Neoadjuvant systemic therapy in managing locally advanced renal cancer before surgery: A systematic review and meta-analysis

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ABSTRACT

Introduction: We aimed to estimate the effectiveness and safety of neoadjuvant systemic therapy in locally advanced renal tumor patients who undergo a nephrectomy in terms of survival, tumor response, and surgical feasibility.
Methods: We included clinical trials, quasi-experimental studies, and cohort studies providing data on the use of neoadjuvant systemic therapy in managing locally advanced renal cancer before surgery in adult patients. The primary outcomes were cancer-specific survival (CSS), overall survival (OS), progression-free survival (PFS), and disease-free survival (DFS). We performed a meta-analysis of proportions in R and assessed the risk of bias with the MINORS tool.
Results: Nine studies were included for qualitative synthesis and seven for meta-analysis. All non-randomized studies assessed had a low risk of bias against the stated objective by clearly stating their purpose. Likewise, most studies had a low risk of bias in the consecutive inclusion of patients, contemporary groups, and equivalence. Change in tumor size ranged from -50% to +7.9%. Partial response was achieved in 26% (95% confidence interval 15–42).
Conclusions: Neoadjuvant therapy in locally advanced renal tumors ≥T3 or N1 has shown positive results regarding clinical tumor regression in about one-third of the patients. It is feasible and safe in this high-risk population.

INTRODUCTION

Renal cell carcinoma (RCC) is the most common solid lesion within the kidney, accounting for approximately 90% of all kidney malignancies (1), and is among the ten most common cancers worldwide (2). Kidney cancer accounts for ~2% of all cancer diagnoses and deaths worldwide, with the incidence higher in developed countries than in developing countries (2,3).
Surgery still represents the cornerstone of treatment with curative intent for patients with localized or locally advanced disease. Nonetheless, some patients will experience disease relapse. According to this, the poor prognosis of these individuals has led to the development of studies assessing adjuvant and neoadjuvant therapies to surgery alone, aiming to reduce the risk of local and distant disease recurrence (4).

Neoadjuvant therapies for RCC have been implemented to reduce the metastatic burden before surgical debulking, make complex surgical resections easier, and select patients who may benefit from surgical debulking, which responds to systemic therapy (4,5). In this sense, Tyrosine kinase inhibitors (TKIs), targeting the VEGF pathway, revolutionized the treatment of metastatic RCC by improving progression-free and overall survival. In recent years, combination strategies of dual immune checkpoint inhibitors (ICI) have also shown benefits in the metastatic RCC setting (6).

In the setting of locally advanced disease, preoperative systemic therapy increases the likelihood of success in surgical resection, offering tumor cytoreduction, converting an otherwise unresectable mass to an attainable resection, particularly in high-risk tumor invading or extensively abutting adjacent organs or great vessels necessitating potential organ resection, vascular reconstruction or in the setting of imperative indication for nephron-sparing surgery (4,7,8).

Pro-angiogenic and/or pro-immunogenic factors from the in-situ tumors may enhance the effects of TKI or ICI agents (6), representing the central rationale for neoadjuvant immunotherapy (4). Despite that, in the case of locally advanced unresectable RCC, systemic therapy is experimental, and neoadjuvant therapy is currently under investigation (1,6), leading that no international guidelines have approved neoadjuvant medical therapies in RCC (4). This study aimed to estimate the effectiveness and safety of neoadjuvant systemic therapy in locally advanced renal tumor patients who undergo a nephrectomy in terms of survival, tumor response, and surgical feasibility.

METHODS

This review was performed according to the recommendations of the Cochrane Collaboration and following the PRISMA Statement.

Eligibility criteria

We included clinical trials, quasi-experimental studies, and cohort studies providing data on the use of neoadjuvant systemic therapy in managing locally advanced renal cancer before surgery in adult patients.

Studies that fulfilled the following criteria were included for the evaluation: age ≥ 18 years, preoperative cross-sectional imaging (CT or MRI) to delineate renal mass and surrounding structures, locally advanced renal tumor ≥T3 or N1, non-metastatic disease, any Fuhrman, any histology, ECOG 0-2 and use of neoadjuvant systemic therapy before renal surgery with TKI, ICI or a combination of the two. We excluded studies that did not meet the criteria above.

