Original Article

Efficacy of presurgical therapy with tislelizumab and axitinib to downsize local lesions in locally advanced and metastatic renal cell carcinoma: a single-institution experience with long-term follow-up

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Background: Systemic therapy with or without surgery is recommended in advanced renal cell carcinoma (RCC). The potential benefits of tislelizumab and axitinib as presurgical therapy in advanced RCC remain unclear. This study aimed to preliminarily assess the efficacy of short-term presurgical tislelizumab and axitinib in downsizing local lesions and its long-term oncological outcome with or without nephrectomy in advanced RCC.

Methods: Data were prospectively collected from patients with advanced RCC who received tislelizumab and axitinib and were scheduled for deferred nephrectomy. Efficacy was evaluated by the remission of all tumor lesions using computed tomography (CT), and oncological outcomes were also reported.

Results: Between March 2021 and May 2022, 11 patients were recruited, 10 of whom presented with metastases. Biopsy results confirmed clear-cell RCC in eight patients, and RCC not otherwise specified in three patients. Following a median of three cycles of presurgical treatment, the overall response rate (ORR) and disease control rate (DCR) were 18.2% (2/11) and 100% (11/11), respectively. The median percentage change in the long-axis diameter was −24.0% (range, −8.2% to −39.7%) for all lesions and −12.2% (range, −7.1% to −39.7%) for local lesions. Open nephrectomy was successfully performed in eight patients with high anatomical complexity. After a median follow-up of 23 months (range, 14–34 months), six patients (6/11, 54.5%) experienced disease progression and died, including three patients without nephrectomy (3/3, 100%) and another three with nephrectomy (3/8, 37.5%). Progression-free survival (PFS) and overall survival (OS) were significantly longer in patients who underwent nephrectomy (P=0.002 and P=0.004).

Conclusions: Short-term presurgical tislelizumab and axitinib can downsize local lesions and facilitate nephrectomy in advanced RCC with high anatomical complexity, potentially improving long-term oncological outcomes when followed by cytoreductive surgery.

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Introduction

According to global cancer statistics from 2022, kidney cancers represent 2–3% of all adult cancers, with over 434,840 new cases and nearly 155,953 deaths reported (1). The most common histological subtype is clear-cell renal cell carcinoma (ccRCC). While a significant proportion of early-stage renal cell carcinoma (RCC) patients can be cured through upfront partial or radical nephrectomy, perioperative systemic therapy with or without surgical resection, within the framework of multidisciplinary evaluation, appears more appropriate for advanced RCC, including locally advanced and metastatic RCC, which account for 20–30% of newly diagnosed cases (2,3). In the era of targeted therapy, owing to the lack of high-level evidence supporting improved oncological outcomes, presurgical therapy based on tyrosine kinase inhibitors (TKIs) is typically recommended for locally advanced cases with high local anatomical complexity, such as those involving vena cava thrombus (VCT), which pose challenges to surgical safety (4). Presurgical therapy with TKIs can reduce the size of the primary tumor and enhance the feasibility and safety of subsequent nephrectomy, as demonstrated by several prospective and retrospective studies (5,6). This treatment approach is also appropriate for intermediate- to high-risk metastatic RCC patients planning to undergo cytoreductive nephrectomy (7), supported by two randomised controlled trials that showed presurgical therapy with sunitinib followed by deferred cytoreductive nephrectomy could improve oncological outcomes in patients who achieved significant overall responses (8,9).

Given that RCC is an immunogenic tumor with inflammatory cell infiltration and is a good candidate for immunotherapy, the advent of immune checkpoint inhibitors (ICIs) allows for the re-evaluation of optimal treatment strategies for RCC (10). However, ICI monotherapy in the presurgical setting has exhibited poor objective response rates (ORRs) for locally advanced ccRCC (4,11,12), although a successful case has been reported (13). Furthermore, prolonged ICI treatment in metastatic RCC may result in increased ORR for both primary and metastatic tumors, but side effects, intraoperative difficulties, and postoperative complications remain significant challenges (14). By contrast, ICIs and TKIs may have complementary and synergistic effects, and presurgical therapy combining ICIs and TKIs has demonstrated considerable ORR (15). Currently, limited studies have focused on the efficacy of short-term presurgical ICI-TKI therapy in RCC for downsizing primary tumors with local

