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Effects of neoadjuvant VEGF-TKI treatment on surgery for renal cell carcinoma: A systematic review and meta-analysis

MEIKAI ZHU[1], ZHIFENG LIU[2], YONGHENG ZHOU[1], ZHIWEN JIANG[1], SHOUZHEN CHEN[1], WENFU WANG[1], BENKANG SHI[1] and YAOFENG ZHU[1]

[1]Department of Urology, Qilu Hospital of Shandong University, Jinan, Shandong 250012; [2]Department of Urology, Tai'an City Central Hospital, Tai'an, Shandong 271000, P.R. China

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Abstract. To evaluate the effects of neoadjuvant vascular endothelial growth factor-tyrosine kinase inhibitor (VEGF-TKI) treatment on surgery in patients with renal cell carcinoma (RCC), sources from Embase, PubMed and the Cochrane Library databases collected from inception to December, 2022 were used for analysis in the present study, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Data regarding surgical outcomes were collected. The pooled effect sizes were calculated in terms of the risk ratio (RR)/standard mean difference (SMD) with 95% confidence intervals (CIs) using the random-effects model. Subgroup and sensitivity analyses were used to explore the source of heterogeneity within the data. In total, 9 identified articles involving 829 patients (336 in the neoadjuvant + surgery group; 493 in the surgery group) were included in the present study, according to the criteria. The results demonstrated that there were no significant differences in blood loss (SMD=-0.11; 95% CI, -0.63-0.41; P=0.68), postoperative length of hospital stay or total length of hospital stay (SMD=0.23; 95% CI, -0.55-1.01; P=0.57) or complications (RR=1.16; 95% CI, 0.80-1.67; P=0.44) between the two groups. However, neoadjuvant therapy reduced the operation time (SMD=-0.67; 95% CI, -1.25- -0.09; P=0.02) and resulted in a greater proportion of patients choosing partial nephrectomy (RR=1.84; 95% CI, 1.47-2.31; P<0.00001). In the subgroup analysis, the blood loss was significantly lower in patients with RCC with inferior vena cava tumor thrombus in the neoadjuvant group (SMD=-1.10; 95% CI, -1.82- -0.38; P=0.003). In conclusion, the results of the present study indicated that neoadjuvant VEGF-TKI treatment in patients with RCC shortened operation time, decreased blood loss and did not cause an increase in perioperative complications. In addition, this treatment modality may encourage patients to opt for partial nephrectomy to preserve renal function.

Correspondence to: Professor Yaofeng Zhu, Department of Urology, Qilu Hospital of Shandong University, 107 Wenhua West Road, Jinan, Shandong 250012, P.R. China
E-mail: feng2209@163.com

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Introduction

Renal cell carcinoma (RCC) is the most common type of kidney cancer and its incidence has increased over the last decade. At present, the incidence of RCC is estimated to be ~3% among all types of cancer, accounting for >130,000 fatalities each year worldwide (1,2). RCC is commonly accompanied by localized tumors (65% of all cases), lymphatic node metastasis (16% of all cases) and distant metastases (16% of all cases) (3,4). Patients with RCC are at high risk of vascular invasion, as the tumor is able to extend from the kidney and through the venous drainage pathway. The malignancy can extend as a venous tumor thrombus (VTT) from the renal vein to the inferior vena cava (IVC). Furthermore, ~8.8% of patients with RCC have VTT at the time of diagnosis.

The most common treatment approach for RCC is complete surgical excision in the form of partial nephrectomy (PN) or radical nephrectomy. For metastatic disease, surgical excision of the original tumor (cytoreductive nephrectomy) can be performed as palliative therapy prior to systemic treatment, which aims to reduce tumor invasiveness and preserve renal function (5,6). Furthermore, systemic treatment of RCC can also be applied during the early stages of the disease. Tyrosine kinase inhibitors (TKIs), such as sunitinib, sorafenib, pazopanib and axitinib, that target vascular endothelial growth factor receptors (VEGFR) or monoclonal antibodies against VEGF are considered as significant strategies for the systemic therapy of RCC (7,8). The effect of neoadjuvant TKI therapy on patients with RCC has been investigated in numerous prospective and retrospective trials (9-12), and it was shown to enhance resectability of the tumor and reduce the need for renal replacement therapy by enabling nephron-sparing surgery. However, whether patients administered neoadjuvant TKI therapy encounter more operative complications due to the effects of TKI on wound healing remains controversial. Moreover, the utility of inducing regression of neoadjuvant TKI therapy on IVC thrombus is unclear (13). At present, there is a lack of systematic meta-analyses regarding the effect of neoadjuvant TKI therapy on the surgery of patients with RCC.