The primary outcomes were cancer-specific survival (CSS), overall survival (OS), progression-free survival (PFS), and disease-free survival (DFS). However, we could not find any study describing these outcomes.

Secondary outcomes were tumor response by RECIST criteria v1.0 or higher, surgical feasibility, tumor size after neoadjuvant systemic therapy, downstaging of tumor after neoadjuvant systemic therapy, renal function by serum creatinine (Scr) or glomerular filtration rate (GFR), toxicity related to neoadjuvant systemic therapy and surgical complications by Clavien-Dindo classification.

Information sources

We searched MEDLINE (OVID), EMBASE, LILACS, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to nowadays (Appendix1). To ensure literature saturation, we scanned references from relevant articles identified through the search, conferences, thesis databases, Open Grey, Google Scholar, and clinicaltrials.gov. There were no setting or language restrictions.

Data collection

Two investigators reviewed each reference by title and abstract, scanned the full text of relevant studies, applied pre-specified inclusion and exclusion criteria, and extracted the data. Disagreements were resolved by consensus to dissolve conflict.

Using a standardized form, we extracted the following information from each article: study design, authors' names, title, number of patients included and its demographic characteristics, type of neoadjuvant intervention, time to surgery and follow-up, tumor features such as size at baseline and histopathology and outcomes measures. If more than one publication was found for the same trial, the most recent, complete, and updated version was included in the final analysis.

Risk of bias

The risk of bias for each study was assessed using the Cochrane Risk of Bias for Clinical trials and MINORS for non-randomized studies.

Data analysis/Synthesis of results

We performed a meta-analysis of proportions with the metaprop command and the inverse method (logit transformed proportions) in R. This statistical approach and subgroup analysis were performed following the expected high clinical heterogeneity and a large proportion of variation between studies. We assessed heterogeneity through the I2 test and values of <50% and >50%, representing low and high levels of heterogeneity, respectively. The results were reported as a forest plots diagram with a 95% confidence interval (95% CI).

Publication bias

We could not perform a publication bias analysis due to the limited number of studies.

RESULTS

Selection of studies

Our research identified 1438 articles, of which nine were included for qualitative synthesis and seven for meta-analysis.

Characteristics of the included studies

Studies included in the meta-analysis were published between 2009 and 2022. Two studies were excluded from the meta-analysis due to the small sample size (less than five patients). Four were prospective, and the other five were retrospective (Figure 1) (9–17).

Two hundred sixty-three participants received intervention with the administration of neoadjuvant therapy. Eight studies included TKI (Pazopanib, Axitinib, Sorafenib, Sunitinib) and one checkpoint inhibitor Nivolumab.

Seven studies reported the age and genre of patients. The median age was 61 years, and 72% were men. Only three studies reported a median follow-up that ranged from 4 to 22.8 months. Likewise, another three studies reported time from the initiation of treatment to surgery that ranged from 9 to 84 days, being open surgery the most frequent approach (52% of cases), followed by laparoscopic (26%) and robotic surgery (22%).

Six studies outline tumor size at baseline ranging between 4.2 cm and 20 cm. Histopathology was also reported in six studies, and all of them included clear cell RCC. The characteristics of all included studies are shown in Table 1.

Risk of bias assessment

All non-randomized studies assessed were at low risk of bias against the stated objective by clearly stating their purpose. Likewise, the majority presented a low risk of bias in the consecutive inclusion of patients, contemporary groups, and equivalence between them. In just over 50% of the studies, the risk of bias was unclear regarding the outcomes and the assessment of bias against these outcomes, as was the time of follow-up and comparison with an appropriate group. On the other hand, compared to the prospective collection of information and the calculation of the sample size, we report a high risk of bias when finding that a large part of the studies did not specify those data. The only randomized clinical study presented an unclear risk

of bias in all aspects to be evaluated due to the little information regarding the methodology (Figure 2).

