Neoadjuvant systemic therapy in managing locally advanced renal cancer before surgery

A systematic review and meta-analysis

Ximena Guzman Robledo, Herney Andrés García-Perdomo

Division of Urology/Uro-oncology, Department of Surgery, School of Medicine, Universidad del Valle, Cali, Colombia

Cite as: Guzman Robledo X, García-Perdomo HA. Neoadjuvant systemic therapy in managing locally advanced renal cancer before surgery: A systematic review and meta-analysis. *Can Urol Assoc J* 2025;19(5):E199-204. http://dx.doi.org/10.5489/cuaj.8901

Published online January 14, 2025

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) accounts for approximately 90% of all kidney malignancies,[1] and is among the 10 most common cancers worldwide.[2] Surgery still represents the cornerstone of treatment for patients with localized or locally advanced disease. Nonetheless, some patients will experience disease relapse and the poor prognosis for these individuals has led to the investigation of adjuvant and neoadjuvant therapies vs. surgery alone to reduce the risk of local and distant disease recurrence.[3]

Neoadjuvant therapies for RCC have been used to reduce the metastatic burden before surgical debulking, to make complex surgical resections easier, and to assist in the selection of patients who may benefit from surgical debulking.[3,4] Tyrosine kinase inhibitors (TKIs), targeting the vascular endothelial growth factor (VEGF) pathway, revolutionized the treatment of metastatic RCC by improving progression-free (PFS) and overall survival (OS). In recent years, combination strategies of dual immune checkpoint inhibitors (ICI) have also shown benefits in the metastatic RCC setting.[5]

In locally advanced disease, preoperative systemic therapy increases the likelihood of success in surgical resection by providing tumor cytoreduction, converting an otherwise unresectable mass to an attainable resection. This is particularly useful in high-risk tumors that are invading or extensively abutting adjacent organs or great vessels, those necessitating

potential organ resection or vascular reconstruction, and in the setting of imperative indication for nephron-sparing surgery.[3,6,7]

Pro-angiogenic and/or pro-immunogenic factors from the in-situ tumors may enhance the effects of TKI or ICI agents,[5] representing the central rationale for neoadjuvant immunotherapy.[3] Despite that, in the case of locally advanced unresectable RCC, systemic therapy is experimental, and neoadjuvant therapy is still currently under investigation.[1,5] In fact, there are currently no international guidelines that recommend neoadjuvant therapy in RCC.[3]

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

Studies that fulfilled the following criteria were included in the evaluation: age ≥18 years, preoperative cross-sectional imaging (computed tomography or magnetic resonance imaging) to delineate renal mass and surrounding structures, locally advanced renal tumor ≥T3 or N1, non-metastatic disease, any Fuhrman, any histology, Eastern Cooperative Oncology Group 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 above criteria.

The primary outcomes were cancer-specific survival (CSS), OS, PFS, and disease-free survival (DFS).

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 or glomerular filtration rate, 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 January 2024. 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 prespecified inclusion and exclusion criteria, and extracted the data. Disagreements were resolved by consensus.

Using a standardized form, we extracted the following information from each article: study design, authors' names, title, number of patients included and their demographic characteristics, type of neoadjuvant intervention, time to surgery and followup, 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.

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 I^2 test, with 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 (CI).

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

RESULTS

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 from 2009–2022. Two studies were excluded from the meta-analysis due to the small sample size (<5 patients). Four were prospective and the other five were retrospective (Figure 1).[8-16]

A total of 263 participants received intervention with the administration of neoadjuvant therapy. Eight studies included TKI (pazopanib, axitinib, sorafenib, sunitinib) and one ICI (nivolumab).

Seven studies reported the age and gender of patients; the median age was 61 years, and 72% were men. Only three studies reported a median followup that ranged from 4–22.8 months. Likewise, another three studies reported time from the initiation of treatment to surgery, which ranged from 9–84 days. Open surgery was the most frequent approach (52% of cases), followed by laparoscopic (26%) and robotic surgery (22%).

Six studies outlined tumor size at baseline, ranging from 4.2–20 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 followup time and comparison with an appropriate group. In contrast, 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 included 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, nor did any have disease progression. Downstaging occurred in 33% (95% CI 14–60%) (Figure 5).