The present meta-analysis aimed to summarize the surgical outcomes of patients with RCC treated with neoadjuvant TKI therapy compared with patients treated with surgery alone, and to evaluate the effect of neoadjuvant TKI therapy on surgery, thus providing novel insights into the potential advances of neoadjuvant TKI therapy in the treatment of RCC.

Materials and methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The present meta-analysis was conducted based on the PRISMA criteria (14) and the review protocol was registered on PROSPERO (registration no. CRD42023387617; https://www.crd.york.ac.uk/PROSPERO/).

Search strategy. The Embase (https://www.embase.com/landing?status=grey), PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Cochrane Library databases (https://www.cochranelibrary.com/) were screened for eligible studies between the review inception and December, 2022. Only articles in English were included in the present review article. The detailed search strategies are shown in Data S1. The relevant cited references from the selected studies were also retrieved to ascertain additional potentially acceptable literature.

Study selection. Only observational or randomized controlled studies published as conference abstracts or full papers were screened in the present analysis. The inclusion criteria according to the PRISMA guidelines were as follows: i) Studies comparing neoadjuvant with non-neoadjuvant therapy prior to surgery in patients with pathologically confirmed RCC; ii) randomized controlled trials (RCTs) or retrospective comparative studies written in English; iii) studies with at least one evaluable surgical outcome; and iv) studies providing sufficient data to support comparisons.

Data extraction. In the present meta-analysis two reviewers independently extracted the data using a standardized extraction form. The differences were then compared by another independent reviewer. The information extracted from the eligible studies, included publication year, study design, first author, country, clinical intervention, number of subjects, age (mean or median), perioperative outcomes (blood loss, operative time and complication), postoperative length of hospital stay or total length of hospital stay and the proportion of patients who underwent partial nephrectomy after neoadjuvant therapy. For studies reporting median and range [or interquartile range (IQR)] values, a validated mathematical model was used to convert the median, range or IQR values to mean ± standard deviation (15,16). For studies that provided statistical charts without values, these values were estimated using a professional graphic processing software (Adobe Photoshop 2021; Adobe Systems, Inc.).

Quality assessment. The quality of the RCTs was assessed using the Cochrane risk of bias tool (17), while the Newcastle-Ottawa Scale (NOS) (18) was adopted for evaluating the cohort studies. The NOS categories included selection, comparability of study groups and outcome (four, two and three stars maximally, respectively). Studies that were rated more than six stars were considered to be of high quality. In addition, two independent reviewers evaluated the risk of bias in all included studies and any inconsistency was discussed and resolved by another independent reviewer to reach an agreement.

Statistical analysis. All statistical analyses were performed using ReviewManager Software (version 5.4; https://training.cochrane.org/online-learning/core-software/revman). The standardized mean difference (SMD) was used as a summary measure for continuous outcomes, while the risk ratio (RR) with 95% confidence interval (CI) was calculated for binary variables. The random-effects model was used for all meta-analyses. Subgroup and sensitivity analyses were conducted to assess the robustness of the findings in studies with high heterogeneity. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Search results and description of eligible studies. The detailed process of literature retrieval and screening is shown in Fig. 1. In total, 9 articles (19-27) were selected after the title, abstract and full texts were screened according to the selection criteria. The time span of publications covered 2011 to 2021, involving 829 patients (336 in the neoadjuvant + surgery group; 493 in the surgery group).

The specific information retrieved from each study is shown in Tables I and SI. Among the 9 included studies, 3 were randomized controlled trials (19,20,22) and the remaining studies were retrospective, non-randomized studies (21,23-27). In the included studies, the patients in the neoadjuvant group had all received the targeted therapy before surgery, and the reported median or average ages of patients ranged from 55.7-71.4 years old. It should be noted that 2 articles (20,22) reported overlapping series of patients, but the type of outcomes were different, so both articles were included in the present analysis without direct comparison.