Response to neoadjuvant treatment

Change in tumor size ranged from -50% to +7.9%. Partial response was achieved in 26% (95% CI 15%-42%) (Figure 3), and 74% remained with stable disease (95% CI 58%-85%) (Figure 4). None of the patients had a complete response, but neither had disease progression. Downstaging was accomplished in 33% (95% CI 14%-60%) (Figure 5).

Other outcomes

Most studies lacked information regarding CSS, OS, PFS, DFS, adverse events associated with pharmacological therapy, and surgical complications. Therefore, we were not able to compare them.

DISCUSSION

In recent years, several agents have been used in neoadjuvant and adjuvant settings in patients with primary renal mass in situ. This study reviewed the use of TKI and checkpoint inhibitors in locally advanced renal tumors without evidence of metastatic disease.

The outcomes of this research are concordance with the epidemiological characteristics of renal tumors, with all patients with biopsy-proven ccRCC presenting most frequently in men with a median age surrounding 60 years, thus achieving the ideal population to test these drugs.

Most of the patients remained stable disease. Only a quarter of the sample achieved a partial response, none with a complete but neither with progressive disease. Even though a non-despicable proportion of patients responded to therapy, this should be interpreted cautiously as most results were heterogeneous, such as tumor size at baseline, median follow-up, and time from the initiation of treatment to surgery. Additionally, although there was variability in tumor size, and the disease remained stable in most patients, no study had surgical feasibility as an outcome.

Likewise, no study used a combination of drugs based only on monotherapy. It is also important to emphasize that only one study used checkpoint inhibitors, and the rest included TKI. Therefore, a reasonable response rate could also be explained by avoiding treating patients with non-RCC tumors who might have minimal to no response with TKI.

In this study, we obtained data regarding CSS, OS, PFS, and DFS using neoadjuvant therapy. However, information was lacking, and we could not report these results. In the adjuvant setting, particularly with TKI, some evidence comes from studies such as the ASSURE trial (adjuvant sunitinib or sorafenib vs. placebo) in pT3, pT4, or N+ disease ccRCC. In this trial, no differences in DFS or overall survival (OS) were seen (18), however in the S-TRAC study comparing sunitinib vs. placebo in patients with ≥pT3 with grade 2–4, pT4 or N+ disease RCC, the median duration of DFS was 6.8 years in the sunitinib group and 5.6 years in the placebo group (HR 0.76; 95% CI, 0.59 to 0.98). OS data were not mature at the time of data cutoff and

were not mature after an additional ten months of follow-up. However, no detrimental effect on OS was observed for sunitinib treatment (19,20).

On the other hand, in the PROTECT study comparing pazopanib vs. placebo in patients with pT2 (high grade) or ≥ pT3, including N1, clear cell RCC, the results of the primary DFS analysis of pazopanib showed no benefit over placebo in the adjuvant setting (21). However, in the ATLAS trial comparing axitinib vs. placebo as an adjuvant treatment in patients with staged ≥pT2 and/or N+, although there was no significant difference in DFS (HR 0.87, 95% CI 0.660–1.147), in the highest-risk subpopulation (pT3, FG ≥ 3 or pT4 and/or N+, any T, any FG) a DFS benefit was observed (HR 0.641, 95% CI 0.468– 0.879) (22).

As stated before, we could not calculate survival measures with the information published to the current date. Nonetheless, as our study, adjuvant therapy has the most robust evidence from TKI.

Finally, other outcomes that could impact the long-term follow-up and the administration of this therapy, such as the change in renal function, the toxicity related to its use, and the possible derived surgical complications, were not reported in any study. Therefore, decision-making regarding these variables continues to be studied.

Currently there are several ongoing trials to delineate neoadjuvant therapy efficacy and safety profile, including the SPARC-1 (IL-1beta blockade canakinumab plus PD-1 blockade spartalizumab) in patients with stage T1b-T4 Nany M0 RCC (23), The NEOAVAX study (neoadjuvant axitinib + avelumab followed by complete surgical resection) in patients with high-risk non-metastatic ccRCC (cT1b-cT2a grade (G) 4, cT2b G3, cT3a G3-4, cT3b-cT4 any G cN0M0, or cT any cN1M0) (24), a phase II study (NCT03680521) of sitravatinib in combination with nivolumab in patients undergoing nephrectomy for locally-advanced clear cell renal cell carcinoma (accRCC) (25) and a phase II study (NCT04022343) of neoadjuvant cabozantinib in patients with locally advanced non-metastatic ccRCC with clinical stage ≥ T3Nx or TanyN+ or deemed unresectable by the surgeon (26). These studies mentioned above showed a non-metastatic population.

