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Targeted Therapy Following Metastasectomy for Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-analysis

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Purpose: The aim of this study was to assess the effects of tyrosine kinase inhibitors (TKIs) following metastasectomy in patients with metastatic renal cell carcinoma (mRCC).

Materials and Methods: A systematic search of multiple electronic databases was conducted. The inclusion criteria encompassed randomized clinical trials evaluating the use of TKIs after metastasectomy in mRCC patients. Study outcomes were relapse-free survival (RFS)/disease-free survival (DFS), overall survival (OS), and adverse events of TKIs.

Results: Two studies with 197 randomized participants that compared TKIs following metastasectomy versus metastasectomy alone were identified. According to these studies, TKIs following metastasectomy may result in little to no difference in RFS/DFS (hazard ratio [HR], 1.01; 95% confidence interval [CI], 0.65–1.57; I^2=29%; low-certainty evidence). TKIs after metastasectomy may slightly increase OS, but the CI crossed the line of no effect (HR, 0.80; 95% CI, 0.06–9.87; I^2=86%; low-certainty evidence). TKIs after metastasectomy likely resulted in a large increase in adverse events (risk ratio, 2.76; 95% CI: 1.65–4.62; I^2=not applicable; moderate-certainty evidence).

Conclusions: TKIs following metastasectomy did not improve RFS/DFS, but slightly improved OS. It is likely that TKIs following metastasectomy increase adverse events compared to surgery only. The certainty of evidence ranged from moderate (signaling confidence that the reported effect size is likely close to the true effect) to low (indicating that the true effect may be substantially different from the effect estimate). The findings of this study should help to inform future guidelines and clinical decision-making at the point of care.

Key Words: Renal cell carcinoma, Metastasectomy, Tyrosine kinase inhibitors, Recurrence, Survival

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- **Conflicts of Interest:** The authors have nothing to disclose.

INTRODUCTION

Metastatic renal cell carcinoma (mRCC) accounts for approximately 20%–30% of all kidney cancer cases; it has limited treatment options and is associated with a poor prognosis [1]. Surgical metastasectomy (i.e., the removal of metastatic lesions) has been considered a treatment option for carefully selected patients with limited metastases, aiming to prolong survival and improve the quality of life [2]. However, mRCC is characterized by a high rate of recurrence and metastasis, even after surgical intervention [3].

Tyrosine kinase inhibitors (TKIs) have transformed the treatment landscape for advanced RCC, demonstrating significant efficacy as both first-line and subsequent therapies [4]. Consequently, the use of TKIs following metastasectomy as an adjuvant therapy has been explored as a possible way to improve outcomes in patients with mRCC [5]. However, the optimal timing, duration, and patient selection for adjuvant TKI therapy after metastasectomy remain debatable.

Several clinical studies have investigated the role of TKIs after metastasectomy in mRCC patients, but the results are unclear. This systematic review and meta-analysis aimed to systematically evaluate the available evidence and quantify the impact of TKIs on relapse-free/disease-free survival (RFS/DFS), overall survival (OS), and adverse events of TKIs in mRCC patients.

MATERIALS AND METHODS

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [6].

1. Literature Search

A comprehensive literature search was conducted using electronic databases, including MEDLINE (Ovid), Embase, Scopus, Web of Science, Cochrane Central Library, KoreaMed, and KMbase, to analyze relevant studies published up to October 6, 2021. The search strategy included keywords related to mRCC, metastasectomy, and TKIs (Supplementary Material). Clinical trial registries were also searched, including the United States National Institutes of Health Ongoing Trials Register Clinical Trials and the World Health Organization International Clinical Trials Registry Platform.

2. Study Selection and Outcomes

Two researchers (ECH and HMG) independently reviewed all studies that appeared to fit the inclusion criteria. All authors were involved in the final decision regarding the inclusion or exclusion of each study. Studies were considered eligible if they met the following criteria: (1) evaluated the use of TKIs after metastasectomy in patients with mRCC; (2) reported survival outcomes (OS and/or RFS/DFS); and (3) were randomized clinical trials (RCTs) published as original articles, abstracts, or brief communications. Prospective or retrospective cohort studies, case reports, and review articles were excluded. If patient data were reported more than once by the same institution, the most informative and recent article was included in the analysis. RFS/DFS was defined as the interval from metastasectomy date until the detection of tumor recurrence. OS extended from the metastasectomy date until death from any cause. Adverse events during TKI therapy were recorded.