Highlight box

Key findings

- Short-term presurgical treatment with tislelizumab and axitinib in locally advanced or metastatic renal cell carcinoma (RCC) achieved an overall response rate (ORR) of 18.2% and a disease control rate (DCR) of 100%.
- The median reduction in local lesions was –12.2%, and –24.0% for all lesions after 3–4 cycles treatment.
- Patients who underwent nephrectomy after presurgical therapy had significantly longer progression-free survival (PFS) and overall survival (OS) compared to those who did not (PFS: P=0.002; OS: P=0.004).

What is known and what is new?

- It is known that presurgical therapy with tyrosine kinase inhibitors (TKIs) alone can reduce tumour size and facilitate nephrectomy in locally advanced RCC. However, the efficacy of combining immune checkpoint inhibitors (ICIs) with TKIs needs further exploration.
- This study demonstrates that tislelizumab plus axitinib can effectively downsize local lesions and improve surgical feasibility, even in complex cases. Additionally, the study highlights the potential long-term oncological benefits of this combination therapy when followed by nephrectomy.

What is the implication, and what should change now?

- Short-term presurgical ICI-TKI combination therapy may be a promising approach for patients with locally advanced or intermediate-risk metastatic RCC, especially those with complex local lesions.
- Nephrectomy should be considered, even in metastatic patients, as it may improve long-term survival.
- Larger prospective studies are needed to further validate these findings and refine patient selection criteria.

anatomical complexity, except for VCT, where promising results have been reported in case studies (16). To balance high efficacy with acceptable toxicity, we evaluated the efficacy and safety of presurgical tislelizumab [an anti-human programmed death receptor-1 (PD-1) monoclonal IgG4 antibody] in combination with axitinib [a TKI that selectively inhibits vascular endothelial growth factor receptor (VEGFR) 1–3, receptor tyrosine kinase (KIT), and platelet-derived growth factor receptor (PDGFR)] in a small cohort of RCC patients, particularly those with local anatomical complexity, from a single institution.

Furthermore, presurgical ICI therapy offers several theoretical advantages, including potentially enhanced immune responses against tumor antigens at the primary site, where adequate antigens delivery is possible, increased tumor antigens presentation in tumor-draining lymph nodes, and avoidance of the potentially immunosuppressive state that can follow surgery, thereby improving oncological outcomes (17-19). Here, we also report the oncological outcomes for these patients, with a relatively long follow-up period. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-585/rc).

Methods

Patients and management

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Peking University Cancer Hospital & Institute (No. 2021KT35). Between March 2021 and May 2022, we prospectively recruited patients with RCC from Peking University Cancer Hospital & Institute. These patients presented with either surgically complex disease or intermediate-risk metastatic disease, and accepted presurgical systemic therapy. Informed consent was obtained from all patients and their families. Surgical complexity was assessed by two experienced surgeons (Y.Y.; N.Z.) and was defined as patients experiencing conditions such as large or confluent retroperitoneal lymph nodes, ipsilateral adrenal metastasis, inferior vena cava tumor thrombus, or a large primary tumor closely associated with adjacent organs, lacking a clear boundary. All patients had a biopsy-confirmed diagnosis of RCC, not limited to ccRCC, and were scheduled to undergo cytoreductive or radical nephrectomy. Tislelizumab (200 mg intravenously every 3 weeks) and axitinib (5 mg orally twice daily) were administered for at least two cycles (3 weeks per cycle) as presurgical therapy. Patients were fully informed of possible adverse events (AEs). Treatment efficacy was evaluated using imaging techniques [computed tomography (CT) and bone scans] within 3 weeks after the final dose. Radical or cytoreductive surgery was performed within 4 weeks following the last dose. Postoperative treatment involved continued tislelizumab and axitinib for those with residual disease, or 6–12 months of tislelizumab for those with no evidence of disease, until intolerable AEs or disease progression occurred. The number of cases in the area during the study period determined the sample size.

