoplastic syndromes and symptoms

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related to compression of adjacent viscera. It has been reported that nephrectomy performed for these palliative measures can result in spontaneous regression of metastases in up to 4 % of cases [5]. Considering the absence of effective chemotherapy agents and the limited usefulness of radiation therapy, the application of CN combined with immunotherapy was used to be the traditional treatment for patients with mRCC. The previous studies reported a decreased risk of death and a 5.8-month survival advantage in patients who underwent CN before immunotherapy [6–8]. The Food and Drug Administration (FDA) has approved targeted agents for use in patients with mRCC since 2005. More and more patients have been benefited from targeted therapy [9]. The value of CN in the era of targeted therapy has become controversial. Some studies have shown an overall survival advantage in patients receiving CN and targeted therapy compared with targeted therapy alone. However, some declared pure targeted therapy could prolong survival in patients with mRCC, regardless of whether they underwent CN or not [10, 11].

Considering that existing studies have involved limited number of patients, randomized controlled trials are not available. The present meta-analysis deals with this important and timely topic by systematically integrating the studies that compared combination therapy with targeted therapy alone in treating mRCC to evaluate the prognostic value of CN combined with targeted therapy.

Methods

Literature search

Two of us independently and systematically searched PubMed and Embase databases from inception to September 17, 2015. Research articles were selected using the following text words or medical subject heading terms: "cytoreductive nephrectomy," or "debulking nephrectomy," or "radical nephrectomy," or "surgery"; "targeted therapy," or "tyrosine kinase inhibitor" or "mammalian target of rapamycin inhibitor," or "vascular endothelial growth factor antibody"; "renal cancer," or "renal cell carcinoma" or "renal tumor," or "kidney cancer." We also scrutinized the reference lists of reviews and selected research articles to identify additional relevant studies. No language restrictions were imposed.

Study selection

The eligibility of each study was assessed independently by two investigators. We included studies that met the following criteria:(a) published as an original article; (b) used a prospective or retrospective cohort design; (c) patients diagnosed with metastatic renal cell carcinoma before enrolled; (d) all patients who received targeted therapy were divided into CN and no-CN groups; and (e) studies were required to have a clear description of at least one item of the results of the hazard ratio (HR), overall survival (OS), progression-free survival (PFS) or reported sufficient data to estimate these. The excluded criteria included: (a) abstracts, expert opinions or reviews without original data; (b) published as a duplicate article or reported the same population; and (c) did not clearly describe the treatment and corresponding effect value. If more than one study used the same cohort and population, the one with the most comprehensive population or reported the most appropriate effect values was included. Discrepancies between two investigators were solved by discussion.

Data extraction and quality assessment

Two investigators independently extracted data, which were cross-checked by another investigator. A standardized data collection protocol for each study included was used including the following information: the first author, publication year, study design, country, sample size, period, mean follow-up, mean age, sex, histology, targeted agents, median OS, median PFS and relative HR. For studies that reported several risk estimates, we used the one that reflected the greatest degree of control for known prognostic variables. We also contacted with the author of some studies for information beyond what was available in their published articles. The quality of the included studies was assessed by using the Newcastle–Ottawa scale, which consisted of three items: patient selection, comparability of combination therapy and targeted therapy alone groups, and assessment of outcome. Studies with higher scores represent studies of higher quality [12].

Statistical analysis

Median OS or PFS distributions were estimated using Kaplan–Meier method in all the studies included. Correlations between outcomes and assessed variables were expressed as the HR and 95 % CI. A fixed- or random-effect model was used to calculate the pooled HR and 95 % CI. To further discuss the difference of median OS between the combination therapy group and targeted therapy alone groups, we extended an effect value, median survival ratio (MSR), which is defined as the ratio of them. The pooled MSR was then calculated.