3. Data Extraction and Risk of Bias Assessment

For studies that fulfilled the inclusion criteria, 2 review authors (ECH and HMG) independently extracted the following information: (1) study characteristics, including the names of the authors, study region, and sample size; (2) treatment regimens, including TKI agents and dosages; and (3) survival data, including OS and RFS/DFS. The risk of bias for RCTs was assessed using the Cochrane Risk of bias tool [7]. When the 2 authors disagreed, a final consensus was decided on by a third author (JHJ).

4. Statistical Analysis

Using a random-effects model, pooled hazard ratios (HRs), relative risk (RR), and 95% confidence intervals (CIs) were calculated for RFS/PFS, OS, and adverse events. The HRs, RR, and 95% CIs were extracted directly from the articles. Heterogeneity among the studies was evaluated using the Cochran chi-square test and the Higgins I^2 statistic. A p-value

less than 0.10 was considered statistically significant for the Cochran chi-square test, and an I^2 greater than 50% indicated substantial heterogeneity among the studies. All statistical tests were 2-sided, and a p-value less than 0.05 indicated statistical significance. A meta-regression or subgroup analysis was not conducted and publication bias was not assessed since only 2 studies were available. All statistical tests were performed using Review Manager 5.4.1 software (Cochrane Collaboration, Copenhagen, Denmark).

5. Summary of Findings

The certainty of evidence (CoE) was rated on a per-outcome basis using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, which considers 5 criteria related to internal validity (risk of bias, inconsistency, imprecision, and publication bias) and external validity (generalizability of the results) [8]. For each comparison, 2 review authors (ECH and HMG) independently rated the CoE for each outcome as "high," "moderate," "low," or "very low" using the GRADEpro software, and summary of findings tables were constructed. Discrepancies were resolved by consensus. For each comparison, these tables provided key information about the best estimate of relative and absolute effects for each outcome [9]. The GRADE guidance was used to describe the CoE and magnitude of the effect size [10].

RESULTS

1. Study Identification and Selection

The initial literature search found 2,117 potentially relevant studies. The systematic review process is shown in the PRISMA flowchart (Fig. 1). Seventeen studies did not meet the inclusion criteria or were irrelevant to the review question. Ultimately, 2 studies met the inclusion criteria and were included in the meta-analysis, comprising 197 RCC patients [11,12].

