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Review article

Adjuvant therapy with tyrosine kinase inhibitors for localized and locally advanced renal cell carcinoma: an updated systematic review and meta-analysis

Ekaterina Laukhtina[a,b], Fahad Quhal[a,c], Keiichiro Mori[a,d], Reza Sari Motlagh[a,e], Benjamin Pradere[a], Victor M. Schuettfort[a,f], Hadi Mostafaei[a,g], Satoshi Katayama[a,h], Nico C. Grossmann[a,i], Pawel Rajwa[a,j], Irene Resch[a], Dmitry Enikeev[b], Pierre I. Karakiewicz[k], Shahrokh F. Shariat[a,b,l,m,n,o,p,*], Manuela Schmidinger[a]

[a] *Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria*
[b] *Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia*
[c] *Department of Urology, King Fahad Specialist Hospital, Dammam, Saudi Arabia*
[d] *Department of Urology, The Jikei University School of Medicine, Tokyo, Japan*
[e] *Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[f] *Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
[g] *Research Center for Evidence Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran*
[h] *Department of Urology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan*
[i] *Department of Urology, University Hospital Zurich, Zurich, Switzerland*
[j] *Department of Urology, Medical University of Silesia, Zabrze, Poland*
[k] *Cancer Prognostics and Health Outcomes Unit, Division of Urology, University of Montreal Health Center, Montreal, Canada*
[l] *Department of Urology, Weill Cornell Medical College, New York, NY, USA*
[m] *Department of Urology, University of Texas Southwestern, Dallas, TX, USA*
[n] *Department of Urology, Second Faculty of Medicine, Charles University, Prague, Czech Republic*
[o] *Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria*
[p] *Division of Urology, Department of Special Surgery, Jordan University Hospital, The University of Jordan, Amman, Jordan*

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Abstract

PURPOSE: Tyrosine kinase inhibitors (TKIs) have been widely used in the management of patients with metastatic renal cell carcinoma (RCC). However, the use of systemic therapies in the adjuvant setting of localized and locally advanced RCC has shown conflicting results across the literature. Therefore, we aimed to conduct an updated systematic review and meta-analysis comparing the efficacy and safety of TKIs in the adjuvant setting for patients with localized and locally advanced RCC.

MATERIALS AND METHODS: The MEDLINE and EMBASE databases were searched in December 2020 to identify phase III randomized controlled trials of patients receiving adjuvant therapies with TKI for RCC. Disease-free survival (DFS) and overall survival (OS) were the primary endpoints. The secondary endpoints included treatment-related adverse events (TRAEs) of high and any grade.

RESULTS: Five trials (S-TRAC, ASSURE, PROTECT, ATLAS, and SORCE) were included in our meta-analysis comprising 6,531 patients. The forest plot revealed that TKI therapy was associated with a significantly longer DFS compared to placebo (pooled HR: 0.88, 95% CI: 0.81−0.96, P= 0.004). The Cochrane's Q test (P = 0.51) and I2 test (I2 = 0%) revealed no significant heterogeneity. Adjuvant TKI was not associated with improved OS compared to placebo (pooled HR: 0.93, 95% CI: 0.83−1.04, P= 0.23). The Cochrane's Q test (P = 0.74) and I2 test (I2 = 0%) revealed no significant heterogeneity. The forest plot revealed that TKI therapy, compared to placebo, was

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*Corresponding author. Tel.: +431-404-002-6150; fax: +431-404-002-3320

E-mail address: shahrokh.shariat@meduniwien.ac.at (S.F. Shariat).

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associated with higher rates of high grade TRAEs (OR: 5.20, 95% CI: 4.10−6.59, $P< 0.00001$) as well as any grade TRAEs (OR: 3.85, 95% CI: 1.22−12.17, $P= 0.02$). The Cochrane's Q tests ($P < 0.0001$ and $P < 0.00001$, respectively) and I2 tests (I2 = 79% and I2 = 90%, respectively) revealed significant heterogeneity.

CONCLUSIONS: The findings of our analyses suggest an improved DFS in patients with localized and locally advanced RCC receiving adjuvant TKI as compared to placebo; however, this did not translate into any significant OS benefit. Additionally, TKI therapy led to significant toxicity. Adjuvant TKI does not seem to offer a satisfactory risk and/orbenefit balance for all patients. Select patients with very poor prognosis may be considered in a shared decision-making process with the patient. With the successful arrival of immune-based therapies in RCC, these may allow a more favorable risk/benefit profile.

Keywords: Adjuvant Therapy; TKI; RCC; Renal Cell Carcinoma; Meta-Analysis

1. Introduction

Up to 40% of patients treated surgically for localized and locally advanced renal cell carcinoma (RCC) can experience recurrence and even develop metastases [1]. Tyrosine kinase inhibitors (TKIs) have been widely used in the management of patients with metastatic RCC [2]. However, despite successful application of adjuvant therapies in various malignancies, there does not seem to be consensus or benefit of adjuvant therapy in localized and locally advanced RCC [3−8]. Except for the NCCN (National Comprehensive Cancer Network) guidelines which includes adjuvant sunitinib as a treatment option [9], guidelines from major urologic societies do not recommend adjuvant targeted therapies following radical nephrectomy for high-risk clear-cell RCC [10]. Multiple reasons impede the widespread uptake of adjuvant therapy in localized and locally advanced RCC, such as the fear of unnecessary toxicity, and the absence of a survival benefit, and/or cost-efficacy. Thereby, the use of adjuvant systemic therapies for high-risk localized and locally advanced RCC patient is still not widely adapted.

In a recent meta-analysis, the authors compared multiple adjuvant treatment options with TKIs in high-risk RCC patients [5]. It was reported that TKIs in the adjuvant setting in these patients did not improve either disease-free survival (DFS) or overall survival (OS). Moreover, a significantly increased risk of toxicity was observed. However, since the last meta-analysis was conducted, updated results of the ASSURE and the S-TRAC trials have been reported [11,12]. Furthermore, the recent release of the SORCE trial has reported new results of sorafenib use in the adjuvant setting of patients with intermediate- and high-risk RCC [13].