Heterogeneity among studies was assessed using the Q and I^2 statistics, which tested total variation across studies that was attributable to heterogeneity rather than to chance [13]. For I^2, the values of 25, 50 and 75 % correspond to cutoff points for low, moderate and high degrees

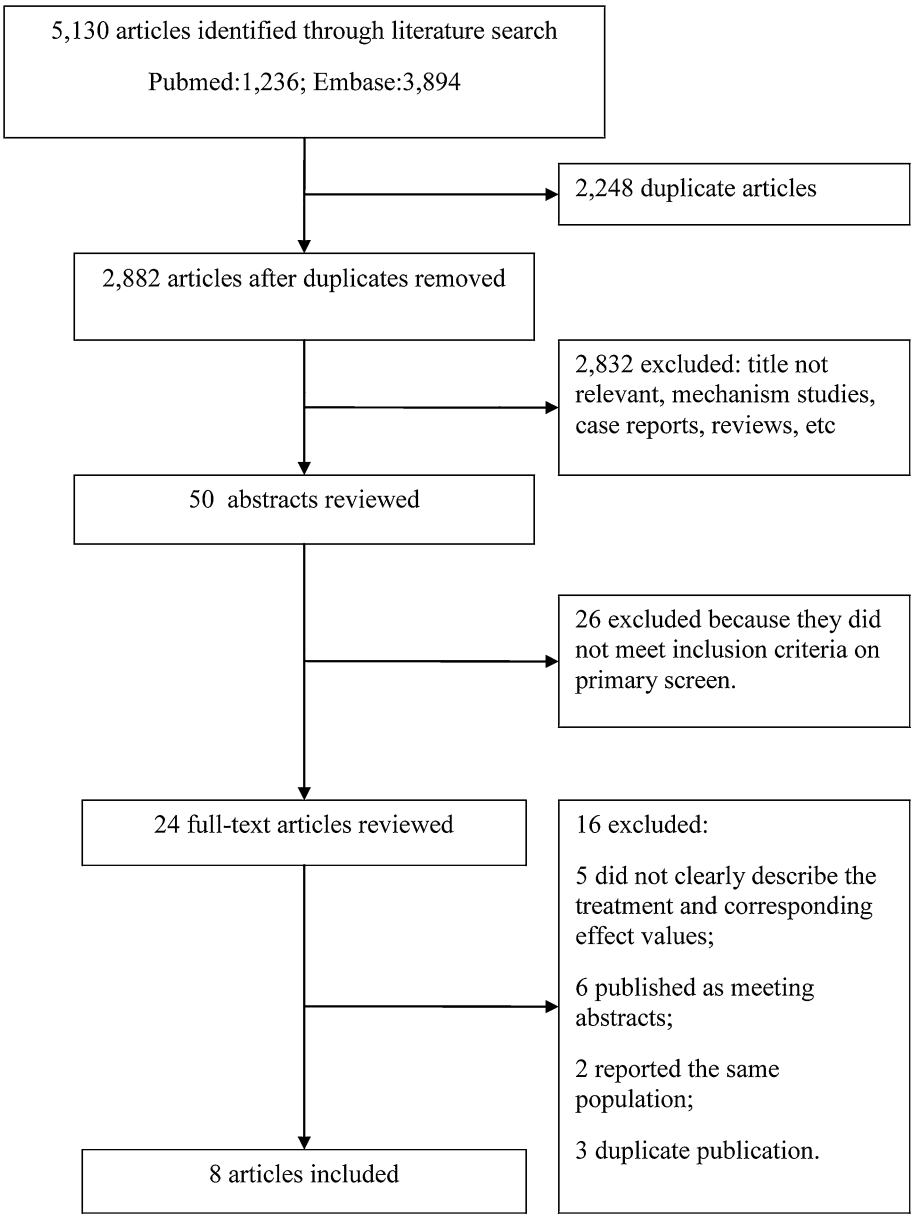

Fig. 1 Flowchart of study selection

of heterogeneity [14]. Sensitivity analyses were conducted by repeating the fixed- or random-effect meta-analysis after omitting one study at a time. We inspected the funnel plots for asymmetry and Egger's test and Begg's test to test the publication bias.

Most of the included studies used Cox proportional hazards regression models to estimate the potential prognostic factors for entire cohort. Considering there were significant imbalances in some baseline characteristics between the CN and non-CN groups, we pooled the HRs and 95 % CIs of these characteristics to evaluate the potential prognostic factors predicting survival, respectively.

All analyses were conducted using Stata version 12.0, and a two-tailed $p < 0.05$ was considered statistically significant.