Quality evaluation. The quality assessment for the 3 RCTs included in the present meta-analysis is shown in Fig. S1. According to the Cochrane risk-of-bias tool, none of the trials were rated with a high risk of bias. For the 6 retrospective observational studies, the quality was assessed following the NOS guidelines. The quality of the studies varied from a NOS score of 7 to 9 (Table SII). Therefore, all 9 studies were included in the subsequent analysis.

Meta-analysis. The differences in operative time, blood loss, complication, postoperative length of hospital stay or the total length of stay in the hospital and the proportion of patients who underwent partial nephrectomy were compared between the two groups. As illustrated in Fig. 2, neoadjuvant treatment before surgery significantly reduced the operation time (SMD=-0.67; 95% CI, -1.25- -0.09; P=0.02; Fig. 2A) and resulted in a greater proportion of patients choosing partial nephrectomy (RR=1.84; 95% CI, 1.47-2.31; P<0.00001; Fig. 2B). However, there were no significant differences in blood loss (SMD=-0.11; 95% CI, -0.63-0.41; P=0.68; Fig. 2C), postoperative length of hospital stay or the total length of stay in the hospital (SMD=0.23; 95% CI, -0.55-1.01; P=0.57;

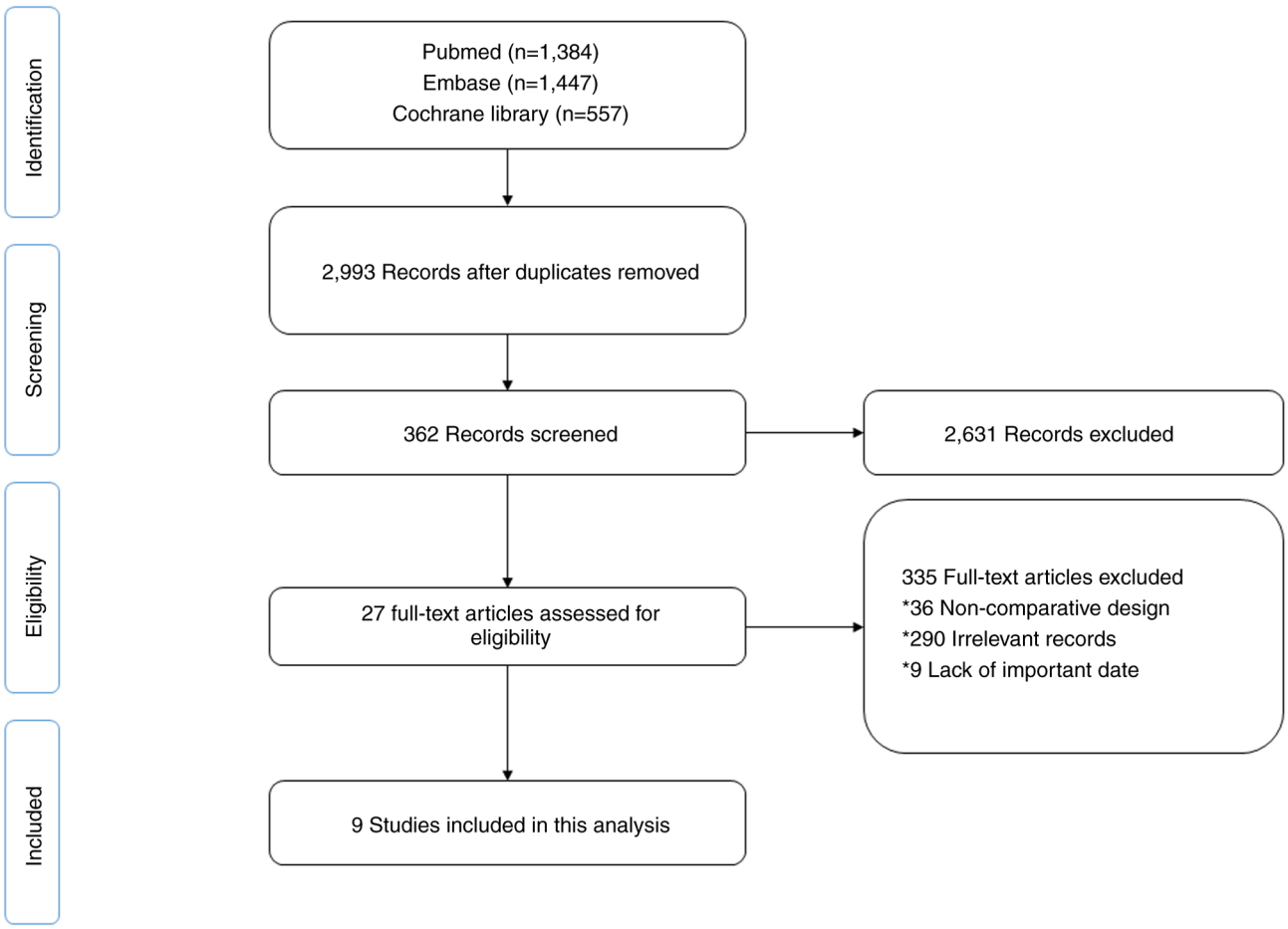

Figure 1. Preferred reporting items for systematic reviews and meta-analysis flow diagram.

Fig. 2D) or complication (RR=1.16; 95% CI, 0.80-1.67; P=0.44; Fig. 2E) with or without neoadjuvant therapy.

Subgroup analysis. Since RCC is a dynamic disease, patient data originating from different phases of the disease may result from different complexities of surgery, which may be a potential source of heterogeneity. Therefore, a subgroup meta-analysis was conducted where patients were divided into 'patients with localized RCC/underwent PN', 'patients with advanced RCC and/or metastatic RCC' and 'patients with RCC and IVC tumor thrombus'. The results demonstrated that neoadjuvant therapy significantly reduced the blood loss during surgery for patients with RCC and tumor thrombus in the IVC (SMD=-1.10; 95% CI, -1.82- -0.38; P=0.003; Fig. 3C). In addition, the