Other outcomes

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

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 ICI in locally advanced renal tumors without evidence of metastatic disease.

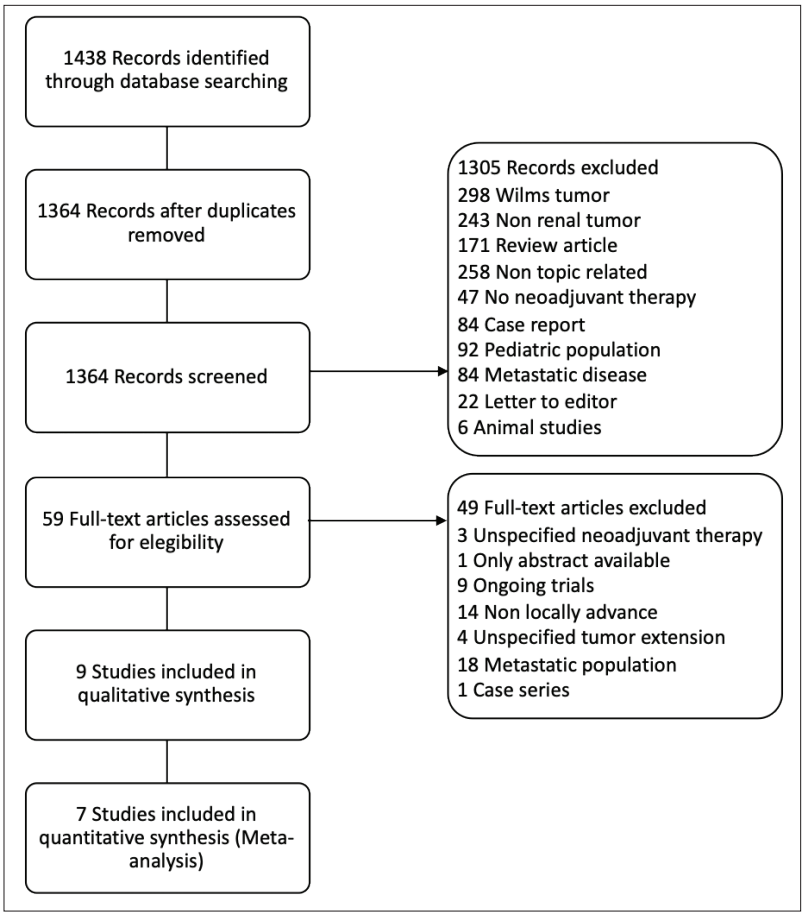

Figure 1. Flowchart of included studies.

All of the patients included in our review had biopsy-proven clear-cell RCC presenting most frequently in men with a median age of approximately 60 years, thus reflecting the general epidemiologic characteristics of renal tumors.

The disease remained stable in most of the patients. Only a quarter of the sample achieved a partial response, with none achieving a complete response, nor any with disease progression. Although a proportion of patients responded to therapy, this should be interpreted cautiously based on the high heterogeneity of the studies. Additionally, although there was some 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 (TKI or ICI monotherapy only). It is also important to emphasize that only one study used ICI, with the rest including TKI. Therefore, a reasonable response rate could also be explained by avoiding treating patients

Table 1. Characteristics of the included studies

Study, year	n	Age, median (yrs)	Male	Female	Tumor size baseline, cm (range)	Histology	Neo-adjuvant	Time to surgery, days (range)	Followup, median months (range)	Surgery		
										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.

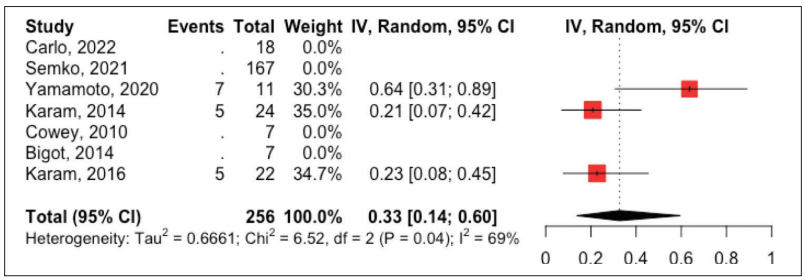

Figure 2A. Risk of bias assessment with studies. CI: confidence interval.