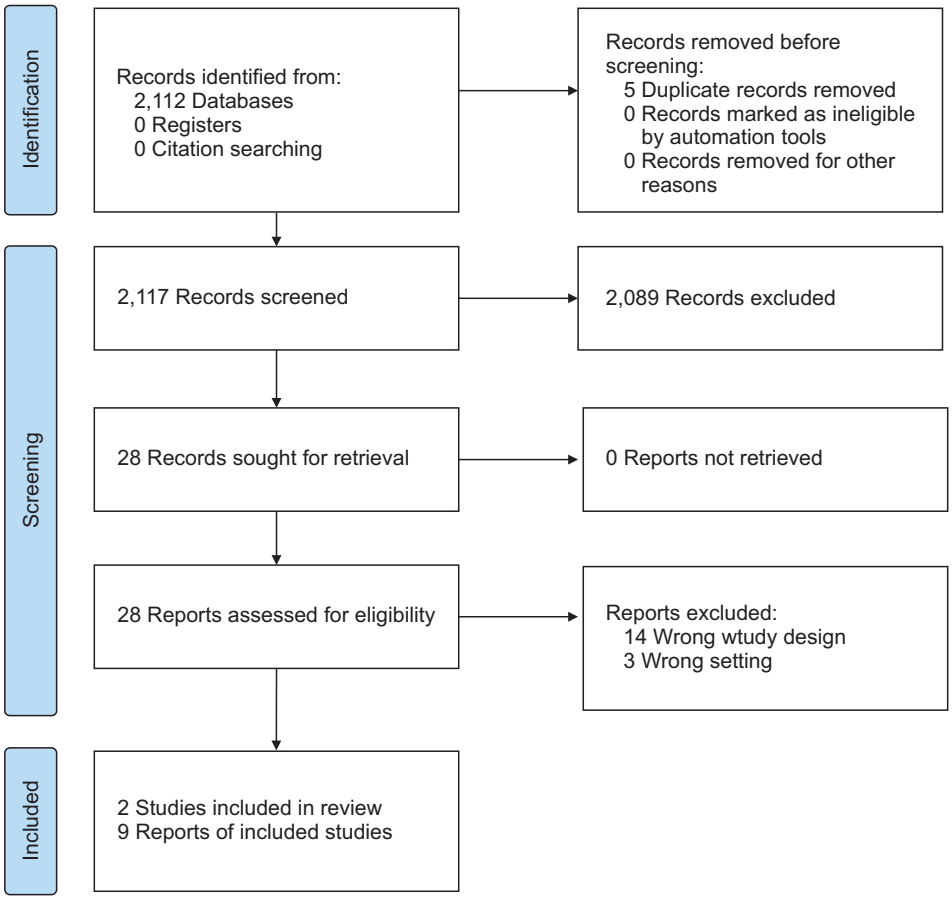

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

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2. Study Characteristics

All randomized patients in the included studies underwent metastasectomy, with or without adjuvant therapy. The studies were performed in the United States [11] and Italy [12]. One study compared pazopanib after metastasectomy to no additional treatment after metastasectomy [11], and the other study compared sorafenib after metastasectomy with metastasectomy only [12]. In the former study, reported as an abstract, the demographic characteristics of the patients were not ascertainable [11]. In the latter study, there was a single site of metastasis in 81% (n=26) of the patients in the sorafenib arm and 80% (n=29) in the observation arm. The lung was the most common metastatic site (27%, n=15), followed by the adrenal gland (22%, n=12) in both arms. In patients with multiple metastatic sites, the lung with other sites were the most common sites, and all included participants had no residual lesions following metastasectomy [12]. Data on OS and RFS/DFS were available in the 2 studies [11,12], but adverse events were only available in 1 study [12]. Table 1 provides additional details of the included studies [11,12].

3. Risk of Bias of the Included Studies

One RCT was only an abstract; therefore, all domains were rated as having an unclear risk of bias [11]. The study by Mennitto et al. [12] had a high risk of performance bias and an unclear risk of detection bias since this study was open-label. The risk of bias summary of the included studies is summarized in Fig. 2.

4. Effect of Intervention

1) Relapse-free survival/disease-free survival

TKIs after metastasectomy may result in little to no difference in RFS/DFS compared to metastasectomy only (HR, 1.01; 95% CI, 0.65–1.57; I^2=29%; 2 studies [11,12]; low-certainty evidence) (Table 2, Fig. 3).

2) Overall survival

TKIs after metastasectomy may increase OS slightly compared to metastasectomy only, but the CI crossed the line of no effect (HR, 0.80; 95% CI, 0.06–9.87; I^2=86%; 2 studies

Table 1. Included studies characteristics

Study cohort	Year	Study region	Research time	Follow-up (mo)	Population	Treatment	Patients characteristics
E2810 [11] abstract only	2019	Probably US	2012–2017	Median (range): 30 (0.4–66.5)	Patients with no evidence of disease after metastasectomy for metastatic renal cell carcinoma	Metastasectomy + pazopanib (800 mg daily) vs. metastasectomy + placebo	NA
Mennitto et al. [12]	2021	Italy	2012–2017	Median (IQR): 42 (31–58)	Patients with no evidence of disease after metastasectomy for metastatic renal cell carcinoma	Metastasectomy + sorafenib vs. metastasectomy only	Sorafenib arm n=32 (%) Age (yr), median (range): 65 (44–76) Sex: male, 20 (62); female, 12 (38) ECOG performance status: 0, 27 (84); 1, 5 (16) Histology, clear cell: 32 (100) Fuhrman grade: high (grade 3 or 4), 15 (47); low (grade 1 or 2), 15 (47) Missing: 2 (6) Disease-free interval between nephrectomy and metastasectomy (mo): ≤12, 9 (28); >12, 23 (72) Observation arm n=36 (%) Age (yr), median (range): 59 (45–80) Sex: male, 27 (75); female, 9 (25) ECOG performance status: 0, 33 (92); 1, 3 (8) Histology, clear cell: 36 (100) Fuhrman grade: high (grade 3 or 4), 22 (61); low (grade 1 or 2), 14 (39) Missing: 0 Disease-free interval between nephrectomy and metastasectomy (mo): ≤12, 15 (42); >12, 21 (58)

NA, not available; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group.