proportion of complications graded as ≥3 [according to the Clavien-Dindo classification system (28)] for all complications were compared between the two treatment groups. As shown in Fig. 3D, neoadjuvant therapy did not increase the proportion of complications with a grade of ≥3 in all identified complications (RR=0.48; 95% CI, 0.20-1.15; P=0.10).

Sensitivity analysis. Sensitivity analysis was performed in analyses with high heterogeneity (postoperative length of hospital stay or the total length of stay in the hospital). After excluding the study by Okamura *et al* (24), the heterogeneity was significantly reduced and the final result was altered, with neoadjuvant therapy significantly increasing the total length of stay in hospital (SMD=0.59; 95% CI, 0.28-0.89; P=0.0001; Fig. S2).

Discussion

Surgery remains the cornerstone for treatment of localized RCC at present. Surgery-related outcomes such as blood loss, operative time and surgical complications, are crucial factors affecting decisions regarding surgery, as well as the operative risk and postoperative management of patients (29,30). Neoadjuvant TKI therapy preliminarily demonstrated promising results with downsizing and/or downstaging of the primary tumor in patients with unresectable tumors or poor surgical candidates (31). Although the study by Bex *et al* (32) demonstrated that for some patients who underwent cytoreductive nephrectomy, preoperative neoadjuvant TKI therapy extended the median overall survival time (32.4 vs. 15.0 months), large-scale clinical studies investigating the effect of neoadjuvant TKI therapy on the prognosis of patients with RCC are still lacking. At present, studies (25,26,31,33-37) have largely focused on the feasibility of neoadjuvant TKI therapy to facilitate surgery and as well as the adverse events associated with this treatment modality. The study by Assi *et al* (38) suggested that the incidence of adverse events following preoperative therapy for RCC might be acceptable. To the best of our knowledge, no study has yet summarized

Table I. Characteristics of the studies included in the present meta-analysis.