A study regarding the use of perioperative Durvalumab (D) +/- Tremelimumab (T) in locally advanced RCC was conducted (NCT02762006) in patients with high-risk localized RCC (clinical stage T2b-4 and/or N1, M0 disease), clinical trial information is reported completed no published paper, however, has been seen yet. Conclusions outline that perioperative durvalumab in locally advanced RCC appears safe, and the addition of tremelimumab is associated with higher toxicity rates (27).

Other ongoing trials include not only locally advanced but metastatic RCC; these are the PIVOT-09 (a phase III randomized open-label comparing Bempegaldesleukin a first-in-class IL-2 receptor pathway agonist plus nivolumab vs. investigator's choice of TKI; sunitinib or cabozantinib in patients with previously untreated advanced or metastatic RCC with a clear-cell component)(28), the PROSPER (a phase III randomized study comparing perioperative nivolumab versus observation in patients with clinical stage ≥T2 or any T N+. Select

oligometastatic disease is permitted ≤3 Metastases; no brain, bone or liver) (29) and the Substudy 03A (NCT04626479- a study of immune and targeted combination therapies in patients with a histologically confirmed diagnosis of locally advanced/metastatic ccRCC including five arms of treatment) (30).

Limitations and strengths

One of the main limitations of this study is the small number of studies included, the lack of safety measurement of the interventions performed and the lack of gender discrimination on the part of the participants, which may lead to further analysis.

Among the strengths found is that this is the first study that seeks to contemplate neoadjuvant therapy for the multi-modal or non-surgical treatment of renal cell carcinoma.

CONCLUSIONS

Neoadjuvant target therapy in patients with surgically complex locally advanced renal tumor ≥T3 or N1 with the non-metastatic disease has shown positive results regarding clinical tumor regression in about one-third of the patients in this reported paper. Despite using different agents with multiple and heterogenous doses, previous studies have shown it is feasible and safe in this high-risk population.

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FIGURES AND TABLES

Figure 1. Flowchart of included studies.