Clinical outcome

ORR was assessed using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and immune-related response criteria. Before and after presurgical therapy, tumor burden was assessed by measuring the largest diameter of the primary tumor and the sum of the largest diameters of target lesions. Local lesions (renal tumor, lymph node metastases, and adrenal metastases) and all lesions (including distant metastases) were calculated separately to assess potential differences in response between them. Other clinical outcomes included safety and surgical complications. AEs during presurgical therapy were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0), while surgical complications were assessed using the Clavien-Dindo classification. The occurrence of AEs was recorded. Oncological outcomes included progression-free survival (PFS), defined as the time from presurgical therapy initiation to the date of progression on imaging, and overall survival (OS), defined as the time from presurgical therapy initiation to death from any cause.

Pathological study

The effect of these agents on the immune environment and their association with oncological outcomes remain largely unknown. In a preliminary exploratory analysis, pathological features were investigated, including the percentage of residual tumor and tumor-infiltrating lymphocytes (TILs) in both renal and extrarenal neoplasms.

Statistical analysis

Baseline clinical characteristics and overall responses were

Table 1 Basic characteristics of patients and perioperative outcomes

Patient	Age (years)	Preoperative biopsy	Side	TN stage	Metastasis	Metastatic site	Neoadjuvant cycles	AEs	Surgical approach	Length of stay (days)	Complication (Clavien-Dindo)	30-day readmission
1	41	ccRCC with sarcomatoid differentiation	Left	cT3aN1†	Yes	Lung, bone (multiple), lymph node	3	Hypertension G1; skin ulceration G2; hypothyroidism G2; transaminase elevation	Open	7	No	No
2	55	ccRCC	Right	cT3aN0†	Yes	Liver	2	No	Open	6	No	No
3	69	ccRCC with sarcomatoid differentiation	Left	cT4N1†	Yes	Lung, lymph node	z	No	Open	13	No	No
4	56	RCC NOS	Left	cT3aN1†	Yes	Adrenal, lymph node	3	Rash G1; glucose elevation G1	Open	5	No	No
5	54	RCC NOS	Right	cT3aN0†	Yes	Lung, adrenal	4	No	Open	4	No	No
6	51	RCC NOS	Left	cT3aN0	Yes	Lung, bone (2 regions)	4	No	–	–	–	–
7	55	ccRCC	Left	cT3aN0†	Yes	Lung	3	No	Open	4	No	No
8	56	ccRCC	Right	cT3bN0†	No	–	3	No	Open	7	No	No
9	58	ccRCC	Right	cT3aN0†	Yes	Lung, bone (single)	3	No	Open	5	No	No
10	56	ccRCC	Left	cT3aN1†	Yes	Lung, lymph node	3	No	–	–	–	–
11	69	ccRCC	Right	cT3aN0	Yes	Lung, adrenal	2	Yes	–	–	–	–

†, surgical complexity was present at initial presentation. AEs, adverse events; ccRCC, clear cell renal cell carcinoma; RCC NOS, renal cell carcinoma not otherwise specified.

analysed using SPSS software (version 26.0; IBM Corp.). Continuous variables were expressed as median (range) or mean ± standard deviation and analysed using non-parametric tests. Paired *t*-tests were used to compare the percentage of residual tumor and TILs between renal and extrarenal lesions. PFS and OS were estimated using the Kaplan-Meier method (nephrectomy *vs.* no nephrectomy; bone metastases vs no bone metastases).

Results

We recruited 11 patients with RCC who received presurgical therapy consisting of tislelizumab and axitinib from March 2021 to May 2022 (*Table 1*). All patients were male, with a mean age of 56.4±7.7 years. Percutaneous needle biopsies of the primary renal or metastatic lesions were performed to confirm the diagnosis of RCC, of which 6 had pure ccRCC, 2 had ccRCC with sarcomatoid differentiation, and 3 had RCC not otherwise specified (NOS). Metastases were present in 10 patients (four with regional lymph nodes, three with adrenal, and nine with distant metastases), while one patient had Mayo level II VCT. Metastatic sites included the lung, bone, liver, and adrenal glands (*Table 1*). Six patients were initially staged as cT3aN0, three as cT3aN1, one as cT3bN0, and one as cT4N1 (*Table 1*). The largest diameters of renal lesions, lymph nodes, and adrenal metastases were 9.8±2.7, 3.7±2.8, and 3.6±2.1 cm, respectively. Nine patients exhibited significant surgical challenges with their local lesions as assessed by two experienced surgeons. The remaining two patients, who did not face such challenges with their local lesions, were metastatic cases characterized by multiple metastases and classified as intermediate risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria.