Therefore, we aimed to conduct an updated systematic review and meta-analysis comparing the efficacy and safety of different TKIs in the adjuvant setting for patients with localized and locally advanced RCC. Such findings would help in decision making and patient counseling.

2. Materials and methods

2.1. Literature search

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [14].

The MEDLINE and EMBASE databases were searched in December 2020 to identify phase III randomized controlled trials (RCT) of patients receiving TKIs in the adjuvant setting for localized and locally advanced RCC. A comprehensive systematic literature search was independently performed by 2 authors. Terms and keywords such as renal cell carcinoma, adjuvant therapy, tyrosine kinase inhibitors, sorafenib, sunitinib, pazopanib, and axitinib were used to perform the search. DFS and OS were the primary endpoints. The secondary endpoints included treatment-related adverse events (TRAEs) of high and any grade.

After removing duplicates, two independent reviewers screened the titles and abstracts. Any citation which either reviewer thought should be included or unclear for inclusion was identified for full text screening. Subsequently, full texts of eligible articles were reviewed for final inclusion and data extraction. Any discrepancies during the primary and secondary literature screenings were resolved by referring to the senior author.

2.2. Inclusion and exclusion criteria

We included phase III RCTs that reported on the oncologic outcomes of adjuvant therapy with TKI in patients with localized and locally advanced RCC. The PICO (population, intervention, control, and outcomes) in this study was the following: patients with localized and locally advanced RCC treated with TKIs in the adjuvant setting compared to the control group who received a placebo. The outcomes were oncologic outcomes, including DFS, OS, as well as TRAEs of high and any grades.

We excluded reviews, letters to editors, editorials, animal studies, study protocols, case reports, meeting abstracts,

replies from authors, brief correspondence, and articles not published in English. Studies were included only if they involved patients who received a placebo in the control arm. References of all papers included were scanned for additional studies of interest.

2.3. Data extraction

Two investigators independently extracted the following information from the included articles: first author's name, update year, study name, national clinical trial number , number of participants, treatment arms, oncologic outcomes, TRAEs outcomes, and follow up. The hazard ratios (HR) and 95% confidence intervals (95% CIs) associated with OS and DFS were retrieved. All discrepancies regarding data extraction were resolved by consensus with the committee of investigators.

2.4. Risk of bias assessment

The quality of articles and the risk of bias evaluation of each study were assessed according to The Cochrane Collaboration's tool for assessing risk of bias [15]. The items under consideration were selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias, and other sources of bias (Supplementary Figures 2 and 3). The risk of bias of each study was assessed independently by two authors. Bias studies were illustrated using Review Manager 5.3 Software (RevMan; The Cochrane Collaboration, Oxford, UK).

2.5. Statistical analyses

Meta-analysis. First, forest plots were used to assess the HRs and 95% CIs to describe the relationships between treatment and survival outcomes (TKIs therapy versus placebo). Subgroup analyses of DFS were performed among patients with a lower and higher risk of tumor relapse. Higher risk patients were patients with 1 or more of the following features: positive lymph nodes, T4 tumors and T3 tumors, with higher Fuhrman grades (3-4). Lower risk patients were patients with none of the above-mentioned features. Second, forest plots were used as the summary variables for dichotomous outcomes and to describe the relationships between treatment and TRAEs of high-grade (grade≥3) and all-grade TRAEs (TKIs therapy versus placebo). Dichotomous variables are presented as proportions and compared with odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity among the outcomes of included studies in this meta-analysis was evaluated using Cochrane's Q test and the I2 statistic. Significant heterogeneity was indicated by a $P < 0.05$ in Cochrane's Q tests and a ratio >50% in I^2 statistics. We used fixed effects models for calculation for non-heterogeneous results. Random effect models were used in cases of heterogeneity. Publication bias was assessed with funnel plots (Supplementary Figure 5). All statistical analyses were performed using Review Manager 5.3 Software (RevMan; The Cochrane Collaboration, Oxford, UK); the statistical significance level was set at $P< 0.05$.

Network meta-analysis. We conducted network meta-analysis with random and fixed effect models using a Bayesian approach for the comparison of direct and indirect treatments, with placebo as the common comparator arm [16,17]. In the assessment for DFS, contrast-based analyses were applied with estimated differences in the log HR and the standard error calculated from the published HR and CI [18]. The relative treatment effects were presented as HR and 95% credible interval (CrI) [17]. For the assessment of the high risk TRAEs (grade≥3), arm-based analyses were performed to estimate ORs and 95% CrI from raw data presented in the selected manuscripts [17]. We also estimated the relative ranking of different treatments for each outcome using the P-score, which can be considered a frequentist analog to the surface under the cumulative ranking curve [19,20]. Network plots were utilized to illustrate the connectivity of the treatment networks in terms of DFS and high risk TRAEs. All statistical analyses were performed using R 3.6.3 and Review manager 5.3; statistical significance was set at$P < 0.05$.

3. Results

The literature search identified 943 unique references. Among them, 91 records were removed due to duplication, and 791 articles were excluded due to unrelated outcomes during the screening process (Supplementary Figure 1). Of the 61 full-text articles assessed for eligibility, 54 were excluded based on the selection criteria.

Five trials (S-TRAC, ASSURE, PROTECT, ATLAS, and SORCE), comprising 6,531 patients, were included in the meta-analysis [11−13, 21−24]. Table 1 summarizes the characteristics of included studies. The TKI agents that were evaluated in the included trial are sorafenib, sunitinib, axitinib, and pazopanib.