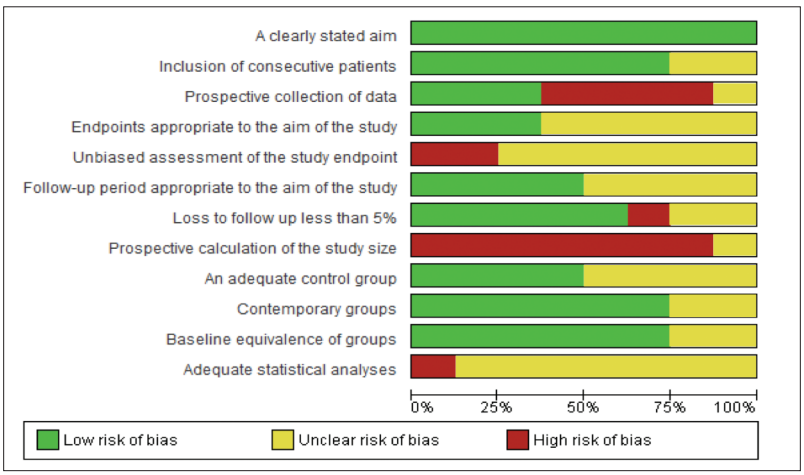

Figure 2B. Risk of bias assessment across studies.

with non-RCC tumors who might have minimal to no response with TKI.

In our analysis, data regarding CSS, OS, PFS, and DFS using neoadjuvant therapy was lacking, and we could not report on 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+ clear-cell RCC. In this trial, no differences in DFS or OS were seen;[17] however in the S-TRAC study comparing sunitinib vs. placebo in patients with ≥pT3 with grade 2–4, pT4, or N+ RCC, the median duration of DFS was 6.8 years in the sunitinib group and 5.6 years in the placebo group (hazard ratio [HR] 0.76, 95% CI 0.59–0.98). OS data were not mature at the time of data cutoff and were not mature after an additional 10 months of followup; however, no detrimental effect on OS was observed for sunitinib treatment.[18,19]

Alternatively, 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;[20] 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).[21]

Finally, other outcomes that could impact the long-term followup and the administration of neoadjuvant systemic therapy — change in renal function, the toxicity related to its use, and the possible derived surgical complications — were not reported in any study. Decision-making regarding these variables continues to be studied.

There are currently several ongoing trials to delineate neoadjuvant therapy efficacy and safety profile: the SPARC-1 (IL-1beta blockade, canakinumab, plus PD-1 blockade, spartalizumab) in patients with stage T1b-T4 Nany M0 RCC;[22] the NEOAVAX study (neoadjuvant axitinib + avelumab followed by complete surgical resection) in patients with high-risk non-metastatic clear-cell RCC (cT1b-cT2a grade [G]4, cT2b G3, cT3a G3-4, cT3b-cT4 any G cN0M0, or cT any cN1M0);[23] a phase 2 study of sitravatinib in combination with nivolumab in patients undergoing nephrectomy for locally advanced clear-cell renal RCC (NCT03680521);[24] and a phase 2 study of neoadjuvant cabozantinib in patients with locally advanced non-metastatic clear-cell RCC with clinical stage ≥T3Nx or TanyN+ or deemed unresectable by the surgeon (NCT04022343).[25]

A study regarding the use of perioperative durvalumab ± tremelimumab in locally advanced RCC was conducted (NCT02762006) in patients with high-risk localized RCC (clinical stage T2b-4 and/or N1 M0 disease). Conclusions outline that perioperative durvalumab in locally advanced RCC appears safe, and the addition of tremelimumab is associated with higher toxicity rates.[26]

Other ongoing trials include not only locally advanced but metastatic RCC; these are the PIVOT-09 (a phase 3, randomized, open-label study comparing bempegaldesleukin, a first-in-class interleukin [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);[27] PROSPER (a phase 3, randomized study comparing perioperative nivolumab vs. observation in patients with clinical stage ≥T2 or any T N+; select oligometastatic disease is permitted with ≤3 metastases [no brain, bone, or liver]);[28] and the Substudy 03A (NCT04626479; a study of immune and targeted combination therapies in patients with a histologically confirmed diagnosis of locally advanced/metastatic clear-cell RCC with five arms of treatment).[29]