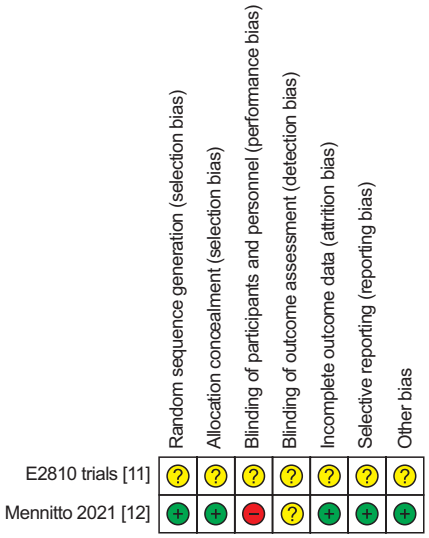

Fig. 2. Risk of bias summary for randomized clinical trials, review authors' judgments about each risk of bias item for each included study

[11,12]; low-certainty evidence) (Table 2, Fig. 3).

3) Adverse events

TKIs after metastasectomy likely resulted in a large increase in adverse events compared to metastasectomy only (risk ratio, 2.76; 95% CI, 1.65–4.62; I^2=not applicable; one study [12]; moderate-certainty evidence) (Table 2, Fig. 3).

DISCUSSION

This meta-analysis provides evidence against the use of TKIs as an adjuvant therapy after metastasectomy in patients with mRCC. These findings show no significant improvement in RFS/DFS with the addition of TKIs to surgery. To some extent, these results align with previous studies demonstrating the efficacy of upfront cytonephrectomy in selected patients with advanced mRCC [13].

Table 2. Metastasectomy after tyrosine kinase inhibitor compared to metastasectomy for metastatic renal cell carcinoma

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Plain language summary
				Risk with metastasectomy	Risk difference with metastasectomy after tyrosine kinase inhibitor	
Relapse-free/disease-free survival MCID: 5% relevant absolute risk difference	197 (2 RCTs)	⊕⊕◯◯: Low[a,b]	HR 1.01 (0.65–1.57)	626 per 1,000	3 fewer per 1,000 (147 fewer to 112 more)	Metastasectomy after tyrosine kinase inhibitor may result in little to no difference in disease-free survival compared to metastasectomy.
Overall survival MCID: 2% relevant absolute risk difference	197 (2 RCTs)	⊕⊕◯◯: Low[a,c,d]	HR 0.80 (0.06–9.87)	111 per 1,000	61 more per 1,000 (111 fewer to 765 more)	Metastasectomy after tyrosine kinase inhibitor may increase overall survival slightly compared to metastasectomy, but the confidence interval crossed the line of no effect.
Adverse events follow-up: median, 42 months MCID: 5% relevant absolute risk difference	68 (1 RCT)	⊕⊕⊕◯: Moderate[a]	RR 2.76 (1.62–4.62)	306 per 1,000	538 more per 1,000 (189 more to 1106 more)	Metastasectomy after tyrosine kinase inhibitor likely results in a large increase in adverse events compared to metastasectomy

Patient or population: Patients with metastatic renal cell carcinoma; Setting: likely outpatient; Intervention: Metastasectomy after tyrosine kinase inhibitor; Comparison: Metastasectomy.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; CI, confidence interval; MCID, minimal clinical important difference; RCT, randomized controlled trial; HR, hazard ratio; RR, risk ratio.

GRADE Working Group grades of evidence—high certainty: we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgrade by one level for risk of bias: High risk of performance bias and unclear risk of detection bias. [b]Downgrade by one level for imprecision: confidence interval crosses assumed clinical important threshold. [c]Downgrade by one level for inconsistency: substantial unexplained heterogeneity I^2=86%. [d]We did not rate down for imprecision because wide confidence interval results from inconsistency.

