

Meta Analysis

Knowledge of the horizon: a meta-analysis of evaluating mortality incidence in multiple modalities therapy for metastatic renal cell carcinoma

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ABSTRACT

The treatment landscape for metastatic renal cell carcinoma (mRCC) has improved with advances in targeted therapy, immunotherapy, and surgical interventions, each showing survival benefits. Although these approaches, used singly or in combination, improve outcomes, the optimal strategy remains to be determined. Yet, limited comparisons across strategies create a need to identify the most effective treatments for mRCC patients. To address this, we conducted a meta-analysis to evaluate combined surgical, targeted, and systemic therapies for mRCC, focusing on survival and mortality risk. Our aim was to offer insights that could guide future treatment approaches and improve patient outcomes. This meta-analysis was performed based on the PRISMA guidelines. Statistical analysis for meta-analyses using dichotomous types. To analyse clinical studies reporting the use of combination therapy (surgery and systemic intervention) for evaluating mortality incidence in mRCC, a systematic search was performed using three electronic databases (PubMed, Science Direct, and Google Scholar). Ten years of studies, English full paper text, and original research retrospective study design were included. Statistical analyses using Review Manager Application 5.4.1 version. From 1019 studies, there are eleven studies were eligible in this meta-analysis and have a low risk of bias. Ten studies comprising 2644 patients were included in this study for qualitative and quantitative analysis. Ten studies report the use of Combination Therapy (surgery and systemic intervention) for evaluating mortality incidence in mRCC. Quantitative synthesis showed Combination intervention was associated with death incidence in metastatic events in renal cell carcinoma with odds ratio (OR) 1.46 (95% CI; 1.37-1.54; I²=98%, p value≤0,0001). Furthermore, this research is still found to be qualitatively controversial. Our review indicates that combination therapies for mRCC improve survival outcomes but entail complex mortality risks. Further research is needed to refine therapy combinations and patient selection, underscoring a personalized approach to balance benefits with risks.

Keywords: Renal cell carcinoma, Metastatic, Therapy

INTRODUCTION

Kidney cancer accounts for 5% of all cancers in men and 3% in women worldwide. Data from GLOBOCAN 2020 shows that renal cell carcinoma (RCC) is the 14th most commonly diagnosed cancer, representing over 85% of all primary kidney tumors. The incidental detection of kidney tumors has increased significantly with the widespread use of radiological imaging. However, survival outcomes are

greatly influenced by the stage at diagnosis. Around one-third of RCC patients present with metastatic disease, and the five-year survival rate for these patients is just 12%.¹

Kidney cancer can spread to any part of the body and manifest in various ways. Lung metastasis occurs in 45–80% of cases, followed by bone (25–35%), lymph nodes (20–25%), and liver (18–20%). Brain metastases are seen less commonly in 4–11% of patients. Additionally, RCC

can metastasize to rare and challenging sites, such as the pancreas, duodenum, or thyroid.¹

The treatment options for metastatic renal cell carcinoma (mRCC) currently include systemic approaches such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs). While these therapies can be administered in sequence, recent developments have seen the introduction of combination therapies aimed at enhancing patient outcomes.

These combined treatments work synergistically by targeting multiple pathways and mechanisms involved in tumor progression. Based on encouraging findings from recent clinical trials, combination therapies are increasingly recognized as a pivotal component in the management of RCC.²

Metastatic renal cell carcinoma (mRCC) remains a formidable challenge in oncology due to its aggressive nature and high mortality rates. Over the years, advances in systemic and combination therapies have revolutionized treatment strategies, yet the optimal approach for improving survival outcomes continues to be debated.

Combination therapies, which include targeted therapies and immune checkpoint inhibitors, have been increasingly utilized to enhance efficacy by addressing tumor progression through multiple mechanisms.³

Despite their widespread adoption, the survival benefits of combination therapies remain variable across studies, with significant heterogeneity in reported outcomes. Understanding the incidence of mortality associated with these therapies is crucial for guiding clinical practice and optimizing patient care. The lack of consolidated evidence on the relative effectiveness of combination therapies compared to single or other modalities further highlights the need for comprehensive analyses.