Author, year	Country	Study design	Interventions	Sample size, n		Age, years		(Refs.)
				Neo + Sur	Sur	Neo + Sur	Sur	
Hatiboglu *et al*, 2017	Germany	RCT	Sorafenib + surgery vs. placebo + surgery	9	3	55.7[a]	62.1[a]	(19)
Voylenko *et al*, 2020	Ukraine	RCT	Pazopanib + surgery vs. surgery alone	75	77	Na	Na	(20)
Semko *et al*, 2021	Ukraine	RCT	Pazopanib + surgery vs. surgery alone	83	84	Na	Na	(22)
McDonald *et al*, 2018	America	Retrospective	Sunitinib + surgery vs. surgery alone	47	78	59[b]	61[b]	(25)
Harshman *et al*, 2013	America	Prospective	sunitinib or sorafenib + surgery vs. surgery alone	14	73	59[a]	65[a]	(27)
Okamura *et al*, 2019	Japan	Retrospective	Pazopanib + surgery vs. surgery alone	9	10	71.4[b]	69.8[b]	(24)
Chapin *et al*, 2011	America	Retrospective	Targeted therapy + surgery vs. surgery alone	70	103	61.4[a]	59.7[a]	(26)
Tanaka *et al*, 2018	Japan	Retrospective	Axitinib + surgery vs. surgery alone	10	31	64[a]	65[a]	(23)
Field *et al*, 2019	America	Retrospective	Sunitinib + surgery vs. surgery alone	19	34	63[b]	61[b]	(21)

[a]Median, [b]mean. RCT, randomized controlled trial; Neo, Neoadjuvant therapy; Sur, surgery; Na, not available.

and evaluated the surgery-related outcomes, such as the blood loss, procedure-related complications and operation time, in patients with RCC following neoadjuvant therapy. The present study therefore aimed to explore the effect of neoadjuvant TKI therapy on surgery in patients with RCC compared with patients who underwent surgery alone. The results demonstrated that neoadjuvant therapy could shorten the operation time, reduce blood loss in patients with IVC tumor thrombus and enable more patients to choose partial nephrectomy for treating RCC. Additionally, although neoadjuvant therapy did not reduce the overall incidence of complications, it did decrease the proportion of complications with a grade of ≥3.

Targeted therapy for RCC has been greatly explored due to an improved understanding of cancer pathophysiology. A number of studies have investigated the efficacy and safety of neoadjuvant TKI therapy in patients with locally advanced disease (19,31,39-41). The results revealed that neoadjuvant therapy may reduce tumor volume to promote the surgical treatment of advanced RCC.

Another motive for investigating the utility of neoadjuvant therapy is in the facilitation of nephron-sparing surgery (25,31,33,34,36,37). It has been reported that nephrectomy can result in dialysis, more particularly in patients with bilateral kidney lesions, single kidney tumors or RCC with simultaneous opposite kidney pathology. Neoadjuvant therapy seeks to increase the possibility of partial nephrectomy, which can prevent the oversubscription of dialysis beds and high cost (42). In the present study, more patients underwent partial nephrectomy after neoadjuvant therapy, which was particularly appealing from the perspective of renal function preservation (43).

The effectiveness of neoadjuvant therapy prior to radical nephrectomy and IVC tumor thrombectomy is controversial. In a retrospective study including 25 patients with IVC thrombi, 12 were treated with sunitinib as a neoadjuvant therapy and the remaining 13 were treated with alternative targeted therapies (44). The results demonstrated that thrombus height was reduced in 44% of patients, while 7 patients (28%) exhibited a measurable increase in thrombus height. Furthermore, treatment with sunitinib induced tumor thrombus regression from level IV to level III in only 1 patient (4%). Similarly, in the study by Bigot *et al* (9), only 1 patient (7%) had thrombus level downstaging and 1 patient (7%) had thrombus level upstaging. Furthermore, stable thrombus level was observed in 12 patients (85%). The aforementioned findings suggested that neoadjuvant therapy may exert a limited effect on the feasibility of surgical extirpation. Since a considerable proportion of patients experienced tumor thrombi progression during treatment, this strategy could potentially expose patients to an increased risk of tumor thrombi progression and render the tumor inextirpable. However, other studies came to a different conclusion. In a multicenter retrospective study, including patients with RCC, after neoadjuvant therapy with sunitinib, tumor thrombi decreased by 1.3 cm (IQR, 0.7-1.5) and 8/19 (42.1%) patients had a lower thrombus stage, while partial response, according to the RECIST criteria, was reported in 5 patients (26.3%) (21). Furthermore, the NAXIVA trial evaluated the response of VTT to axitinib prior to surgery and reported that 15/20 (75%) patients