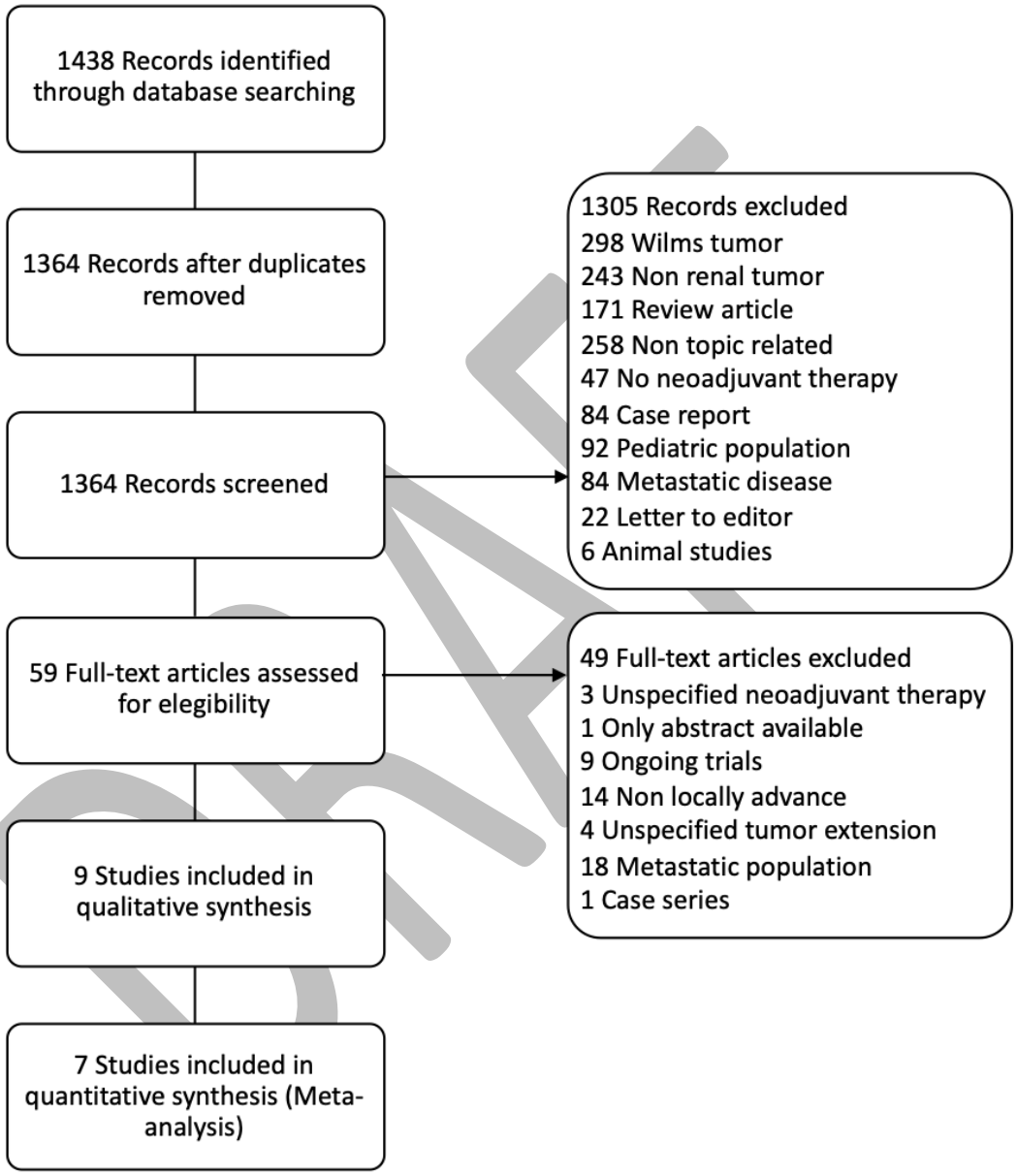

Figure 2A. Risk of bias assessment with studies. CI: confidence interval.

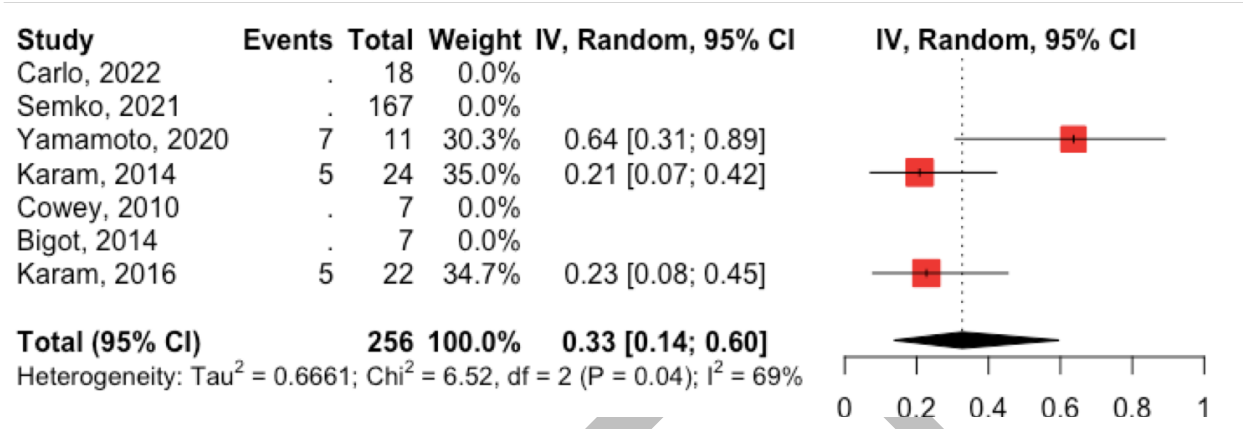

Figure 2B. Risk of bias assessment across studies.