4. Meta-analysis

4.1. Disease-free survival (DFS)

Five studies provided data on DFS in patients receiving adjuvant TKIs versus placebo for localized and locally advanced RCC [13, 21−24]. The forest plot (Fig. 1A) revealed that TKI therapy was associated with a significantly longer DFS compared to placebo (pooled HR: 0.88, 95% CI: 0.81−0.96, $P = 0.004$). The Cochrane's Q test ($P = 0.51$) and I2 test (I2 = 0%) revealed no significant heterogeneity among trials.

In the subgroup analysis of patients with clear-cell histology, the forest plot (Supplementary Figure 4) revealed that TKI therapy was associated with a significantly longer

Table 1
Characteristics of included phase III randomized control trials of adjuvant therapies for localized and locally advanced renal cell carcinoma.

Author, publication year	Updated results	Trial name	NCT	Number of patients (treatment/ control)	Treatment	Control	Follow-up, median (range)	Definition of high risk of relapse
Ravaud, 2016 [21]	2018	S-TRAC	NCT00375674	309 / 306	Sunitinib	Placebo	6.6 yr	T3 High and T4 and any T, N+
Haas, 2016 [20]	2017	ASSURE	NCT00326898	647 / 649 / 647	Sunitinib or sorafenib	Placebo	5.8 yr (4.9−6.9)	Very high risk: pT3/4 grade 3/4 or any T N+
Motzer, 2017 [23]	-	PROTECT	NCT01235962	571 / 564 (600mg) 198 / 205 (800mg)	Pazopanib 600 mg or Pazopanib 800 mg	Placebo	NR	NR
Gross-Goupil, 2018 [22]	-	ATLAS	NCT01599754	363 / 361	Axitinib (5 mg twice daily)	Placebo	NR	Highest risk: pT3 with Fuhrman grade ≥3 or pT4 and/or N+, any T, any Fuhrman grade, M0
Eisen, 2020 [12]	-	SORCE	NCT00492258	642 / 639 / 430	Sorafenib 1yr or Sorafenib 3 yr	Placebo	6.5 yr (4.9-8.0)	Highest risk: Leibovich high risk

DFS compared to placebo (pooled HR: 0.88, 95% CI: 0.81 −0.96, $P = 0.003$). The Cochrane's Q test ($P = 0.58$) and I2 test (I2 = 0%) revealed no significant heterogeneity.

Three studies provided DFS data on the subgroup of patients with a lower risk of tumor relapse [21−23]. The forest plot (Fig. 2A) revealed that TKI therapy was not

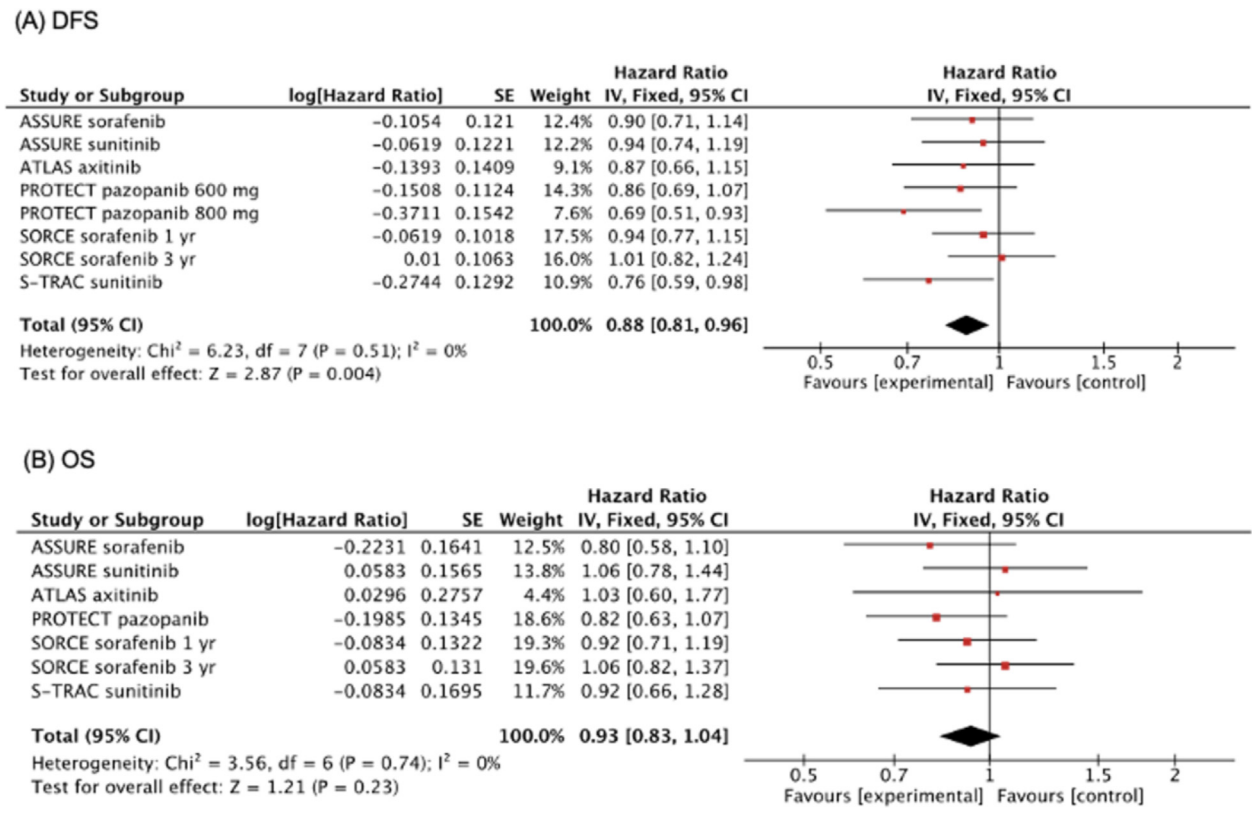

Fig. 1. The forest plot showing the association between adjuvant therapies and oncologic outcomes in renal cell carcinoma: (A) disease-free survival (DFS) and (B) overall survival (OS).