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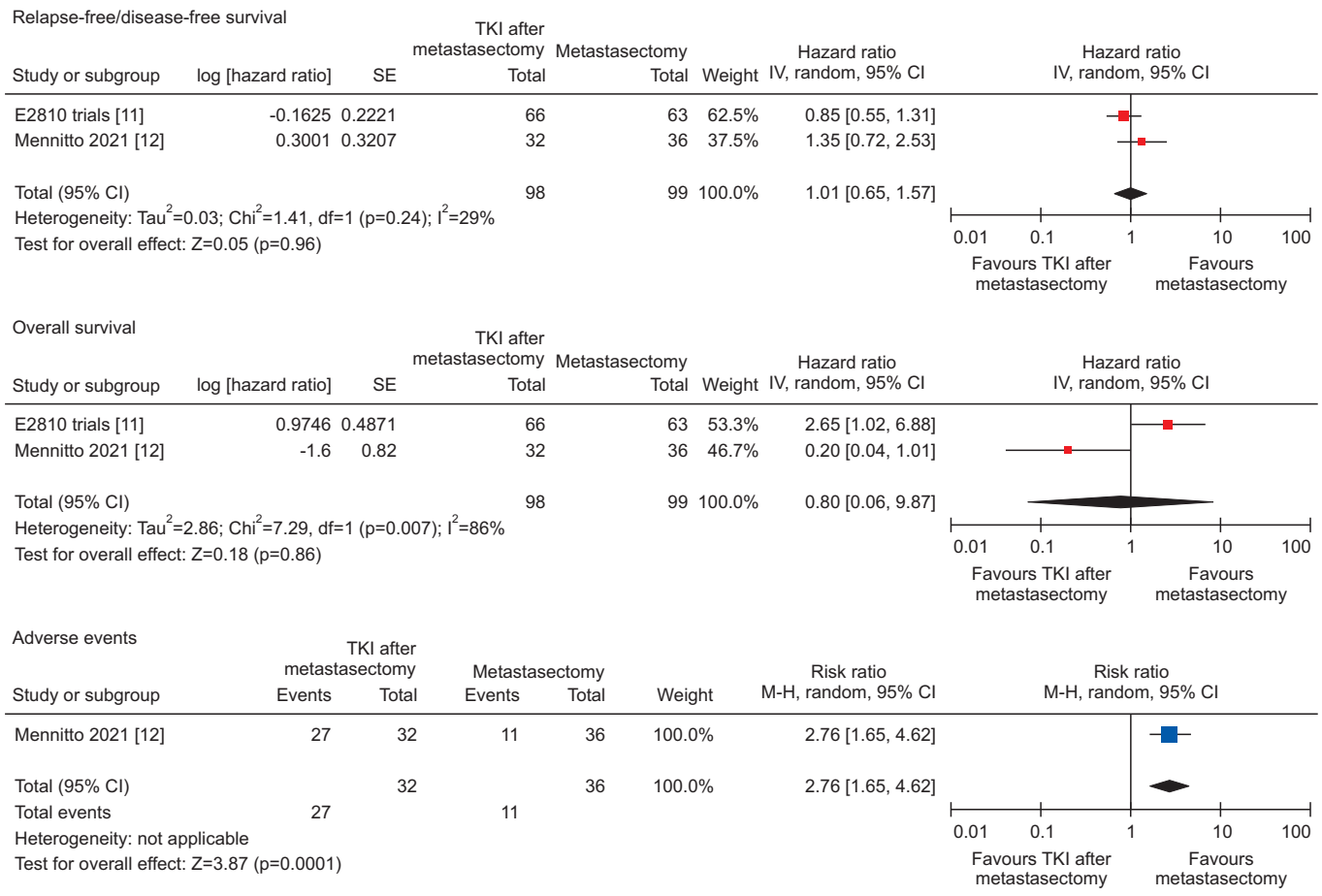

Fig. 3. Forest plots for relapse-free/disease-free survival, overall survival, and adverse events. TKI, tyrosine kinase inhibitor; SE, standard error; IV, inverse variance; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