After a median of three cycles (range, 3–4 cycles) of

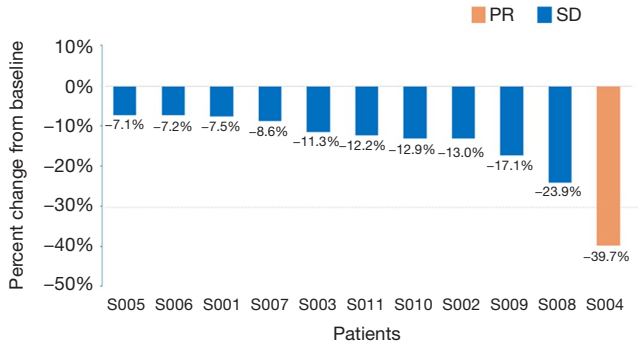

Figure 1 Percentage change in the long-axis diameter of local lesions (renal tumor, regional lymph nodes, and adrenal gland) after 3–4 cycles of presurgical therapy (%). PR, partial regression; SD, stable disease.

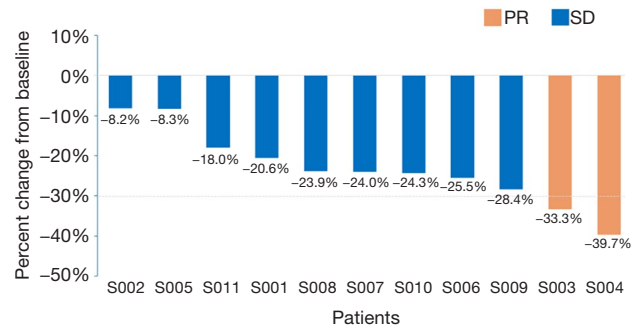

Figure 2 Percentage change in the long-axis diameter of all target lesions after 3–4 cycles of presurgical therapy (%). PR, partial regression; SD, stable disease.

presurgical therapy, the ORR was 18.2% (2/11). Two patients achieved partial regression (PR) as their best response, while the remaining nine patients exhibited stable disease (SD). The DCR was 100% (11/11). During presurgical therapy, radiotherapy for bone metastasis was administered to three patients to control bone lesions. No new bone lesions were detected, and existing bone lesions remained stable, as confirmed by bone scans and CT during the presurgical therapy period. CT scans of representative cases before and after presurgical therapy are shown in Figure S1. The median reduction in the largest diameter for local lesions and all evaluable lesions was −12.2% (range, −7.1% to −39.7%; *Figure 1*) and −24.0% (range, −8.2% to −39.7%; *Figure 2*), respectively. Specifically, the median reduction in the largest diameter for the renal primary lesion, lymph node metastases, and ipsilateral adrenal metastases was −13.0% (range, −4.5% to −42.9%), −18.4% (range, −4.2% to −57.1%), and −25.0% (range, −13.8% to −48.3%), respectively.

During presurgical therapy, two out of 11 patients reported AEs. One patient experienced grade 1 (hypertension and transaminase elevation) and grade 2 (skin ulceration and hypothyroidism) AEs, while the other reported grade 1 AEs (rash and glucose elevation). No grade 3/4 AEs, AEs leading to treatment discontinuation, or AEs requiring glucocorticoids were observed.

Of the 11 patients, eight (72.7%) with surgical complexity completed open surgery by two experienced surgeons without any additional delays, while three (27.3%) declined surgery and continued with combinational systemic therapy. Local R0 resection was successfully performed in all eight patients, including two tumor thrombectomies, three lymphadenectomies, and two ipsilateral adrenalectomies. One patient with two liver lesions underwent simultaneous liver metastasis resection and achieved a disease status termed "M1 with no evidence of disease (NED)" after nephrectomy and metastasectomy. A total of three patients achieved NED status after surgery. The median estimated blood loss, operating time, and postoperative length of stay were 200 mL (range, 50–2,000 mL), 176 minutes (range, 84–206 minutes), and 6.5 days (range, 4–13 days), respectively. One patient required an intraoperative blood transfusion. No surgical complications or 30-day readmissions occurred. Combinational therapy was resumed four weeks postoperatively for patients with existing distant metastases, while ICI alone were administered to patients with NED status (one out of three patients declined systemic medication and opted for active surveillance).