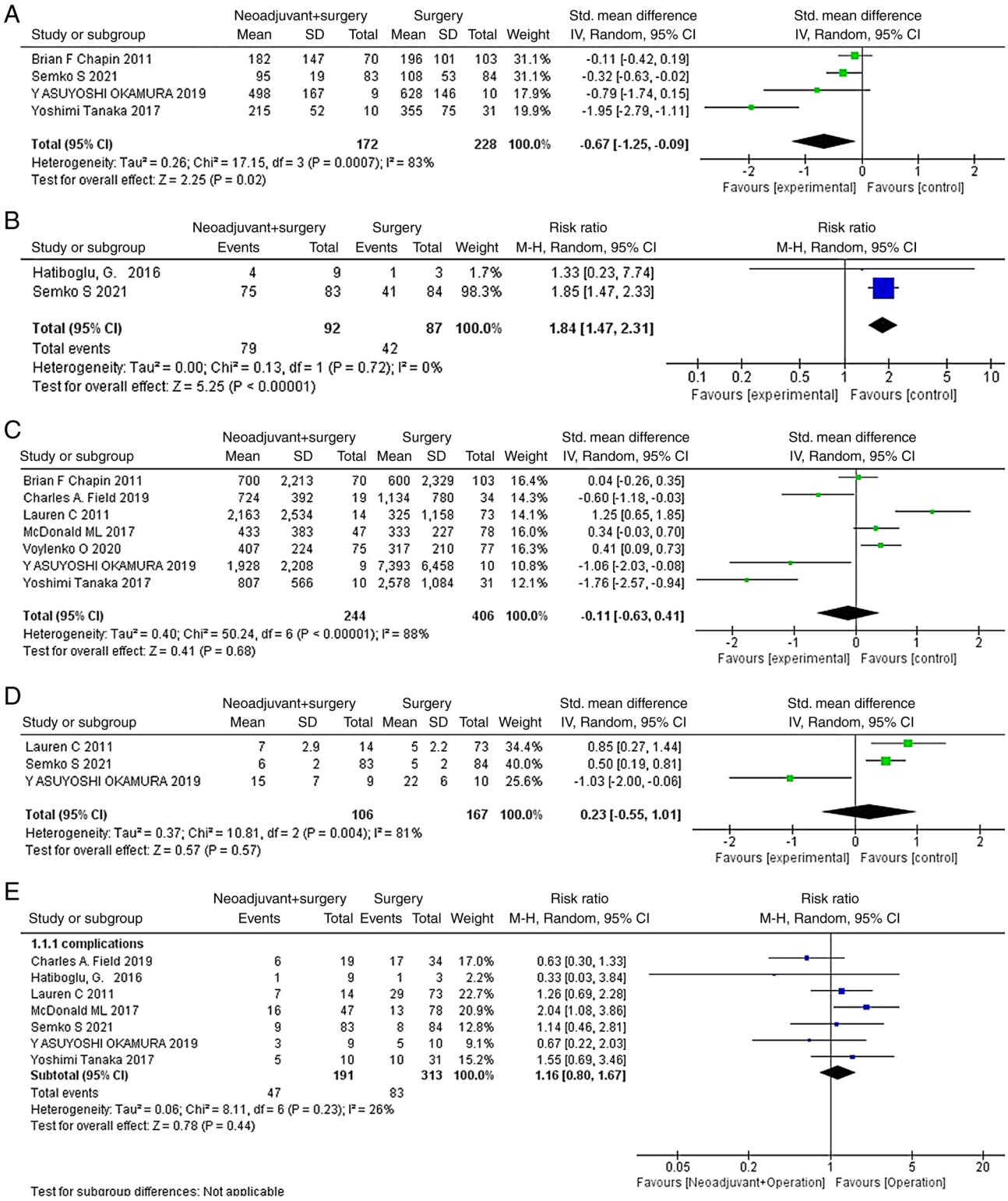

Figure 2. Meta-analyses of the related outcomes of patients administered neoadjuvant therapy + surgery vs. surgery alone. Meta-analyses of the (A) operative time (min), (B) number of patients who underwent partial nephrectomy, (C) estimated blood loss (ml), (D) postoperative hospitalization duration or total length of hospital stay (day) and (E) perioperative complications. CI, confidence interval; df, degree of freedom; IV, inverse variance; M-H, Mantel-Haenszel; SD, standard deviation.