Results

Search results and study characteristics

Figure 1 shows the flowchart of our search and selection process. A total of 2882 citations were generated according to our search strategy, and 50 were selected for further analysis after excluding not relevant articles, mechanism studies, case reports or reviews. Of these 50 articles, 26 failed to meet the selection criteria after screening by abstracts. The other 24 articles received full-text review, of which five articles did not clearly describe the treatment regarding targeted therapy and corresponding effect value; furthermore, other six articles were published as meeting abstract that could not reach more detailed information.

Another two articles were excluded due to overlap of the same study population with that of another study. Three duplicate published articles were also excluded. Finally, a total of eight retrospective cohort studies with a sample size of 2688 patients were included in our meta-analysis. All articles included were published in English. Characteristics of the studies included are presented in Table 1.

Overall survival

OS was examined across eight studies that enrolled a total of 1689 cases and 999 controls. No significant heterogeneity was found (Q statistic $p = 0.490$; $I^2 = 0.0$ %). A fixed-effect model was performed and found the pooled HR was 0.60 (95 % CI 0.53–0.67, $p < 0.0001$; Fig. 2). Among the included studies, all studies reported the median OS of both groups. The calculated MSR and median OS of each study are given in Table 2. The pooled MSR was 2.11 (95 % CI 1.78–2.49), indicating that patients who received CN combined with targeted therapy were associated with a more than twofold prolonged OS compared with targeted therapy alone.

In sensitivity analysis excluding one study at a time, the pooled HR of OS ranged from 0.59 (95 % CI 0.52–0.66) to 0.60 (95 % CI 0.54–0.68). The results were consistent in each exclusion analysis, which proved that our result was reliable and robust. No statistical evidence of publication bias was found in studies of OS by Begg's or Egger's tests (Begg $p = 0.900$, Egger $p = 0.580$).

Table 3 shows analysis for potential prognostic factors predicting OS in patients treated with targeted therapy combined with CN or not. We evaluated ten baseline characteristics which reported significant imbalances between the CN and non-CN groups in some of the included studies. Our analysis revealed that Karnofsky performance status (KPS) less than 80 %, more than one metastatic site, non-clear cell type RCC, anemia, neutrophil count greater than upper limit of normal (ULN), platelet count greater than ULN, hypercalcemia and increased lactic dehydrogenase were significantly associated with adverse survival. In the absence of analysis of preoperative characteristics predicting OS in patients treated with CN, the significant prognostic factors predicting OS may be helpful for identifying patients who will benefit from CN in some degree.

Progression-free survival

PFS was reported by four studies that enrolled a total of 1134 cases and 792 controls. Considering there was evidence of significant heterogeneity among the studies (Q statistic $p = 0.054$; $I^2 = 61.0$ %), a random-effect model was performed and found the pooled HR was 0.82 (95 % CI 0.57–1.19), demonstrating that CN was associated with neither PFS advantage nor increased risk of progression (Fig. 3).

Sensitivity analysis was performed and found the pooled HR of PFS ranged from 0.74 (95 % CI 0.45–1.23) to 0.92 (95 % CI 0.65–1.31). No significant pooled HR and 95 % CI were detected by omitting any single study. This suggests the result of our meta-analysis was stable. There was also no statistical evidence of publication bias among the studies on PFS (Begg $p = 1.000$, Egger $p = 0.750$).

Only one study [24] used Cox proportional hazards model to evaluate prognostic factors predicting PFS. Multivariable analysis in this study revealed that non-clear cell type RCC and lymph node metastasis were independent predictors of progression [non-clear cell vs. clear cell (HR 3.46, 95 % CI 1.41–8.54, $p = 0.007$); positive vs. negative (HR 2.31, 95 % CI 1.52–7.19, $p = 0.003$)]. Considering the limited number of patients, the results should be evaluated cautiously.

Discussion

The application of targeted agents has changed the treatment strategy for mRCC. Clinical data have clearly shown that targeted therapy could have longer OS and better prognosis in patients with advanced RCC [15]. CN should be reconsidered in the light of the effect of targeted therapy. Conti et al. [16] made an analysis based on the Surveillance Epidemiology and End Results (SEER) database. While utilization of CN declined slightly at a rate of 0.6 % per year since 2005, they found that CN remains associated with a survival benefit in the targeted therapy era. Richey et al. [11] reported that the OS of mRCC patients was shown to be improved by targeted therapy, without ever undergoing CN. The result suggested that targeted therapy alone can prolong survival. In the absence of data from randomized trials in the era of targeted therapy, the current guideline recommendation for patients with mRCC is based on the prospectively confirmed survival benefit achieved after CN in the cytokine era [8]. Considering controversy exists regarding the prognostic value of CN combined with targeted therapy for mRCC, our meta-analysis, which synthesized the existing evidence, is particularly important.