The percentage of residual tumors in renal and extrarenal lesions was 33.4%±20.8% and 70.8%±20.6%, respectively. The presence of TILs was reported at 35.6%±23.5% in renal lesions and 30.0%±21.9% in extrarenal lesions. Detailed data are presented in *Table 2*. Among the six patients with both renal and extrarenal lesions, the percentage of residual tumors was significantly lower in renal lesions than in extrarenal lesions (P=0.02). Additionally, a trend towards a higher percentage of TILs in renal lesions compared to extrarenal lesions was observed (37.5%±24.4% *vs.* 30.0%±21.9%), although this difference was not statistically significant (P=0.51).

After a median follow-up of 23 months (range, 14–34 months), 6 out of 11 patients (54.5%) experienced disease progression and died. This included three patients who did not undergo nephrectomy (3/3, 100%) and another three who underwent nephrectomy (3/8, 37.5%).

Table 2 Tumor response according to RECIST v1.1 criteria and pathological evaluation of residual cancer

Patient	Neoadjuvant cycles	Percentage change for local lesions[†] (%)	Percentage change for all lesions (%)	Tumor response	Postoperative pathology	Percentage of residue tumor	Percentage of TILs	Postoperative treatment
1	3	−7.5%	−20.6%	SD	ccRCC, ISUP grade 4, with sarcomatoid differentiation	Renal tumor 30% Extrarenal lesions 70%	Renal tumor 40% Extrarenal lesions 20%	Tislelizumab and axitinib
2	2	−13%	−8.2%	SD	ccRCC, ISUP grade 2	Renal tumor 50% Extrarenal lesions 60%	Renal tumor 30% Extrarenal lesions 10%	Tislelizumab
3	3	−11.3%	−33.3%	PR	ccRCC, ISUP grade 4, with sarcomatoid differentiation	Renal tumor 2%	Renal tumor 50%	Axitinib
4	3	−39.7%	−39.7%	PR	FH-deficient RCC	Renal tumor 10% Extrarenal lesions 85%	Renal tumor 70% Extrarenal lesions 70%	Tislelizumab and axitinib (6 months)
5	4	−7.1%	−8.3%	SD	ccRCC, ISUP grade 3	Renal tumor 60% Extrarenal lesions 100%	Renal tumor 5% Extrarenal lesions 40%	Tislelizumab and axitinib
6	4	−7.2%	−25.5%	SD	–	–	–	–
7	3	−8.6%	−24.0%	SD	ccRCC, ISUP grade 3	Renal tumor 55%	Renal tumor 10%	Tislelizumab and axitinib
8	3	−23.9%	−23.9%	SD	ccRCC, ISUP grade 3	Renal tumor 30% Extrarenal lesions 40%	Renal tumor 20% Extrarenal lesions 20%	–
9	3	−17.1%	−28.4%	SD	ccRCC, ISUP grade 4	Renal tumor 30% Extrarenal lesions 70%	Renal tumor 60% Extrarenal lesions 20%	Tislelizumab and axitinib
10	3	−12.9%	−24.3%	SD	–	–	–	–
11	2	−12.2%	−18.0%	SD	–	–	–	–

[†], local lesions included renal tumor, ipsilateral adrenal metastases and ipsilateral lymph nodal metastases. ccRCC, clear cell renal cell carcinoma; FH, fumarate hydratase; ISUP, International Society of Urological Pathology; PR, partial regression; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TILs, tumor infiltrate lymphocytes.

There was a significant difference in PFS and OS between patients who underwent nephrectomy and those who did not (P=0.002, Figure S2; P=0.004, Figure S3). Of the five surviving patients, two had unresectable lung metastases, and three had no evidence of disease (one with resected liver metastases, one with resected VCT, and one with resected adrenal and lymph node metastases). In the nephrectomy group, a significant difference in PFS and OS was observed between patients with and without bone metastases (P=0.008, Figure S4; P=0.01, Figure S5).