had a reduction in VTT length, while 7/17 (41.2%) patients who underwent surgery experienced a less invasive surgery compared with that originally planned (45). This aforementioned study provided the first level II evidence that axitinib could downstage VTT in a large proportion of patients and reduce the extent of surgery. Another two studies indicated that preoperative neoadjuvant therapy was beneficial in reducing surgical risk and improving surgical outcomes (23,24). Neoadjuvant therapy may improve venous flow in the IVC via promoting tumor shrinking

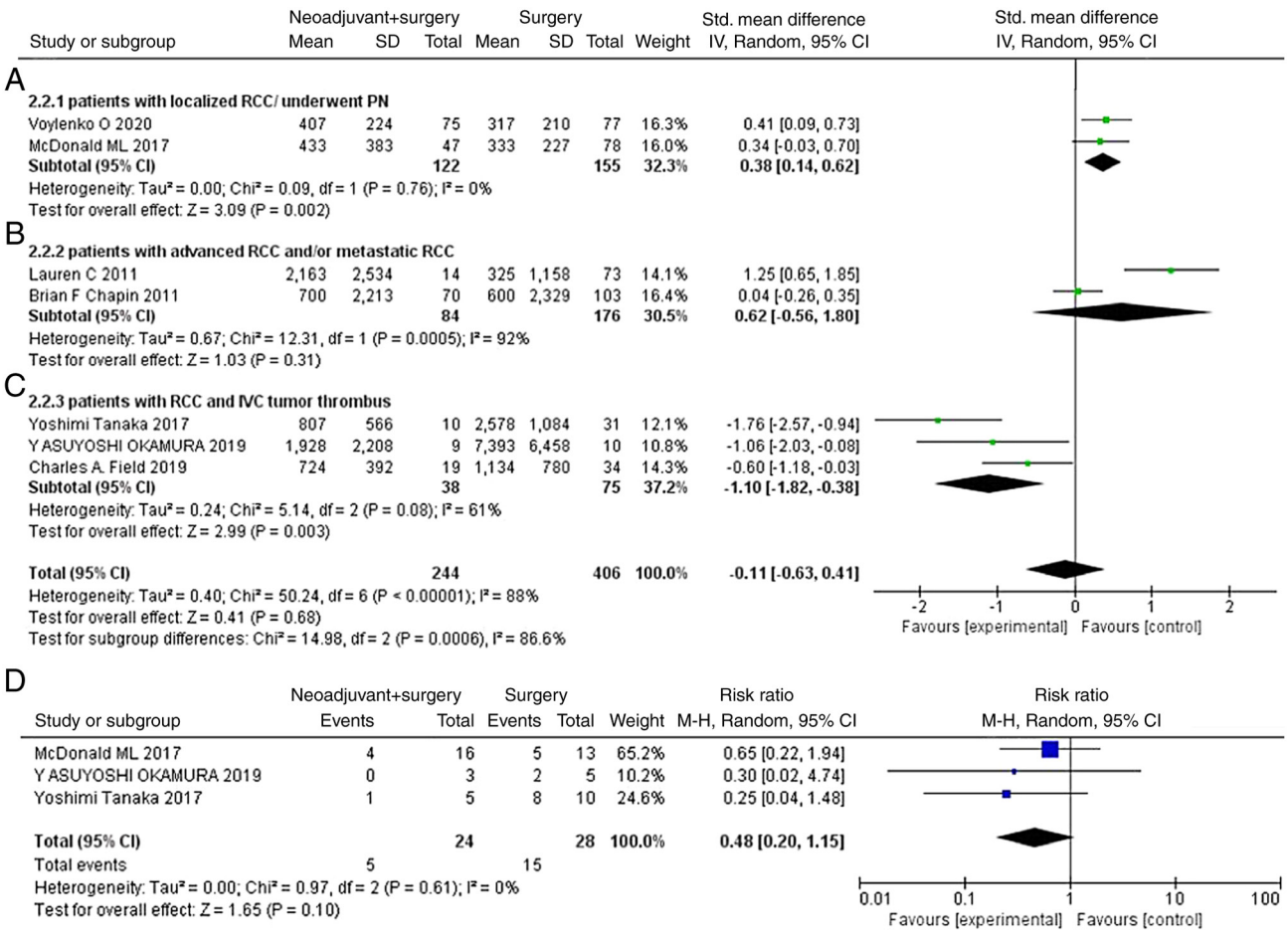

Figure 3. Subgroup analysis on the estimated blood loss. Analysis of the (A) patients with localized RCC/underwent PN, (B) patients with advanced RCC and/or metastatic RCC, (C) patients with RCC and IVC tumor thrombus and (D) complications with a grade of ≥3 (Clavien-Dindo) in all complications. CI, confidence interval; df, degree of freedom; IV, inverse variance; M-H, Mantel-Haenszel; IVC, inferior vena cava; RCC, renal cell carcinoma; SD, standard deviation; PN, partial nephrectomy.