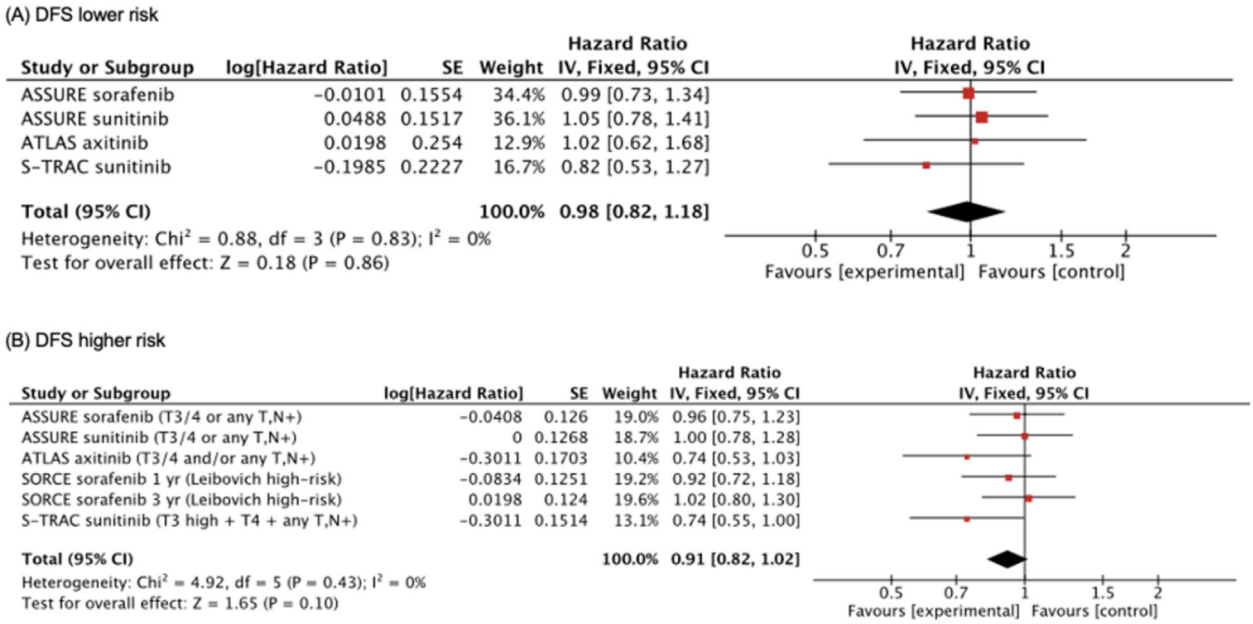

Fig. 2. The forest plot showing the association between adjuvant therapies and disease-free survival (DFS) in renal cell carcinoma comparison among patients with: (A) low risk and (B) high risk of tumor relapse.

associated with a longer DFS compared to placebo (pooled HR: 0.98, 95% CI: 0.82−1.18, $P = 0.86$). The Cochrane's Q test ($P = 0.83$) and I2 test (I2 = 0%) revealed no significant heterogeneity.

Four studies provided DFS data on the differential impact of TKI therapy versus placebo in localized and locally advanced RCC patients with a higher risk of tumor relapse [1321−23]. The forest plot (Fig. 2B) revealed that TKI therapy was not associated with a longer DFS compared to placebo (pooled HR: 0.91, 95% CI: 0.82−1.02, $P = 0.10$). The Cochrane's Q test ($P = 0.43$) and I2 test (I2 = 0%) revealed no significant heterogeneity.

4.2. Overall survival (OS)

Five studies provided OS data on patients receiving adjuvant TKI therapy versus placebo in localized and locally advanced RCC [13,21]−24]. The forest plot (Fig. 1B) revealed that adjuvant TKIs were not associated with improved OS compared to placebo (pooled HR: 0.93, 95% CI: 0.83−1.04, $P = 0.23$). The Cochrane's Q test ($P = 0.74$) and I2 test (I2 = 0%) revealed no significant heterogeneity.

4.3. Treatment related adverse events (TRAEs)

Four studies provided data on high-grade TRAEs of adjuvant TKIs versus placebo in patients with localized or locally advanced RCC [13,21,22,24]. The forest plot (Fig. 3A) revealed that TKI therapy was associated with significantly higher rates of high-grade TRAEs compared to placebo (OR: 5.20, 95% CI: 4.10−6.59, $P < 0.00001$). The Cochrane's Q test ($P < 0.0001$) and I2 test (I2 = 79%) revealed a significant heterogeneity, therefore, a random-effect model was used for the analysis.

Three studies provided data on all-grade TRAEs [13,22,24], the forest plot (Fig. 3B) revealed that TKI therapy was associated with higher rates of all-grade TRAEs compared to placebo (OR: 3.85, 95% CI: 1.22−12.17, P= 0.02). The Cochrane's Q test ($P < 0.00001$) and I2 test (I2 = 90%) revealed a significant heterogeneity, therefore, a random-effect model was used for the analysis.

5. Network meta-analysis

Networks of eligible comparisons were graphically represented in network plots with respect to DFS and high grade TRAEs (Fig. 4A and B). Network plots show interconnections between different therapy regimens (represented by a node). Connections between different therapy regimens are represented through links, the numbers indicate the number of studies.

5.1. Disease-free survival (DFS)

A network meta-analysis of eight treatments was performed with regards to DFS. Compared with placebo, only sunitinib resulted in significantly improved DFS (HR 0.62, 95% CrI 0.41−0.93) (Fig. 5A). Based on analysis of the treatment ranking, sunitinib had the highest likelihood of providing the longest DFS (P score: 0.9610) (Table 2).