Discussion

In the era of targeted therapy, numerous studies have evaluated the efficacy of short-term presurgical use of sunitinib, pazopanib, axitinib, and sorafenib in locally advanced and metastatic RCC (20-23). These studies demonstrated reductions in primary tumor diameter ranging from –9.6% to –29%, with ORR between 5% and 46% (4). With the development of next-generation TKIs targeting broad-spectrum receptors, better responses have been achieved. For instance, in the CARBOPRE trial, cabozantinib was used before cytoreductive nephrectomy, where all four patients with metastatic ccRCC experienced significant primary tumor shrinkage (change in long-axis diameter of –15.7% to –31.2%), with two patients achieving PR, facilitating subsequent nephrectomy (24).

Presurgical ICI monotherapy has also been studied, although only minimal tumor shrinkage was observed in two studies. In a phase II prospective study administering four doses of neoadjuvant nivolumab (at 2-week intervals) for locally advanced ccRCC, the best response was SD, with a median change in the largest tumor diameter of –0.85% (range, –6.2% to +7.9%) (12). In another similar clinical trial, the best response to neoadjuvant nivolumab was also SD, with minimal changes, except for one patient who experienced a –15.7% reduction in the largest tumor diameter (11).

Better ORR have been reported in advanced RCC using combination therapy of ICIs and TKIs, such as pembrolizumab plus lenvatinib (71%), pembrolizumab plus axitinib (59.3%), nivolumab plus cabozantinib (55.7%), avelumab plus axitinib (59.3%) and toripalimab plus axitinib (56.7%) (25-29). However, the high ORR in these studies was based on longer courses of treatment and a higher percentage of prior nephrectomy, without specific evaluation of their effect on primary renal tumors or local lesions. In a phase II study of neoadjuvant sitravatinib and nivolumab (6–8 weeks) in patients with locally advanced ccRCC, the ORR was 11.8%, and the median change in the largest diameter of the primary renal tumor was –14% (range, 0 to –33%) (30).

The definitive efficacy of local lesion reduction, including primary renal tumors, regional lymph nodes, and ipsilateral adrenal metastases, through short-term ICI plus TKI as presurgical therapy has not yet been reported. It is anticipated that presurgical therapy with ICI plus TKI may provide improved tumor shrinkage compared to "traditional" TKIs alone, and related studies with different inclusion criteria are currently underway (31,32). In our cohort study, the results showed that the median change in the largest diameter for local and all evaluable lesions was –12.2% (range, –7.1% to –39.7%) and –24.0% (range, –8.2% to –39.7%), respectively, which is superior to the previously reported results from single-agent nivolumab (11,12). Notably, tumor response in the primary renal lesion, lymph node metastases, and ipsilateral adrenal metastases was investigated, showing a median change in the largest diameter of –13.0% (range, –4.5% to –42.9%), –18.4% (range, –4.2% to –57.1%), and –25.0% (range, –13.8% to –48.3%), respectively. These results indicate a remarkable response, significantly reducing the complexity of surgery, even in patients with large or confluent lymph nodes and adrenal metastases.

Unlike most of the previously mentioned studies, the pathology in our cohort was not limited to simple ccRCC, with one case of RCC NOS and one case of fumarate hydratase (FH)-deficient RCC, both exhibiting a favourable response in local lesions to presurgical therapy (–33.3% and –39.7%, respectively). Therefore, ICI-TKI presurgical therapy may also be applicable to non-ccRCC cases, such as FH-deficient RCC. Superior oncological outcomes have been reported in a real-world retrospective study from China (33).