or thrombus reduction, which could eliminate the fragile collateral venous flow and decrease intraoperative blood loss. Furthermore, neoadjuvant therapy may induce a sclerosing change in the thrombus and decrease potential risks during surgery. However, the results of the subgroup analysis of the present study demonstrated that neoadjuvant therapy could lead to enhanced blood loss in patients with localized RCC (20) and patients who underwent partial nephrectomy (25), which seemed to contradict previous conclusions. The anti-angiogenic effects of VEGF-TKI may affect wound revascularization, strength and epithelialization, as well as induce wound complications and potentially impair renorrhaphy integrity (46). In general, surgery in patients with RCC with tumor thrombus in the IVC is more complicated and bleeding during the operation can be profuse. Therefore, the benefit of neoadjuvant therapy using TKIs could overcome the shortcomings of their anti-angiogenic effects and the defects in patients with localized RCC who undergo partial nephrectomy.

In terms of perioperative complication, Margulis *et al* (35) compared the surgical outcomes of 48 patients who received preoperative therapy with a cohort of 58 patients who underwent immediate surgery. The results demonstrated that there were no statistically significant differences in the incidence of perioperative (30 day) morbidity and mortality, suggesting that a longer time may be required when reporting complications. Another study showed that preoperative therapy was not an independent predictor for overall postoperative complication risk (P=0.064) (26). These findings therefore supported the safety of preoperative systemic therapy. The results of the present study showed that neoadjuvant therapy could reduce severe complications (Clavien-Dindo grade, ≥3). However, statistical significance was not reached (P=0.06). Nevertheless, due to the limitation of the small number of patients and the nature of the included studies, the results should be interpreted with caution.

Although a considerable number of the aforementioned studies explored the effects of neoadjuvant TKI therapy on RCC, they did not meet the inclusion criteria of the present study due to a lack of comparisons with patients who had surgery alone. Clinical trials evaluating the benefits of neoadjuvant VEGF/TKI therapy on the long-term survival of patients with RCC are unlikely to be conducted in the future since VEGFR-TKI as a monotherapy treatment is gradually being surpassed by or used in combination with immunotherapy-based regimens (47). In the present study, the meta-analysis evaluated the safety and effectiveness of neoadjuvant VEGFR-TKI therapy alone. As such, it is considered

that the evidence provided by the present meta-analysis could provide some benefits to clinical practice. Although combination therapies could enhance the objective response of the tumor compared with the use of single agents, the high toxic effects of the combined therapies could compromise the fitness of the patient to undergo surgery (3). Notably, radiographic overestimation of tumor size and the fibrotic changes induced by immunotherapy have an effect on the surgical decision-making process and intimate some difficulties with the operation (48,49). In addition, the combination therapies may become a challenge for the operating surgeon (50). Overall, further exploration of the effect of different neoadjuvant therapies on the surgery of patients with RCC is still required.

In conclusion, the results of the present meta-analysis suggested that neoadjuvant VEGF-TKI treatment may shorten the operation time and reduce blood loss, while it also did not cause an increase in the incidence of severe complications. In addition, neoadjuvant therapy-induced primary tumor shrinkage could reduce the complexity of the surgery and therefore some patients may get the chance to choose partial nephrectomy to preserve renal function. However, more well-designed and high-quality prospective randomized controlled trials with larger sample sizes are required to provide additional evidence to validate these results.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MKZ performed the statistical analysis and wrote the manuscript. MKZ, ZFL, YHZ, ZWJ, SZC and WFW were in charge of acquisition of data. BKS and YFZ participated in the study design and in revising the manuscript. All authors contributed to the article and read and approved the final version of the manuscript. MKZ, ZFL, YHZ, ZWJ, SZC and WFW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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