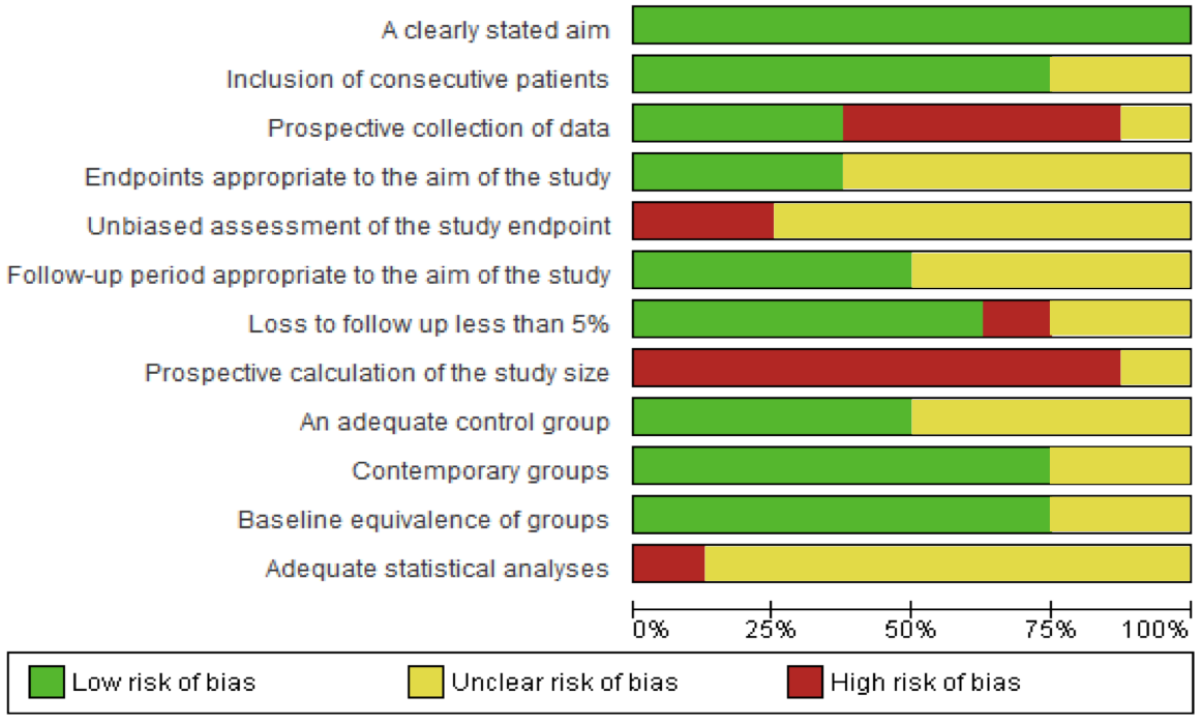

Figure 3. Partial response.