This meta-analysis aims to evaluate the quality of life in mRCC patients treated with combination therapy by synthesizing data from various studies.

By analyzing outcomes such as odds ratios and mortality incidence, the study seeks to provide clarity on the effectiveness of combination therapies, address important gaps in the existing literature, and offer insights for evidence-based decision-making in the management of mRCC.

METHODS

This meta-analysis includes retrospective studies with human studies published in English from 2014 to September 2024. In addition, the inclusion criteria used were Patients diagnosed with metastatic renal cell carcinoma (mRCC), any age and gender. Patients were treated with surgical therapy, systemic therapy, and a combination of surgical therapy with systemic therapy.

Outside the criteria mentioned, the study was not included. This systematic literature search was in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA).

This study used Odds Ratio (OR) with 95% confidence intervals to compare treatment effects, and in single-arm analysis, we considered proportions with 95% confidence intervals.

The I² statistic was used to assess heterogeneity, p value less than 0.05 and I²<35% were considered significant. Statistical analysis was performed using PubMed, Google Scholar, and ScienceDirect databases searched independently by three reviewers until September 2024.

The search algorithm included a combination of terms "renal cell carcinoma" or "kidney neoplasms" or "kidney cancer" or "metastatic renal cell carcinoma" and "surgical procedures, operative" or "surgery" or "nephrectomy" or "surgical therapy" and "systemic therapy" or "targeted therapy" or "immunotherapy" or "systemic treatment". In addition, references for listed papers were manually checked to find new publications that may have been missed by the initial search.

Three independent reviewers evaluated relevant publications, and data were extracted for each study using a standard extraction form in an Excel spreadsheet and the online tool from Rayyan.

Risk of bias analysis of studies was carried out using the online tool Revised Cochrane risk-of-bias tool (RoB 2 tool) and meta-analysis statistics were carried out using the Review Manager application version 5.4. Any disagreements were discussed to reach consensus. No ethics board approval was required because the primary data had been previously published.

RESULTS

A systematic search for this study yielded 1,019 articles, with 19 articles found on PubMed, 913 articles on Science Direct, and 87 articles on Google Scholar. A total of 12 articles were removed and marked as duplicates. After screening, 823 studies were excluded. Articles that were not relevant to the topic led to the exclusion of 67 studies.

A total of 129 studies were reported for further assessment. After filtering based on abstract relevance, 67 studies were excluded due to irrelevant abstracts. Subsequently, 129 articles were evaluated for eligibility. Of these, 118 studies were excluded for not meeting the inclusion criteria.

Finally, 10 studies relevant to the topic were included in this meta-analysis and systematic review. This search strategy is summarized in figure 1. Article included are listed on Table 1. All selected studies demonstrated a low risk of bias and summarized in Figure 2.