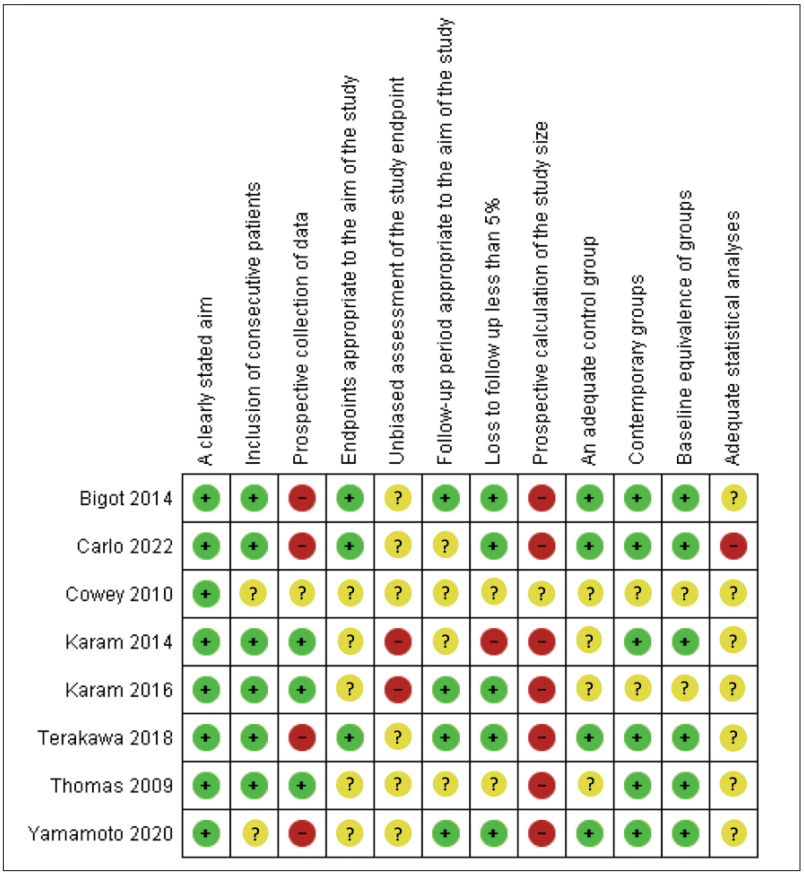

Figure 3. Partial response.

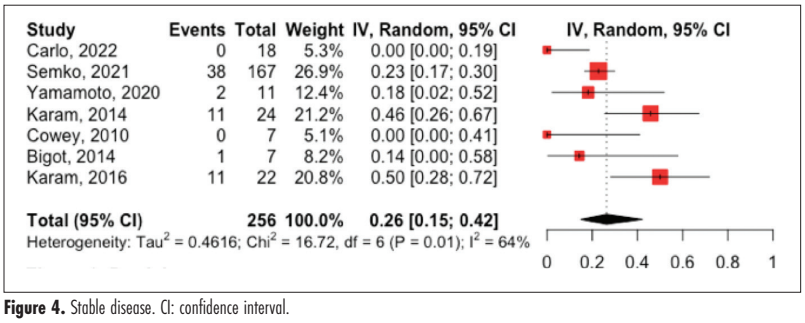

Figure 4. Stable disease. CI: confidence interval.

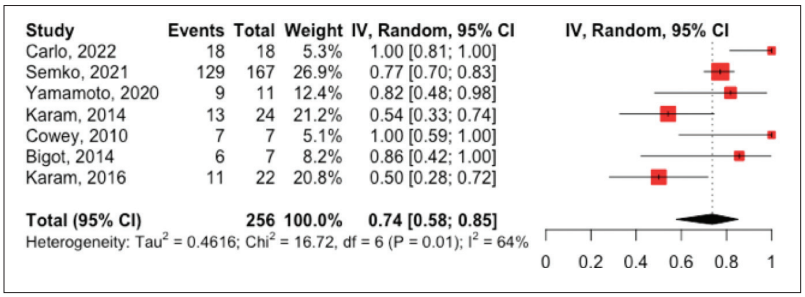

Figure 5. Downstaging. CI: confidence interval.