Like other cancers, RCC is a heterogeneous disease with various histopathological subtypes, molecular phenotypes, and clinical features. Tumor biology determines the response to targeted therapies (TTs), and a remission period after the beginning of a TT is often followed by disease progression as tumors adapt and utilize alternative molecular pathways. This clinical pattern of tumor behavior may be explained by the significant genetic heterogeneity that exists between regions of the same primary tumor or between the primary tumor and metastatic lesion [14]. Alterations in the mammalian target of rapamycin pathway (SETD2, PTEN, and KDM5C) have been identified in different metastatic lesions within the same patient. In addition, Callea et al. [15] showed discordance in programmed cell death protein 1 expression between primary clear cell RCCs and metastatic sites in approximately 20% of patients. Various characteristics of the tumor phenotype and microenvironment play an important role in the progression and development of metastasis. In RCC, tumor progression and metastasis have been linked to the upregulation of VEGRF, MET, and AXL [14]. Therefore, developing a precision oncological approach deriving from molecular profiling of an individual's tumor may allow for personalized therapeutic targets. This approach may also identify patients more likely to benefit from metastasectomy.

TKIs targeting angiogenesis through the inhibition of vascular endothelial growth factor receptor (VEGFR) were associated with substantial response rates and improved survival, thus transforming the prognosis of mRCC [16]. However, most patients eventually developed drug resistance and disease progression while on therapy, including in the adjuvant setting after nephrectomy [17-19]. The biological rationale related to the failure of adjuvant TKI treatment remains unclear. It is possible that the differential TKI inhibitor activity of these drugs, as well as discrepancies in trial inclusion criteria, might have influenced the conflicting results observed in the S-TRAC [20] and ASSURE trials [21].

In the light of the failure of the ASSURE trial, we could speculate on the possible mechanisms of action of sunitinib or sorafenib in the biological scenario of micrometastatic residual disease; hypothetical possibilities could include a limited weight of angiogenesis-driven tumor growth, decreasing the sensitivity to VEGF/VEGFR inhibition, or a limited or even bad impact on immune response of sunitinib or sorafenib [12,22,23]. However, further studies are needed to clarify the biological pathways underlying these results.

The European Association of Urology (EAU) guidelines on managing mRCC strongly recommend not offering TKI treatment to mRCC patients with no evidence of disease (NED) after metastasectomy [24]. This recommendation is driven by the same trial results [11,12] that we meta-analyzed. Based on the recommendation of the EAU guidelines and the results of our meta-analysis, we conclude that TKI therapy provides no survival benefit to mRCC patients with NED after metastasectomy.

Recently, immune checkpoint inhibitors (ICIs), which target tumor or immune cell surface receptors triggering immune tolerance, have been shown to be effective in both pretreated and treatment-naïve patients with mRCC [19]. The randomized, phase 3 KEYNOTE-564 study was designed to investigate adjuvant pembrolizumab monotherapy (novel ICI) versus placebo after nephrectomy for participants with high-risk localized RCC or complete metastasectomy for mRCC patients [25]. In an updated analysis after 30 months of follow-up, subgroup analyses showed the benefit of adjuvant pembrolizumab irrespective of the disease risk category, in particular, metastatic patients after metastasectomy (DFS: HR, 0.28; 95% CI, 0.12–0.66). However, only 6% of patients were included in the experimental and placebo arm, and the results should be interpreted cautiously [26]. Another adjuvant ICI study with the PD-L1 inhibitor atezolizumab (IMmotion010) also included a complete metastasectomy subgroup, but showed no DFS advantage [27], contradicting the KEYNOTE-564 study. Patients who have undergone a successful nephrectomy or complete metastasectomy are considered to be disease-free but remain at a high risk of recurrence or mortality within 5 years after surgery in the absence of suitable adjuvant options [26,27]. Therefore, an optimal biomarker study to find suitable patients who respond to adjuvant therapy is needed.

This study has several limitations. First, the enrolled studies and sample sizes are too small to draw definitive conclusions. Second, the follow-up durations varied, and the TKIs differed (pazopanib and sorafenib) among the studies. Despite these limitations, to our knowledge, this is the first systematic review conducted with a rigorous methodology using the GRADE approach.

CONCLUSIONS

TKIs following metastasectomy did not improve RFS/DFS, but slightly improved OS. Furthermore, TKIs following metastasectomy increased adverse events compared with surgery only. The CoE ranged from moderate (signaling confidence that the reported effect size is likely close to the true effect) to low (indicating that the true effect may differ substantially from the estimated effect). The findings of this study should help to inform future guidelines and clinical decision-making at the point of care.

NOTES

- **Supplementary Material:** Supplementary material can be found via https://doi.org/10.22465/juo.244600140007.
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