This meta-analysis was performed with larger sample size on the basis of multicenter retrospective cohort studies aiming to identify the roles of CN combined with targeted therapy for mRCC. Among the studies included, six studies reported CN was beneficial in mRCC patients treated with targeted therapy [17–22]. However, two studies found no significant difference in survival for those who received combination therapy compared with targeted therapy alone [23, 24]. Our findings indicated that a significant

Table 1 Baseline characteristics of studies included in the meta-analysis

References	Country	Sample size [CN: no-CN]	Period	Mean follow-up (months)	Mean age [CN: no-CN]	Sex (male/female)	Histology (clear/non-clear)	Median OS [CN: no-CN]	Median PFS [CN: no-CN]	Targeted agents	NOS score
You [23]	Korea	171 [96:75]	2006–2012	14.7	56.5: 60.2	2.17: 1	10.40: 1	19.9: 11.7	8.7: 8.4	Sunitinib, sorafenib, pazopanib, temsirolimus	8
Tatsugami [17]	Japan	128 [103:25]	2001.1–2010.12	NA	63.0: 67.0	2.79: 1	NA	30.9: 15.5	NA	TKIs	6
Heng [19]	IMDC	1658 [982:676]	NA	39.1	59.9: 59.3	2.69: 1	6.59: 1	20.9: 9.5	7.6: 4.5	Sunitinib, sorafenib, axitinib, bevacizumab, temsirolimus, pazopanib, everolimus	7
Mutlu [18]	Turkey	52 [28:24]	NA	NA	53.6: 67.5	2.71: 1	NA	15.1: 5.4	8.5: 3.0	IFN + TKIs (sunitinib, sorafenib, pazopanib)	6
Kwon [24]	Korea	45 [28:17]	2005.4–2012.12	21.8	53.3: 63.3	2.75: 1	4.00: 1	17.3: 19.7	4.1: 3.5	TKIs (sunitinib, sorafenib, pazopanib)	7
Bamias [20]	Greece, France, Belgium	186 [150:36]	2006.1–2011.3	34.0	58.0	2.80: 1	14.42: 1	23.9: 9.0	NA	Sunitinib, IFN + sunitinib	7
Choueiri [21]	USA, Canada	314 [201:113]	2004.8–2008.7	16.3	NA	2.41: 1	13.45: 1	19.8: 9.4	NA	Sunitinib, sorafenib, bevacizumab	7
Warren [22]	Canada	134 [101:33]	2003.11–2007.6	18.6	59.8	3.08: 1	NA	22.3: 6.6	NA	TKIs (sunitinib, sorafenib)	7

NA data not applicable, *CN* cytoreductive nephrectomy, *OS* overall survival, *PFS* progression-free survival, *NOS* Newcastle–Ottawa scale, *IMDC* international metastatic renal cell carcinoma database consortium, *TKI* tyrosine kinase inhibitor, *IFN* interferon