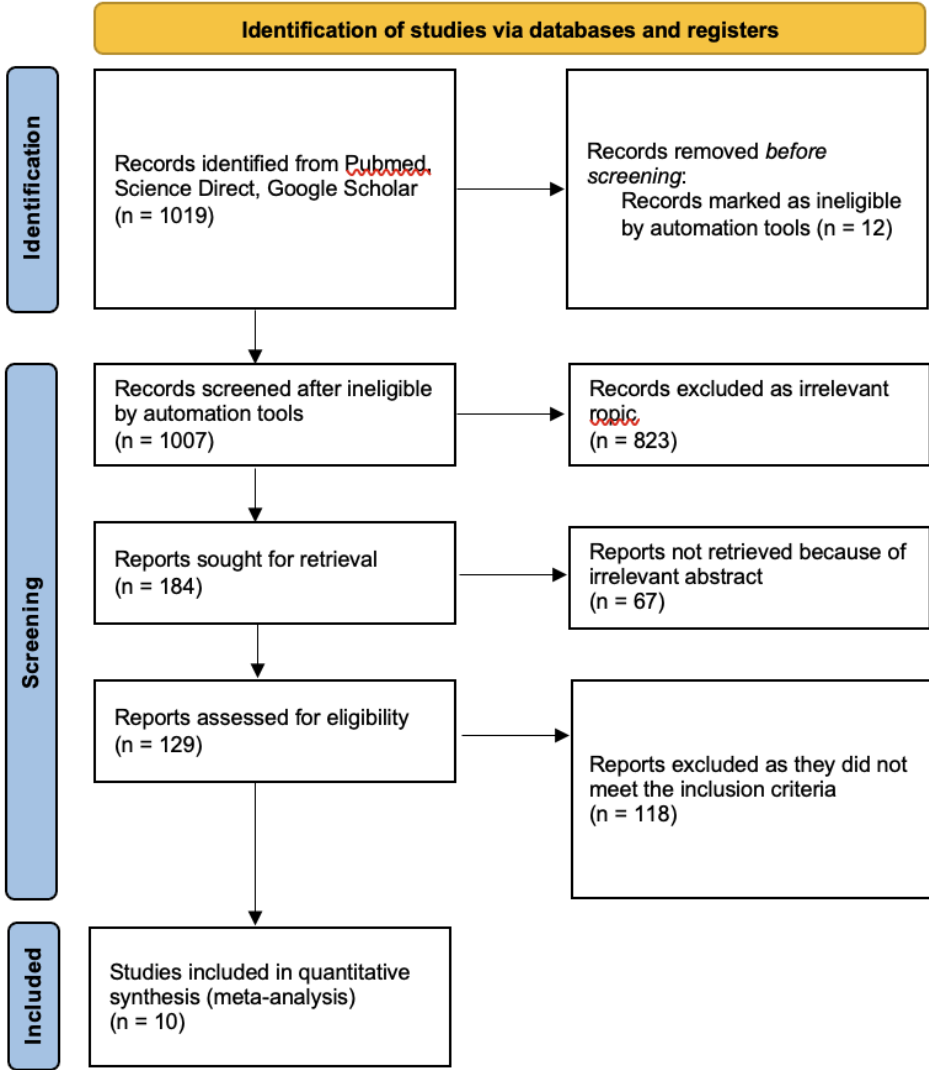


Figure 1. Flow chart on the articles selection process.

Study ID	D1	D2	D3	D4	D5	Overall	
Heng et al 2014	+	+	+	+	+	+	Low risk
Mitchell et al 2015	+	+	+	+	+	+	Some concerns
Gershman 2016	+	+	+	+	+	+	High risk
Groot et al 2016	+	+	+	!	+	+	
Blute et al 2017	+	+	+	+	+	+	D1 Randomisation process
Colombia 2017	+	+	+	+	+	+	D2 Deviations from the intended interventions
Lyon et al 2018	+	+	+	+	+	+	D3 Missing outcome data
Bhindi et al 2020	+	+	+	+	+	+	D4 Measurement of the outcome
Singla et al 2020	+	+	+	+	+	+	D5 Selection of the reported result
Eschudier et al 202	+	+	+	+	+	+	

Figure 2: Risk of bias assessment.

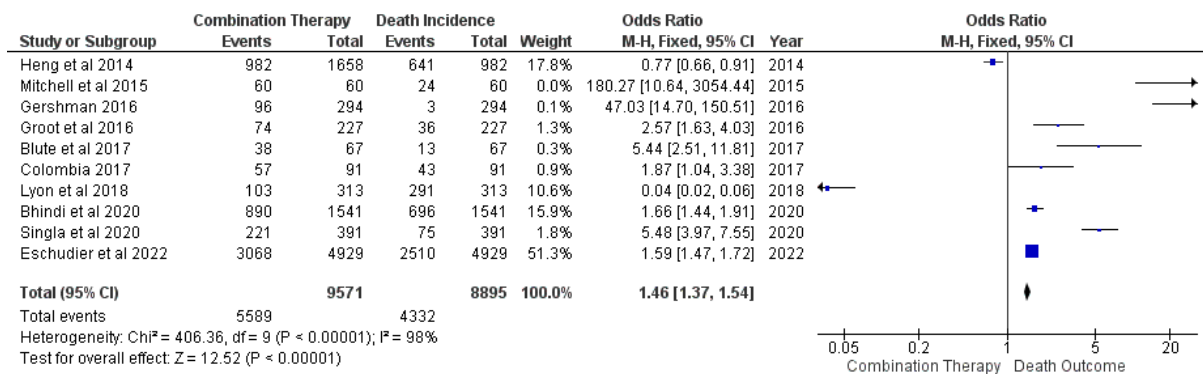


Figure 3: Forest plot mortality incidence in multiple modalities therapy for metastatic renal cell carcinoma.