5.2. High-grade treatment related adverse events (TRAEs)

A network meta-analysis of seven treatments was performed with regards to TRAEs of high grade. Compared

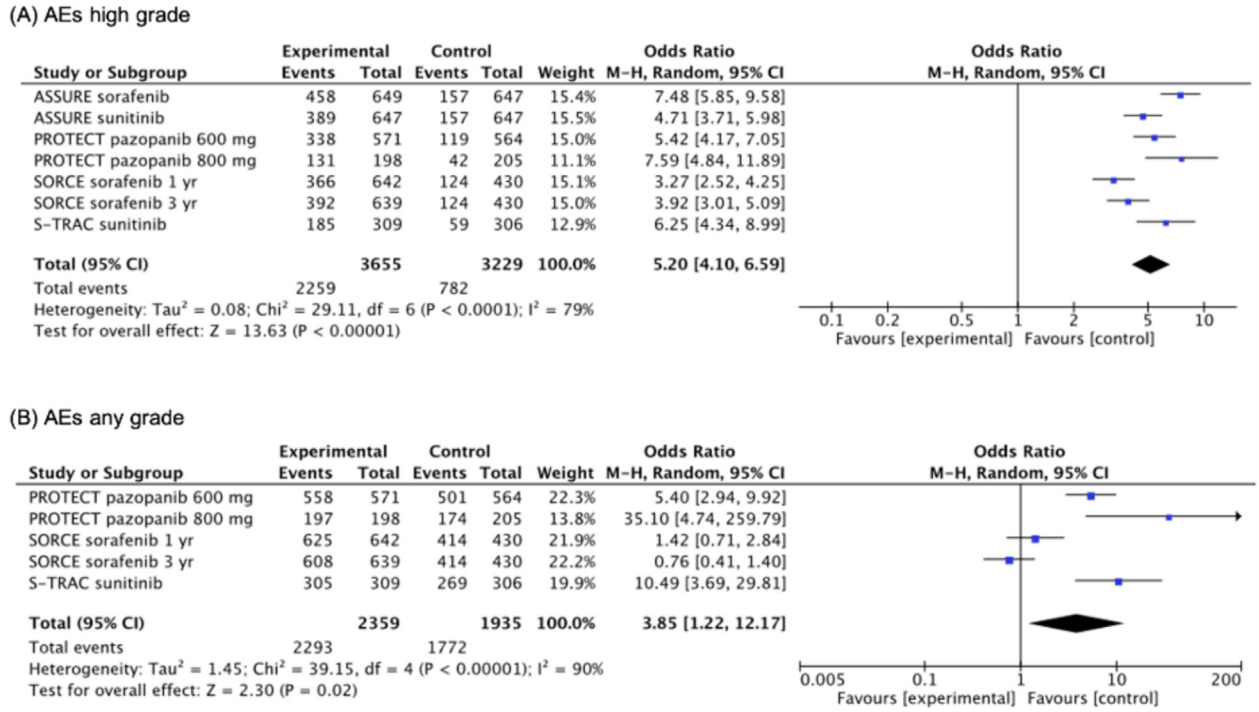

Fig. 3. Forest plots showing the association of adjuvant therapies with adverse events (AEs) in renal cell carcinoma: (A) high grade AEs and (B) any grade AEs.

with placebo, all treatments resulted in significantly higher rates of high grade TRAEs. Among them, pazopanib 800 mg and sorafenib with long treatment duration had the highest likelihood of high-grade TRAEs (OR 7.59, 95% CrI 4.55−12.65 and OR 7.92, 95% CrI 5.71−11.00, respectively) (Fig. 5B). Based on analysis of the treatment ranking, sorafenib for 1-year treatment duration had the lowest likelihood of high-grade TRAEs (*P* score: 0.8224) (Table 2).

6. Discussion

We conducted an updated systematic review and meta-analysis to compare the efficacy and safety of TKIs in the adjuvant setting in patients with localized and locally advanced RCC. We also performed a network meta-analysis to compare the DFS and high-grade TRAEs of these therapies indirectly. These approaches led to several important findings of interest.

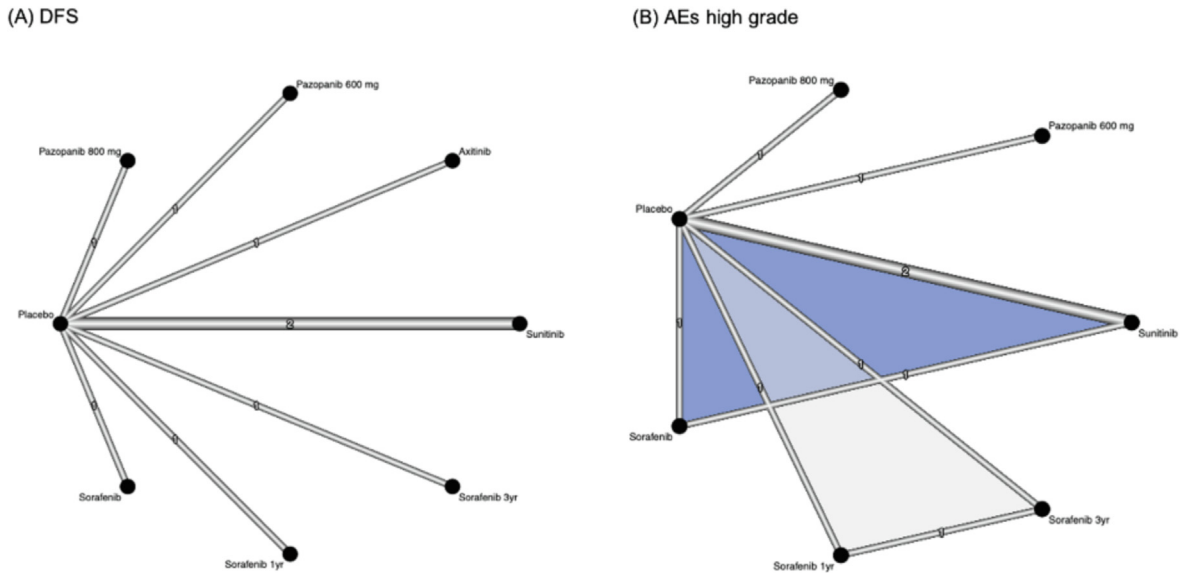

Fig. 4. Network plot showing the association of adjuvant therapy with: (A) disease-free survival (DFS) and (B) high grade AEs in localized and locally advanced renal cell carcinoma.