In our study, we observed several notable phenomena, including a significantly lower percentage of residual tumor and a relatively higher percentage of TILs in renal lesions compared to extrarenal lesions (synchronously resected lymph nodes, adrenal, and liver metastases) following presurgical therapy. Thus, beyond downsizing the primary tumor and improving the ORR, ICI-based presurgical therapy may also enhance the oncological prognostic value of nephrectomy for both locally advanced and metastatic RCC, irrespective of the number or site of metastasis. The differences in the tumor immune microenvironment may be related to the variable responses to systemic therapy (34). Theoretically, presurgical immunotherapy may elicit a stronger anti-tumor immune response than postsurgical immunotherapy due to enhanced immune activity against antigens in primary tumors, increased tumor-antigens presentation in tumor-draining lymph nodes, and the absence of a possible immunosuppressive state post-surgery (17-19). Further clinical studies are needed to determine the oncological benefits of ICI plus TKI as presurgical therapy for RCC patients, including those who are nephrectomy candidates without surgical complexity.

Our study found that the clinical response of the primary tumor was generally less robust than that of metastatic

lesions according to RECIST criteria, particularly in comparison to lung metastases. Therefore, nephrectomy remains essential when metastatic sites respond well, even if the primary tumor does not achieve optimal control. Complete surgical resection of both local and metastatic lesions offers the greatest potential to improve long-term oncological outcomes following a favourable response to presurgical therapy, as demonstrated in the SURTIME study. In our cohort, patients who underwent nephrectomy and metastatectomy experienced significantly improved PFS and OS (Figures S2,S3). However, bone metastases were associated with significantly reduced PFS and OS within the nephrectomy group (Figures S4,S5), despite a similar ORR to other metastatic sites as reported in the CLEAR subgroup analysis presented at European Society for Medical Oncology (ESMO) 2023 (35). Consequently, bone metastasis is a negative prognostic factor, and surgery in such cases should be carefully considered. This topic continues to be explored through longer follow-up periods and the inclusion of a larger patient cohort. Delayed nephrectomy may increase the risk of progression of the primary lesion due to tumor heterogeneity (24).

Notwithstanding, several retrospective studies have indicated that inflammatory tissue reactions following ICI treatment may impact the safety of surgery, which is a key consideration limiting the application of ICIs in neoadjuvant therapy. In metastatic RCC, a series of 11 patients who underwent delayed nephrectomy after 10 months of ICI treatment showed that over 80% experienced difficulties in identifying dissection planes. Another series of 21 patients, following 13 months of ICI-based combination therapy, reported severe adhesions in 38% of cases (36,37). A shorter course of ICI therapy may reduce technical challenges associated with inflammatory reactions. In a study involving 17 patients with high-risk RCC, no changes in tissue planes or intraoperative complications were observed after administering three doses of neoadjuvant nivolumab at 2-week intervals (11). Similarly, in a prospective phase II trial administering four cycles of neoadjuvant nivolumab in locally advanced RCC, no intraoperative complications were reported (12). In our study, no grade 3/4 AEs or therapy discontinuations were observed after a median of three cycles of tislelizumab and axitinib. All surgeries were successfully completed without delay, and the anticipated reduction in surgical difficulties was achieved. No significant surgery-related complications were noted postoperatively.

There are several limitations to our study. Firstly, the sample size was small, and the inclusion criteria were varied. Most patients with either metastatic or locally advanced RCC presented with resectable renal masses and preferred upfront nephrectomy, making it difficult to recruit RCC patients with highly complex local lesions from a single institution. Moreover, TKI monotherapy remains the most common presurgical therapy in routine clinical practice in China. Secondly, the assessment of surgical difficulty was influenced by the subjective judgment of attending physicians. Finally, we only recorded the AEs reported by patients during presurgical therapy, which may have led to an underestimation of AEs incidence.

Conclusions

Short-term presurgical treatment with tislelizumab and axitinib is feasible and safe for patients with locally advanced or intermediate-risk metastatic RCC with local anatomical complexity, and is not limited to ccRCC. This combination therapy can facilitate subsequent nephrectomy. Presurgical tislelizumab and axitinib, followed by complete excision of primary and metastatic lesions, may enhance the immune response and improve long-term prognosis. Patients with nephrectomy may have better PFS and OS. Bone metastases were associated with poorer prognoses. Cytoreductive nephrectomy for advanced RCC should be chosen with caution for patients with multiple bone metastases, a high metastatic burden (with or without a low primary tumor burden). Larger cohort studies are required to further confirm these findings.

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None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-585/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-585/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Ethics Committee of Peking University Cancer Hospital & Institute (No. 2021KT35). Informed consent was obtained from all patients and their families.

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