Table 1: Article included.

S. no.	Retrospective cohort study	Total sample (N)	Combined therapy (N)	Progressive	Mortality	Survival rate	Recurrency
1	Heng et al, 2014 ⁴	1.658	982	Median PFS: 7.6 months	68.6%	Median OS: 20.6 months	not reported
2	Mitchell et al, 2015 ⁵	60	36	83% non-progressive at diagnosis	41% (5 years)	59% (5 years)	7% recurrence-free (5 years)
3	Gershman et al, 2016 ⁶	294	198	88% progressive within 1 year	1% (30 days)	Not Reported	not reported
4	Groot et al, 2016 ⁷	227	153	not reported	91,2%	Median OS (CN + Sunitinib): 17.9 months	not reported
5	Blute et al, 2017 ⁸	67	38	not reported	73%	Median OS: 16.7 months	not reported
6	Colomba et al, 2017 ⁹	91	57	Median PFS (Sunitinib): 6.1 months	58 deaths	Median OS: 20.8 months	not reported
7	Lyon et al, 2018 ¹⁰	313	103	not reported	Not Reported	OS without CN: 8-9 months	not reported
8	Bhindi et al, 2020 ¹¹	1.541	890	not reported	78%	46 months (deferred CN)	not reported
9	Singla et al, 2020 ¹²	391	221	not reported	Not Reported	CN + IO: Median OS not reached	not reported
10	Eschudier et al, 2022 ¹³	4.929	2.134	not reported	50.9%	Median OS: 20 months	not reported

The results of the risk of bias assessment of the included studies are presented in Figure 2. The risk of bias arising from the randomization process (D1), the risk of bias due to deviation from the intended intervention (D2), the risk of bias due to missing outcome data (D3), the risk of bias in outcome measurement (D4), the risk of bias in the selection of reported outcomes (D5), and the overall domain in 10 studies were categorized as low risk, so the bias scoring with the RoB 2 tool in these studies was low

risk, indicating that the quality of the research methods of all studies was good with a low risk of bias.

Based on the selected articles, a critical review was conducted on 10 studies with a retrospective study design covering various populations from several centers in various countries. The number of samples listed in the overall study was 9571 samples and the number of deaths in this systematic review was 8895 samples. The characteristics of the sample are listed in Table 1.

The combination of multiple modality therapies used were cytoreductive nephrectomy with everolimus sunitinib, sorafenib, axitinib, bevacizumab, temsirolimus, and pazopanib. In the study sample each intervention given was followed by placebo.

Meta-analysis was conducted to show the comparison mortality incidence in multiple modalities therapy for metastatic renal cell carcinoma. Forest plot in figure 3 shows that there is a significant relationship between the administration of multiple modalities therapy to metastatic renal cell carcinoma patients with an odds ratio (OR) of 1.46 (95% CI: 1.37 to 1.54; I²=98%, p value=<0.0001).

DISCUSSION

This systematic review includes 10 retrospective studies evaluating the effectiveness of combination therapies in patients with metastatic renal cell carcinoma (mRCC). These studies highlight various strategies, including the combination of cytoreductive nephrectomy (CN) with targeted therapies (such as sunitinib, sorafenib, pazopanib, and everolimus), radiotherapy, immunotherapy, and other combination therapies. The emphasis is placed on comparing the effectiveness of these approaches in improving overall survival (OS), preventing progression, and reducing recurrence rates.