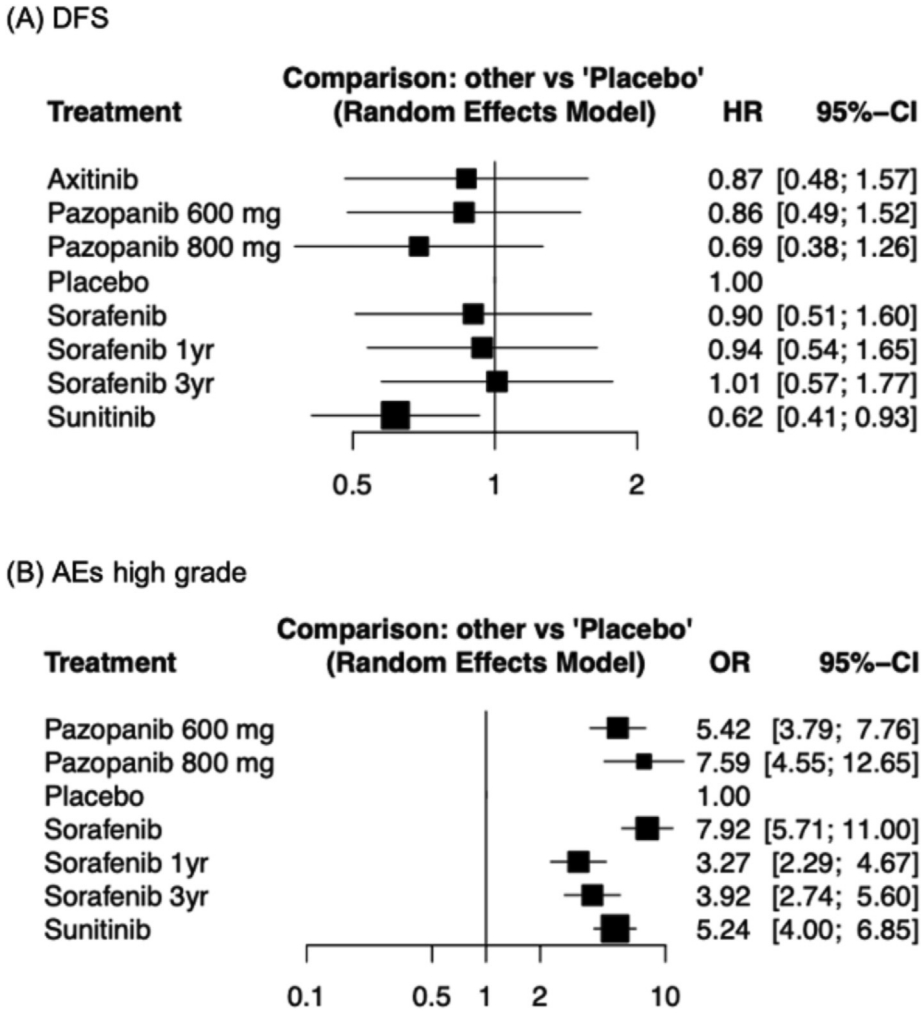

Fig. 5. Forest plots showing the association of adjuvant therapy with: (A) disease-free survival (DFS) and (B) high grade AEs in localized and locally advanced renal cell carcinoma.

Table 2
Analysis of the treatment rankings in patients with localized and locally advanced renal cell carcinoma.

Disease-free survival	*P*-score (fixed)	*P*-score (random)
Sunitinib	0.9610	0.8457
Pazopanib 800 mg	0.8317	0.7125
Pazopanib 600 mg	0.5354	0.4956
Axitinib	0.5012	0.4830
Sorafenib	0.4416	0.4470
Sorafenib 1 yr	0.3517	0.4001
Sorafenib 3 yr	0.1973	0.3253
Placebo	0.1800	0.2909
G≥3 Adverse events		
Placebo	1.0000	1.0000
Sorafenib 1 yr	0.8224	0.8014
Sorafenib 3 yr	0.6589	0.6528
Sunitinib	0.4387	0.4288
Pazopanib 600 mg	0.3819	0.3931
Pazopanib 800 mg	0.1203	0.1380
Sorafenib	0.0778	0.0860

Interestingly, our analyses showed that TKIs in the adjuvant setting were associated with a significantly longer DFS compared to placebo. However, these results were driven by only a single positive trial, while the other four trials have not reported a DFS benefit. Our results are in contrast with the results of the previously published meta-analyses [4–6]. Riaz et al. reported no significant DFS improvement with adjuvant TKI therapy when compared to placebo (HR: 0.92, 95% CI: 0.83-1.01, $P = 0.08$) [5]. The discrepancy in our findings could be explained by the inclusion of the updated results of ASSURE trial. Although the updated results from ASSURE remained non-significant for DFS, there was a slight tendency toward improving DFS. The pooled analysis of these results might have contributed to the improved DFS in our meta-analysis. Moreover, the updated trial only included patients with clear-cell histology. Furthermore, due to our aim to compare all different previously reported TKIs schedules, we separately analyzed the outcomes of the two pazopanib groups (600 mg and 800 mg) of the PROTECT trial in contrast to previously

published analyses using pazopanib as a single group. The only trials that reported a positive impact on DFS were the pazopanib 800 mg of the PROTECT trial, and the sunitinib of the S-TRAC trial. However, our network meta-analysis found that only sunitinib resulted in a significantly improved DFS compared to placebo and might be considered for the adjuvant setting of localized and locally advanced RCC. On the other hand, sorafenib showed the lowest likelihood of DFS improvement. The recent SORCE trial has failed to show the benefit of sorafenib in the adjuvant setting of intermediate- and high-risk RCC. Moreover, there was no advantage of a longer treatment period with sorafenib (3 years) compared to either short treatment period with sorafenib (1 year of sorafenib followed by 2 years of placebo) or placebo alone. The SORCE trial results confirm that sorafenib should not be used as adjuvant therapy for patients with resected RCC at intermediate or high risk of relapse. Nevertheless, the further updated results and novel trials in that field might explain the discrepancy in the findings.