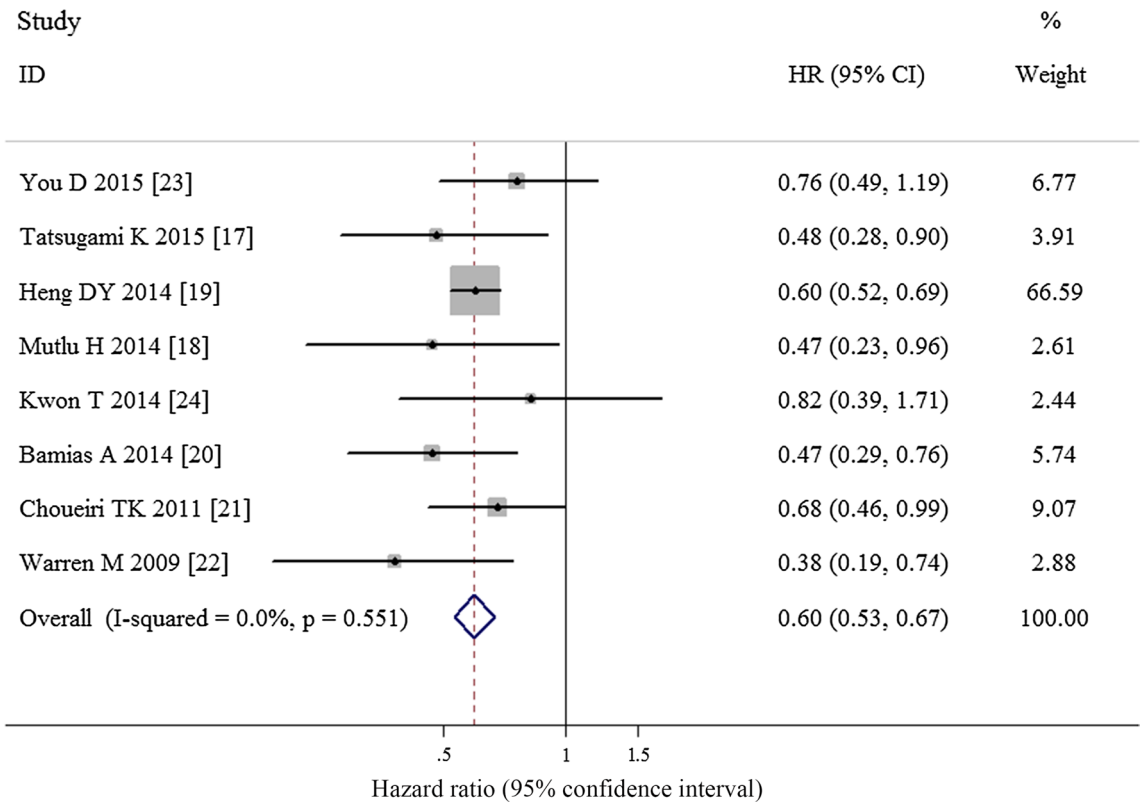

Fig. 2 Forest plot revealing the pooled HR of overall survival for combination therapy compared with targeted therapy alone

Table 2 Median OS and MSR of CN + TT group and TT alone group

References	Median OS (months)		MSR	95 % CI
	CN + TT group	TT alone group	(CN + TT)/TT alone	
You [23]	19.9	11.7	1.7	(1.46, 1.98)
Tatsugami [17]	30.9	15.5	1.99	(1.68, 2.37)
Heng [19]	20.6	9.6	2.15	(2.05, 2.25)
Mutlu [18]	15.1	5.4	2.8	(2.13, 3.67)
Kwon [24]	17.3	19.7	0.88	(0.66, 1.18)
Bamias [20]	23.9	9	2.66	(2.30, 3.07)
Choueiri [21]	19.8	9.4	2.11	(1.89, 2.35)
Warren [22]	22.3	6.6	3.38	(2.85, 4.00)
Pooled MSR			2.11	(1.78, 2.49)

OS overall survival, *MSR* median survival ratio, *CI* confidence interval, *CN* cytoreductive nephrectomy, *TT* targeted therapy

prolonged OS in the combination therapy group compared with the targeted therapy alone group (HR 0.60, 95 % CI 0.53–0.67); moreover, no statistically significant difference was observed in PFS between the two groups (HR 0.82, 95 % CI 0.56–1.19). Furthermore, sensitivity analysis found the results for OS and PFS were consistent in each single exclusion analysis. In addition, there was no significant publication bias in these analyses with either Begg's or Egger's tests.