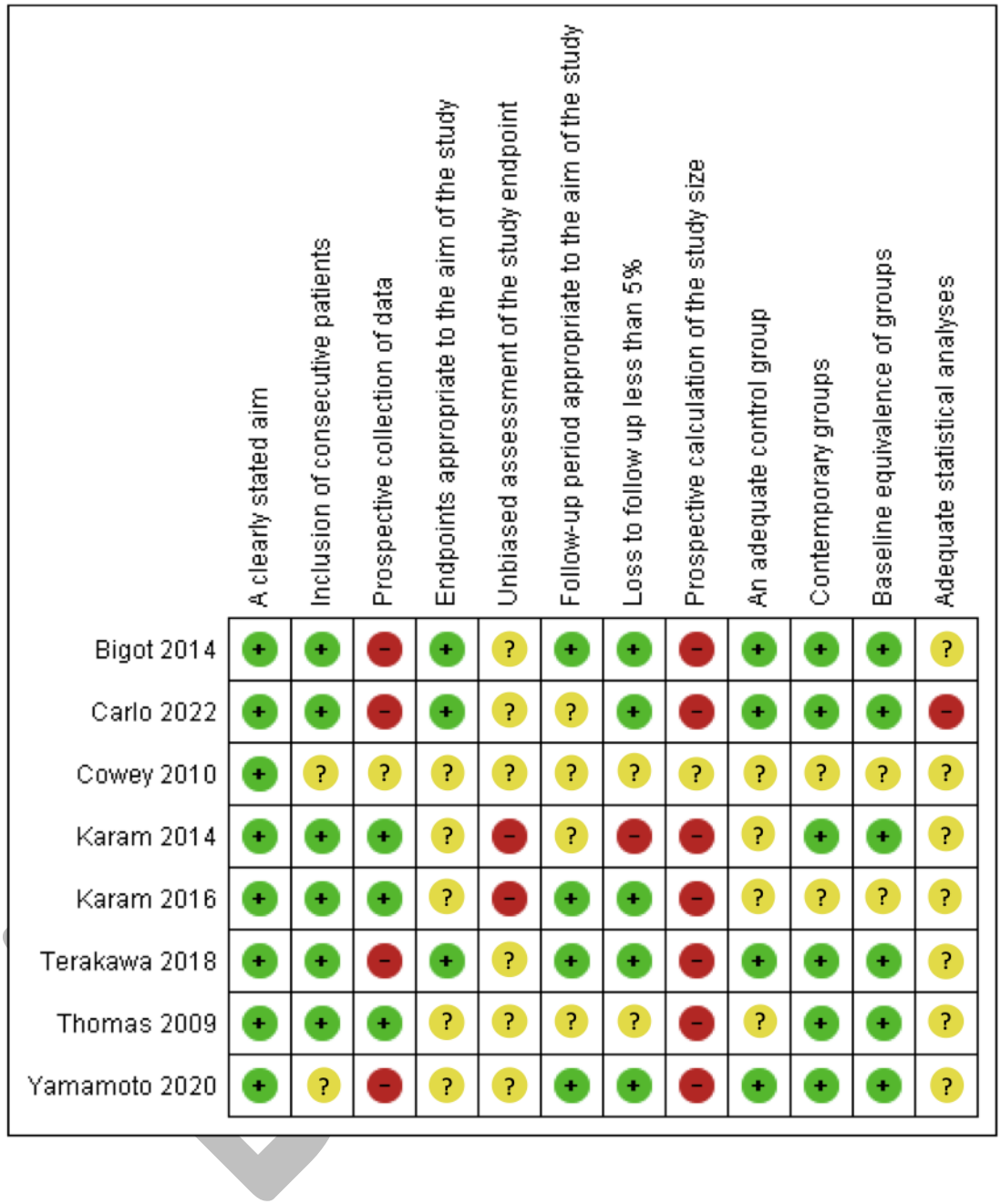

Figure 4. Stable disease. CI: confidence interval.

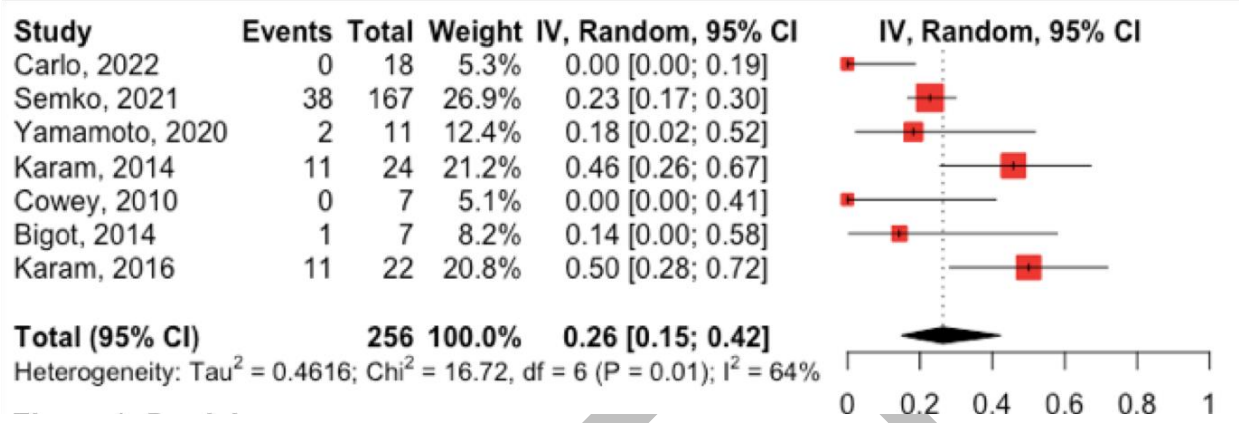

Figure 5. Downstaging. CI: confidence interval.