We did not also observe the positive effect of TKI therapy in separate analyses of DFS data in localized and locally advanced RCC patients with a lower and higher risk of tumor relapse. Whereas, in a previous meta-analysis of four trials (S-TRAC, ASSURE, PROTECT, and ATLAS), Massari et al. reported a significant DFS benefit in patients with a higher risk of tumor relapse [6]. It should be highlighted that one of the main limitations of our meta-analysis was the discrepancy across the included studies in the definition of the grades of risk of disease relapse; that might contribute to heterogeneity among the studies. For example, the SORCE trial used the Leibovich scoring system [25], while most of the other studies reported a population with a higher risk of tumor relapse as patients with T3/T4 tumors, higher Fuhrman grades, and/or lymph nodes involvement. This heterogeneity highlights the need for a standardized grading system to assess the risk of disease relapse. Consequently, this will guide appropriate selection of RCC patients who are the best candidates for adjuvant therapy.

According to our meta-analysis results, TKIs in the adjuvant setting were not associated with improved OS compared to placebo. It is in agreement with the results of previous meta-analysis, reporting no OS benefit after TKI therapy compared to placebo (HR: 1.01, 95% CI: 0.89-1.15, $P = 0.43$) [5]. Similarly, the recent SORCE trial as well as the updated ASSURE and S-TRAC trials did not translate into any significant OS benefit. From one side, such results can be explained with the immature short follow-up period; however, DFS results for RCC could be translated into OS in general, so maybe it is unlikely that we will see OS benefit in these adjuvant trials. On the other hand, due to the significant quality of life-impacting toxicities of TKIs, it is unlikely that patients can remain on treatment for long enough periods of time that may ultimately translate into a meaningful change in overall survival [26]. So, longer follow-up does not seem to bring any different results. The lack of a significant positive effect of TKIs in the adjuvant setting of non-metastatic RCC compared to its benefits as systemic therapy of metastatic RCC is quite puzzling [27]. Some researchers hypothesized that compared to macro-metastases, micro-metastases may not require such enhanced vascularization that is as susceptible to the effects of anti-angiogenic TKI-therapy [28,29].

Finally, we found that all TKIs in the adjuvant settings are associated with a high rate of high and any grade TRAEs compared to placebo. Among the most common TRAEs, diarrhea, fatigue, hypertension, and palmar and/or plantar dysesthesia were reported [5]. According to our network meta-analysis, the highest likelihood of TRAEs was observed among patients who received pazopanib 800 mg and sorafenib with a long treatment period. While based on analysis of the treatment ranking, sorafenib with 1-year treatment period in the SORCE trial had the lowest likelihood of high grade TRAEs. Obviously, such results are associated with higher dosing and longer treatment period, leading to the prolong DFS as well as higher toxicity. The introduction of more tolerable therapies such as immune checkpoint inhibitors could alleviate this major limitation and help incorporate adjuvant systemic therapies in the treatment strategy of high-risk and locally advanced RCC [30]. The upcoming EVEREST (Everolimus for Renal Cancer Ensuing Surgical Therapy) trial might provide further understanding of the role of adjuvant mTOR-inhibition in RCC patients. Moreover, we believe that better selection criteria for patients with localized and locally advanced RCC that are more likely to benefit from adjuvant therapy is an unmet clinical need. Specific molecular signatures in RCC may translate into different recurrence risks and hopefully allow for a more accurate adjuvant therapy assignment. Further large-scale trials along the phased biomarker validation paradigm might shed a light on the decision-making process.

To the best of our knowledge, the present study was the first network meta-analysis to compare the efficacy and safety of different TKIs in the adjuvant setting in patients with high-risk localized and locally advanced RCC. Nevertheless, there are several potential limitations in this study. The main limitation is the heterogeneity across the included studies in terms of different dosing regimens, the difference in population and risk stratification, and the variable duration of follow-up. Second, the significant heterogeneity across the studies was detected in the analysis of TRAEs, thus limiting the value of these findings. Although the random effects model was used to address heterogeneity among studies, our conclusions should still be interpreted with caution. Third, while an indirect comparative approach was employed in the network meta-analysis to compare outcomes from the RCTs, this approach is not equivalent to a head-to-head treatment comparison. Thus, well-designed comparative trials are required to validate the findings of this study.

7. Conclusions

The findings of our analyses suggest an improved DFS in patients with localized and locally advanced RCC receiving adjuvant TKI as compared to placebo; however, this did not translate into any significant OS benefit. Additionally, TKI therapy led to significant toxicity. Adjuvant TKI does not seem to offer a satisfactory risk/ benefit balance for all patients. Select patients with very poor prognosis may be considered in a shared decision-making process with the patient. With the successful arrival of immune-based therapies in RCC, these may allow a more favorable risk/benefit profile.

Conflict of interest

All authors state that they have no conflict of interest that might bias this work.

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Ethical standards

None applicable.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2021.07.022.

References

[1] Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin N Am 2003. https://doi.org/10.1016/S0094-0143(03)00056-9.

[2] Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. N Engl J Med 2017;376(4):354–66. https://doi.org/10.1056/NEJMra1601333.