One of the major concerns surrounding CN combined with targeted therapy is disease progression during postoperative recovery which may delay or even prevent targeted therapy. Our meta-analysis found no significant difference in PFS between the combination therapy group and targeted therapy alone group, indicating that CN may neither promote disease progression nor affect the tumor response to targeted therapy. Considering the limited studies that reported PFS, no significant association may need further

Table 3 Potential prognostic factors predicting OS

Prognostic factor	No. of studies	Pooled HR (95 % CI)	*p*
Age			
<65(60) versus ≥65(60)	4	0.92 (0.69–1.23)	0.565
KPS			
<80 versus ≥80	6	2.37 (1.68–3.34)	0.000
No. of metastatic sites			
>1 versus 1	5	1.60 (1.34–1.90)	0.000
Time from diagnosis to treatment			
<1 versus ≥1 year	2	0.86 (0.31–2.33)	0.761
Pathologic type			
Clear cell versus non-clear cell	2	0.41 (0.24–0.71)	0.001
Anemia			
Yes versus no	5	1.77 (1.52–2.06)	0.000
Neutrophil count			
>ULN versus normal	3	2.34 (1.10–5.00)	0.028
Platelet count			
>ULN versus normal	3	1.44 (1.12–1.85)	0.005
Hypercalcemia			
Yes versus no	5	1.83 (1.52–2.20)	0.000
Increased LDH			
Yes versus no	4	2.12 (1.67–2.68)	0.000

OS overall survival, *HR* hazard ratio, *CI* confidence interval, *KPS* Karnofsky performance status, *ULN* upper limit of normal, *LDH* lactate dehydrogenase

exploration. Although there is an OS advantage in the combination therapy group, it is not entirely clear what mechanism of improved OS is in the absence of an improvement in PFS. This likely reflects the selection bias for patients who are healthier to undergo CN.

CN may also work independently of targeted therapy. Several biologic mechanisms may contribute to the association between CN and the prolonged survival. (i) CN can decrease the inflammatory response and enhance immune response. It can reverse the TH1/TH2 ratio and increase the activity of natural killer cell activity and thus decrease immunosuppression [25, 26]. (ii) CN can remove a source of growth factors like transforming growth factor (TGF)-β1, platelet-derived growth factor type BB (PDFG-BB) and vascular endothelial growth factor (VEGF) which might associate with a poor prognosis [27]. (iii) CN can also be associated with a chronic low-grade metabolic acidosis and mild azotemia, which may alter the microenvironment in the tumor and peritumoral normal tissue to reduce tumor growth rate and prolong survival [28].

Other concerns surrounding CN combined with targeted therapy include timing of CN and identifying patients suitable for CN. Although our study can well prove CN combined with targeted therapy could yield better OS than targeted therapy alone, there is still limitation of revealing the optimal timing of CN. Procopio et al. [29] reported that time from nephrectomy is an independent prognostic factor for OS in patients with mRCC and treated with targeted therapy. They validated nephrectomy performed