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.

Among the strengths is that this is the first study that seeks to contemplate neoadjuvant therapy for the multimodal or non-surgical treatment of RCC.

CONCLUSIONS

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

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer reviewed.

REFERENCES

1. Ljungberg B, Albiges L, Bedke J, et al. EAU guidelines on renal cell carcinoma. *Eur Urol* 2021.
2. Hsieh JJ, Purdue MP, Signoretti S, et al. Renal cell carcinoma. *Nat Rev Dis Primers* 2017;3:1-19. https://doi.org/10.1038/nrdp.2017.9
3. Martini A, Fallara G, Pellegrino F, et al. Neoadjuvant and adjuvant immunotherapy in renal cell carcinoma. *World J Urol* 2021;39:1369-76. https://doi.org/10.1007/s00345-020-03550-z
4. Ghali F, Patel SH, Derweesh IH. Current status of immunotherapy for localized and locally advanced renal cell carcinoma. *J Oncol* 2019;2019:7309205. https://doi.org/10.1155/2019/7309205
5. Gleeson JP, Motzer RJ, Lee CH. The current role for adjuvant and neoadjuvant therapy in renal cell cancer. *Curr Opin Urol* 2019;29:636-42. https://doi.org/10.1097/MOU.0000000000000666
6. Bindayi A, Hamilton ZA, McDonald ML, et al. Neoadjuvant therapy for localized and locally advanced renal cell carcinoma. *Urol Oncol* 2018;36:31-7. https://doi.org/10.1016/j.urolonc.2017.07.015
7. Borregales LD, Adibi M, Thomas AZ, et al. The role of neoadjuvant therapy in the management of locally advanced renal cell carcinoma. *Ther Adv Urol* 2016;8:130-41. https://doi.org/10.1177/1756287215612962
8. Carlo MI, Attalla K, Mazaheri Y, et al. Phase 2 study of neoadjuvant nivolumab in patients with locally advanced clear cell renal cell carcinoma undergoing nephrectomy. *Eur Urol* 2022;81:570-3. https://doi.org/10.1016/j.eururo.2022.01.043
9. Semko S, Pikul M, Stakhovsky E, et al. Oncological outcome of neoadjuvant target therapy in patients with localized RCC. *Eur Urol* 2021;79:S770. https://doi.org/10.1016/S0302-2838(21)00946-5
10. Yamamoto Y, Otori T, Inoue R, et al. Pharmacokinetics of neoadjuvant axitinib influenced the efficacy in patients with advanced renal cell carcinoma. *J Clin Pharmacol* 2020;60:256-63. https://doi.org/10.1002/jcph.1521
11. Terakawa T, Hussein AA, Bando Y, et al. Presurgical pazopanib for renal cell carcinoma with inferior vena caval thrombus: A single-institution study. *Anticancer Drugs* 2018;29:565-71. https://doi.org/10.1097/CAD.0000000000000627
12. Karam JA, Devine CE, Urbauer DL, et al. Phase 2 trial of neoadjuvant axitinib in patients with locally advanced non-metastatic clear cell renal cell carcinoma. *Eur Urol* 2014;66:874-80. https://doi.org/10.1016/j.eururo.2014.01.035
13. Cowey CL, Amin C, Pruthi RS, et al. Neoadjuvant clinical trial with sorafenib for patients with stage II or higher renal cell carcinoma. *J Clin Oncol* 2010;28:1502-7. https://doi.org/10.1200/JCO.2009.24.7759
14. Bigot P, Fardoun T, Bernhard JC, et al. Neoadjuvant targeted molecular therapies in patients undergoing nephrectomy and inferior vena cava thrombectomy: Is it useful? *World J Urol* 2014;32:109-14. https://doi.org/10.1007/s00345-013-1088-1
15. Thomas AA, Rini BI, Lane BR, et al. Response of the primary tumor to neoadjuvant sunitinib in patients with advanced renal cell carcinoma. *J Urol* 2009;181:518-23. https://doi.org/10.1016/j.juro.2008.10.001