[3] Patel HD, Kates M, Allaf ME. Adjuvant therapy for urothelial and renal cell carcinoma. Eur Urol Focus 2020. https://doi.org/10.1016/j.euf.2019.04.007.

[4] Sun M, Marconi L, Eisen T, et al. Adjuvant vascular endothelial growth factor−targeted therapy in renal cell carcinoma: a systematic review and pooled analysis [Figure presented]. Eur Urol 2018. https://doi.org/10.1016/j.eururo.2018.05.002.

[5] Riaz IB, Faridi W, Husnain M, et al. Adjuvant therapy in high-risk renal cell cancer: a systematic review and meta-analysis. Mayo Clin Proc. 2019. https://doi.org/10.1016/j.mayocp.2019.01.045.

[6] Massari F, Di Nunno V, Mollica V, Graham J, Gatto L, Heng D. Adjuvant tyrosine kinase inhibitors in treatment of renal cell carcinoma: a meta-analysis of available clinical trials. Clinical Genitourinary Cancer 2019. https://doi.org/10.1016/j.clgc.2018.12.011.

[7] Bandini M, Smith A, Marchioni M, et al. Adjuvant therapies in non-metastatic renal-cell carcinoma: a review of the literature. Clin. Genitourin Cancer. 2018. https://doi.org/10.1016/j.clgc.2018.01.003.

[8] Karakiewicz PI, Zaffuto E, Kapoor A, et al. Kidney Cancer Research Network of Canada consensus statement on the role of adjuvant therapy after nephrectomy for high-risk, non-metastatic renal cell carcinoma: a comprehensive analysis of the literature and meta-analysis of randomized controlled trials. Can. Urol. Assoc. J. 2018. https://doi.org/10.5489/cuaj.5187.

[9] Motzer RJ, Jonasc E, Boyle S, et al. Kidney cancer, version 1.2021: Featured updates to the nccn guidelines. JNCCN J. Natl. Compr. Cancer Netw. 2020;18(9):1160–70. https://doi.org/10.6004/jnccn.2020.0043.

[10] Ljungberg B, Bensalah K, Canfield S, et al. Renal cell carcinoma EAU guidelines on renal cell carcinoma: 2020. Eur. Urol. 2020. https://doi.org/10.1016/j.eururo.2015.01.005.

[11] Motzer RJ, Ravaud A, Patard JJ, et al. Adjuvant sunitinib for high-risk renal cell carcinoma after nephrectomy: subgroup analyses and updated overall survival results. Eur. Urol. 2018. https://doi.org/10.1016/j.eururo.2017.09.008.

[12] Haas NB, Manola J, Dutcher JP, et al. Adjuvant treatment for high-risk clear cell renal cancer: updated results of a high-risk subset of the ASSURE randomized trial. JAMA Oncol 2017. https://doi.org/10.1001/jamaoncol.2017.0076.

[13] Eisen T, Frangou E, Oza B, et al. Adjuvant sorafenib for renal cell carcinoma at intermediate or high risk of relapse: Results from the SORCE randomized phase III intergroup trial. J Clin Oncol 2020. https://doi.org/10.1200/JCO.20.01800.

[14] Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. Ann. Intern. Med. 2015;162(11):777–84. https://doi.org/10.7326/M14-2385.

[15] Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011. https://doi.org/10.1136/bmj.d5928.

[16] Dias S, Sutton AJ, Ades AE, Welton NJ. A generalised linear modelling framework for pairwise and network meta-analysis of randomized controlled trials. Medical Decision Making 2012, 33(5), 607−617.

[17] van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. Res. Synth. Methods 2012. https://doi.org/10.1002/jrsm.1054.

[18] Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: A tutorial. BMC Med. Res. Methodol. 2010. https://doi.org/10.1186/1471-2288-10-54.

[19] Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. J. Clin. Epidemiol. 2011. https://doi.org/10.1016/j.jclinepi.2010.03.016.

[20] Rücker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med. Res. Methodol. 2015. https://doi.org/10.1186/s12874-015-0060-8.

[21] Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet 2016. https://doi.org/10.1016/S0140-6736(16)00559-6.

[22] Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. N. Engl. J. Med. 2016. https://doi.org/10.1056/nejmoa1611406.

[23] Gross-Goupil M, Kwon TG, Eto M, et al. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. Ann. Oncol. 2018. https://doi.org/10.1093/annonc/mdy454.

[24] Motzer RJ, Haas NB, Donskov F, et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients

with localized or locally advanced renal cell carcinoma. J Clin Oncol. 2017. https://doi.org/10.1200/JCO.2017.73.5324.

[25] Leibovich BC, Blute ML, Cheville JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma. Cancer 2003. https://doi.org/10.1002/cncr.11234.

[26] Gyawali B, Goldstein DA. The US food and drug administration's approval of adjuvant sunitinib for renal cell cancer: a case of regulatory capture? JAMA Oncology 2018. https://doi.org/10.1001/jamaoncol.2017.5697.

[27] Massari F, Di Nunno V, Ciccarese C, et al. Adjuvant therapy in renal cell carcinoma. Cancer Treat Rev 2017. https://doi.org/10.1016/j.ctrv.2017.09.004.

[28] Ebos JML, Lee CR, Cruz-Munoz W, Bjarnason GA, Christensen JG, Kerbel RS. Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. Cancer Cell 2009. https://doi.org/10.1016/j.ccr.2009.01.021.

[29] Schor-Bardach R, Alsop DC, Pedrosa I, et al. Does arterial spin-labeling MR imaging-measured tumor perfusion correlate with renal cell cancer response to antiangiogenic therapy in a mouse model? Radiology 2009. https://doi.org/10.1148/radiol.2521081059.

[30] Lenis AT, Donin NM, Johnson DC, et al. Adjuvant therapy for high risk localized kidney cancer: emerging evidence and future clinical trials. J Urol 2018. https://doi.org/10.1016/j.juro.2017.04.092.