A study by Bhindi et al, reported that the combination of sunitinib followed by deferred CN resulted in a median OS of 46 months, which was significantly higher than the outcomes of direct CN or sunitinib monotherapy. This approach suggests that administering systemic therapy first can help identify patients who respond well to treatment, making them more likely to benefit from surgery. In contrast, the direct CN approach followed by sunitinib had a median OS of 19 months. This indicates that direct CN may be less effective in patients with high disease risk or poor systemic response.¹¹

Similar findings were reported by Heng et al, who found that the combination of CN and targeted therapy resulted in a median OS of 20.6 months for patients with mRCC. This study emphasizes the importance of systemic therapy as postoperative support to extend patient survival.¹⁴ Additionally, Groot et al, noted that the combination of CN and sunitinib resulted in a median OS of 17.9 months, which is comparable to other approaches involving targeted therapy. On the other hand, Escudier et al, evaluated the effectiveness of combining CN with radiotherapy. The study found that the median OS for patients receiving this combination was 20 months. Although radiotherapy can offer palliative benefits, data on recurrence and progression rates in this group were inconsistently reported, making it difficult to compare its effectiveness with targeted therapies like sunitinib or immunotherapy.¹³

Immunotherapy based on checkpoint inhibitors (ICPIs) is emerging as a potentially superior treatment option in

several studies. Singla et al. (2020) reported that the combination of CN with ICPI resulted in a median OS that had not been reached at the time of analysis. This suggests that immunotherapy can provide significant long-term benefits, especially for patients who can tolerate the therapy. However, it is important to note that immunotherapy may have immune-related side effects that require careful management.¹²

In terms of safety, Bhindi et al, reported a survival rate of 78% at 46 months for patients undergoing the deferred CN approach. Nevertheless, recurrence remains a significant challenge.¹¹ For example, Mitchell et al, reported that only 7% of patients were recurrence-free after five years, despite undergoing surgical metastasectomy. This data suggests that while combination therapy can extend survival, the risk of recurrence remains high in most mRCC patients.⁵

The combination approach involving CN and sunitinib appears to offer significant benefits compared to other therapies, particularly in the context of deferred CN. This strategy allows for better patient selection based on their response to initial systemic therapy. Thus, patients undergoing CN are more likely to achieve long-term benefits. However, it is important to note that this approach may not be suitable for all patients, especially those who experience rapid progression before systemic therapy can demonstrate effectiveness.

Meanwhile, immunotherapy based on ICPIs is showing promising results, particularly in combination with CN. The potential of immunotherapy to generate longer OS compared to conventional targeted therapies like sunitinib is an important area of research. However, the high cost and serious immune-related side effects may be barriers to its widespread implementation. The combination of CN with radiotherapy, while offering palliative benefits, seems less effective compared to approaches based on systemic therapies. Radiotherapy may be more appropriate for patients with specific clinical conditions where systemic therapy cannot be given.

Overall, the combination of CN with sunitinib, especially in the deferred CN strategy, appears to be the most effective approach for prolonging survival in patients with mRCC. However, immunotherapy based on ICPIs shows potential to replace targeted therapies as the gold standard in the future, particularly for patients with high-risk disease. Further studies are needed to evaluate the long-term effectiveness and safety profiles of these combination approaches, as well as to identify patient subgroups that would benefit most from each strategy.

CONCLUSION

The treatment options for metastatic renal cell carcinoma (mRCC) currently include systemic approaches such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs). While these therapies can be

administered in sequence, recent developments have seen the introduction of combination therapies aimed at enhancing patient outcomes. These combined treatments work synergistically by targeting multiple pathways and mechanisms involved in tumor progression. Oncologists often encounter the difficult task of choosing among different approved treatment options based mainly on subgroup analysis and expert opinion. This systematic review highlights the evolving landscape of combination therapies for metastatic renal cell carcinoma (mRCC).

Among the evaluated approaches, the combination of cytoreductive nephrectomy (CN) with systemic therapies. This strategy enables better identification of candidates likely to benefit from surgery following systemic therapy response. Immunotherapy based on immune checkpoint inhibitors (ICPIs) emerges as a promising alternative, offering potentially longer OS compared to traditional targeted therapies, albeit with challenges such as high costs and immune-related side effects. These findings underscore the importance of individualized treatment planning, as not all patients may tolerate or respond similarly to specific therapeutic combinations. Future research should focus on optimizing patient selection, addressing recurrence rates, and further exploring the potential of ICPIs to establish them as a gold-standard therapy for mRCC.

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