16. Karam JA, Devine CE, Fellman BM, et al. Variability of inter-observer agreement on feasibility of partial nephrectomy before and after neoadjuvant axitinib for locally advanced renal cell carcinoma (RCC): Independent analysis from a phase 2 trial. *BJU Int* 2016;117:629-35. https://doi.org/10.1111/bju.13188
17. 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;3:1249-52. https://doi.org/10.1001/jamaoncol.2017.0076
18. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med* 2016;375:2246-54. https://doi.org/10.1056/NEJMoa1611406
19. 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;73:62-8. https://doi.org/10.1016/j.eururo.2017.09.008
20. Motzer RJ, Haas NB, Donskov F, et al. Randomized phase 3 trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. *J Clin Oncol* 2017;35:3916-23. https://doi.org/10.1200/JCO.2017.73.5324
21. Gross-Goupil M, Kwon TG, Eto M, et al. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: Results from the phase 3, randomized ATLAS trial. *Ann Oncol* 2018;29:2371-8. https://doi.org/10.1093/annonc/mdy454
22. Dallos M, Aggen DH, Ager C, et al. The SPARC-1 trial: A phase I study of neoadjuvant combination interleukin-1 beta and PD-1 blockade in localized clear cell renal cell carcinoma. *J Clin Oncol* 2021;39. https://doi.org/10.1200/JCO.2021.39.6_suppl.TPS373
23. Bex A, Van Thienen J V., Schrier M, et al. A phase 2, single-arm trial of neoadjuvant axitinib plus avelumab in patients with localized renal cell carcinoma who are at high risk of relapse after nephrectomy (NEOAVAX). *Future Oncol* 2019;15:2203-9. https://doi.org/10.2217/fon-2019-0111
24. Karam JA, Msaouel P, Matin SF, et al. A phase 2 study of sitravatinib (Sitra) in combination with nivolumab (Nivo) in patients (Pts) undergoing nephrectomy for locally-advanced clear cell renal cell carcinoma (accRCC). *J Clin Oncol* 2021;39:312. https://doi.org/10.1200/JCO.2021.39.6_suppl.312
25. Bilen MA, Liu Y, Nazha B, Brown JT, et al. Phase 2 study of neoadjuvant cabozantinib in patients with locally advanced non-metastatic clear cell renal cell carcinoma. *J Clin Oncol* 2022;40:340. https://doi.org/10.1200/JCO.2022.40.6_suppl.340
26. Ornstein MC, Zabell J, Wood LS, et al. A phase 1b trial of neoadjuvant/adjuvant durvalumab +/- tremelimumab in locally advanced renal cell carcinoma (RCC). *J Clin Oncol* 2020;38:5021. https://doi.org/10.1200/JCO.2020.38.15_suppl.5021
27. Tannir NM, Agarwal N, Pal SK, et al. PIVOT-09: A phase 3, randomized, open-label study of bempegaldesleukin (NKTR-214) plus nivolumab vs. sunitinib or cabozantinib (investigator's choice) in patients with previously untreated advanced renal cell carcinoma (RCC). *J Clin Oncol* 2020;38:TPS763. https://doi.org/10.1200/JCO.2020.38.6_suppl.TPS763
28. Allaf ME, Kim SE, Master VA, et al. PROSPER: Phase 3 randomized study comparing PERioperative nivolumab vs. observation in patients with renal cell carcinoma (RCC) undergoing nephrectomy (ECOG-ACRIN EA8143). *J Clin Oncol* 2021;39:TPS4596. https://doi.org/10.1200/JCO.2021.39.15_suppl.TPS4596
29. Plimack ER, Hammers HJ, Choueiri TK, et al. A phase 1b/2 umbrella study of investigational immune and targeted combination therapies as first-line therapy for patients with advanced renal cell carcinoma (RCC). *J Clin Oncol* 2021;39:TPS4594. https://doi.org/10.1200/JCO.2021.39.15_suppl.TPS4594

CORRESPONDENCE: Dr. Herney Andrés García-Perdomo, Division of Urology/Uro-oncology, Department of Surgery, School of Medicine, Universidad del Valle, Cali, Colombia; herney.garcia@correounivalle.edu.co