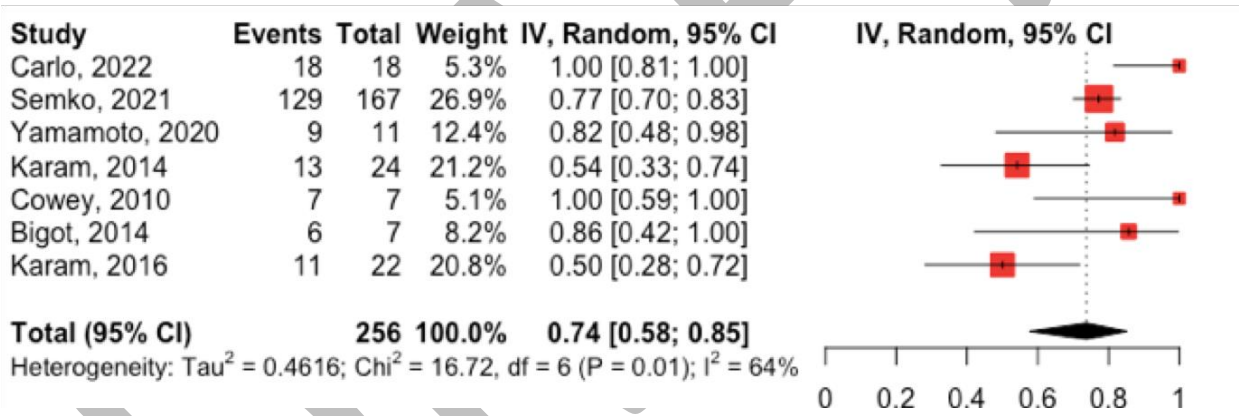

Table 1. Characteristics of the included studies

										Surgery		
Study, year	**n**	**Age, media (yrs)**	**Male**	**Female**	**Tumor size baseline, cm (range)**	**Histology**	**Neo-adjuvant**	**Time to Sx, days (range)**	**Followup, median months (range)**	**Open**	**Lap**	**Robotic**
Carlo, 2022	18	60	61%	39%	8.8 (6.4–14.2)	Clear-cell RCC	Nivolumab	10.5 (9–13)	22.7 (4–29.9)	33%	0%	67%
Semko, 2021	167	N/A	N/A	N/A	6.13±1.95 (5.65-6.57)	N/A	Pazopanib	N/A	N/A	N/A	N/A	N/A
Yamamoto, 2020	11	62	55%	45%	N/A	Clear-cell RCC	Axitinib	N/A	N/A	N/A	N/A	N/A
Terakawa, 2018	1	79	100%		N/A	N/A	Pazopanib	N/A	N/A	N/A	N/A	N/A
Karam, 2014	24	60	79%	22%	10.0 (4.2–16.6)	Clear-cell RCC	Axitinib	77 (49–84)	17	79.20%	21.80%	0%
Cowey, 2010	7	54	57%	43%	8.6 (6.1–12)	Clear-cell RCC	Sorafenib	36 (10–59)	N/A	43%	57%	0%
Bigot, 2014	2	N/A	N/A	N/A	N/A	Clear-cell RCC	Sorafenib	N/A	17 (3–35)	N/A	N/A	N/A
Thomas, 2009	4	73.5	75%	25%	9.4 (6.4–20)	N/A	Sunitinib	N/A	14.5 (13–16)	N/A	N/A	N/A
Karam, 2016	22	61	77%	23%	9.7 (4.2–16.6)	Clear-cell RCC	Axitinib	N/A	N/A	N/A	N/A	N/A

N/A: not available; RCC: renal cell carcinoma.