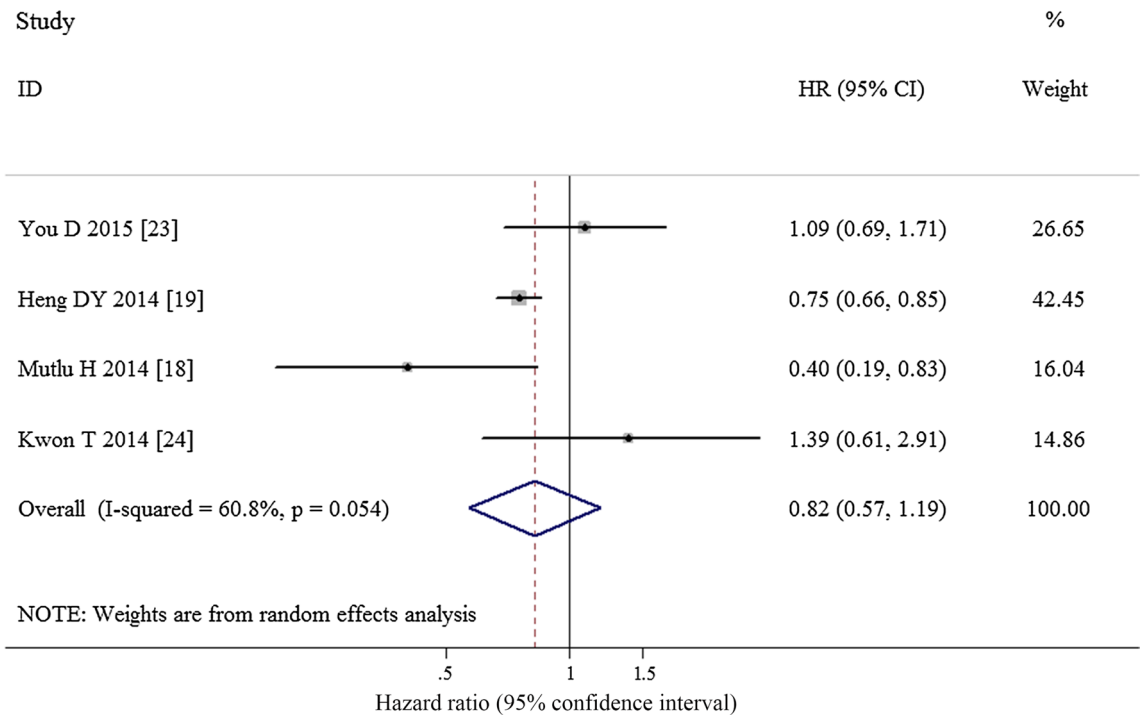

Fig. 3 Forest plot revealing the pooled HR of progression-free survival for combination therapy compared with targeted therapy alone

before the diagnosis of metastatic disease was associated with a better prognosis. Besides, Stroup et al. [30] made a study to compare outcomes of patients with mRCC who received primary targeted therapy before CN versus those who underwent CN followed by targeted therapy. They found that responders to primary targeted therapy had better prognosis than those who underwent primary CN followed by targeted therapy; however, prognosis was poor for nonresponders. For better identifying beneficial candidates for CN, You et al. [23] made a study and found KPS, hemoglobin, neutrophils and clinical N stage were suitable preoperative variables for selection of patients. Considering the limited studies, further investigation is required to assess timing of CN and selection of patients.

Strengths of our study include as follows: (i) As a multicenter and large sample meta-analysis, our study can truly represent real-world evidence which suggested that CN may confer an independent survival benefit in patient with mRCC who receives contemporary targeted therapy. (ii) Only those studies that stick to the clear grouping design of undergoing CN combined with targeted therapy versus receiving targeted therapy alone were included in this meta-analysis, and thus, a reliable conclusion about whether CN can prolong survival in the targeted therapy era would be reached. (iii) Sensitivity analysis was conducted to clarify whether the results were simply due to one large study or a study with an extreme result and found the results for OS and PFS were consistent in each single exclusion analysis.

Our study has some limitations. First, because of its nonrandomized and retrospective nature, patients may be prone to potential selection bias. Although we have used the risk estimates that reflected the greatest degree of adjustment for known prognostic variables, there may be bias for which adjustments could not be made. Second, since PFS was not reported in all included studies, the pooled HR of PFS is based on a rather limited number of studies. This meta-analysis may not achieve enough power to detect significant PFS advantage. In addition, although statistical heterogeneity was noted in the analysis of PFS, subgroup analysis was not performed due to the limited number of studies. Third, among the included studies, only one study conducted an analysis of preoperative characteristics in patients treated with CN which might identify factors that aid the selection of patients [23]. Finally, our study is unable to account for perioperative mortality and surgery-related morbidity.

Two ongoing randomized trials are initiating to define the role and sequence of CN combined with targeted therapy. The CARMENA trial is aimed to answer the question whether nephrectomy is necessary and the SURTIME trial is aimed to determine the optimal timing of nephrectomy [31, 32]. Since the results of these trials will not be reported before the end of 2017, our study has an important reference value by integrating the existing retrospective population-based studies.

Conclusions

The findings from our meta-analysis indicate that CN combined with targeted therapy has a significant OS advantage in patients with mRCC. However, the evidence is limited due to the retrospective nature of the existing studies regarding this issue with its inherent limitations and potential biases. Although we reveal some significant prognostic factors predicting OS, further research should be made to identify factors that aid the selection of patients. Additional studies, especially large prospective cohort studies, are required to confirm these findings.

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Author contributions Xuwei Hong and Fei Li conducted analysis and wrote the manuscript; Kaiqiang Tang and Shiyu Pang were involved in data collection and management; Guangzheng Lin verified the data; Shi Li assisted in statistical analyses; Jiming Bao edited figures and tables; Wanlong Tan was involved in project development and proofread the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval As the study was a meta-analysis based on the existing population-based studies, we did not apply for the approval of institutional review board.

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