ELSEVIER

Urologic Oncology: Seminars and Original Investigations 000 (2024) 1−8

UROLOGIC ONCOLOGY

Clinical-Kidney cancer

Delayed partial nephrectomy following complete response to immunotherapy: feasibility and results (UroCCR n°157)

Gaëlle Margue, M.D.[a,b,*], Clément Klein, M.D.[a], Bastien Parier, M.D.[c], Laurence Albiges, M.D., Ph.D.[b,d], Géraldine Pignot, M.D.[e], Gwenaëlle Gravis, M.D.[f], Pierre Bigot, M.D., Ph.D.[b,g], Nathalie Baize, M.D.[h], Alexandre Ingels, M.D., Ph.D.[b,i], Charlotte Joly, M.D.[j], François Audenet, M.D., Ph.D.[k], Yann Vano, M.D., Ph.D.[l], Thibaut Waeckel, M.D.[b,m], Romain Levard, M.D.[n], Philippe Barthelemy, M.D., Ph.D.[b,o], Damien Ambrosetti, M.D., Ph.D.[p], Virginie Verkarre, M.D., Ph.D.[q], Mokrane Yacoub, M.D.[r], Marine Gross-Goupil, M.D., Ph.D.[s], Jean-Christophe Bernhard, M.D., Ph.D.[a,b]

[a] *Bordeaux University Hospital, Urology department, Bordeaux, France*
[b] *Kidney Cancer group of the French Association of Urology Cancer Committee, Paris, France*
[c] *Kremlin-Bicêtre -APHP, Urology department, Paris, France*
[d] *Gustave Roussy Institute, Medical oncology department, Paris, France*
[e] *Paoli Calmette Institute, Urology department, Marseille, France*
[f] *Paoli Calmette Institute, Medical oncology department, Marseille, France*
[g] *Angers University Hospital, Urology department, Angers, France*
[h] *Angers University Hospital, Medical oncology department, Angers, France*
[i] *Henri Mondor hospital-APHP, Urology department, Paris, France*
[j] *Henri Mondor hospital-APHP, Medical oncology department, Paris, France*
[k] *HEGP-APHP, Urology department, Paris, France*
[l] *HEGP-APHP, Medical oncology department, Paris, France*
[m] *Caen University Hospital, Urology department, Caen, France*
[n] *Caen University Hospital, Medical oncology department, Caen, France*
[o] *ICANS, Medical oncology department, Strasbourg, France*
[p] *Nice University Hospital, Pathology department, Nice, France*
[q] *HEGP-APHP, Pathology department, Paris, France*
[r] *Bordeaux University Hospital, Pathology department, Bordeaux, France*
[s] *Bordeaux University Hospital, Medical oncology department, Bordeaux, France*

Received 19 August 2024; received in revised form 23 October 2024; accepted 1 November 2024

Abstract

Background: Complete responses to immunotherapy in metastatic kidney cancer have led to a renewed interest in primary-site surgery. The prolonged survival of these patients has prompted consideration for nephron-sparing surgery when technically feasible. Given the surgical difficulties reported in the literature, it is essential to assess the feasibility as well as functional and oncological results of partial nephrectomy (PN) after immunotherapy.

Methods: Multicentric retrospective study based on UroCCR database, including all metastatic patients who underwent PN after a complete response to immunotherapy at metastatic sites. Morbidity, renal function, positive margin rate, and oncological outcomes were assessed.

Results: Thirteen patients underwent PN after immune checkpoint inhibitor (ICI), between January 2019 and September 2023. Median age at surgery was 64 [50−68]; 84.6% received ICI as first-line treatment with a median duration of 11.7 [7.7−14.9] months. None of the patients had positive surgical margins, five patients (38.5%) were ypT0. Two patients (15.4%) presented intraoperative complications and 1 a severe postoperative complication. Median GFR at 3 months was 84.7 [66.6−95.2] mL/min/1.73 m2 with no significant difference from

*Corresponding author.
E-mail address: gaelle.margue@chu-bordeaux.fr (G. Margue).

https://doi.org/10.1016/j.urolonc.2024.11.003

preoperative GFR. After surgery, immunotherapy was not reintroduced in ten patients (77%). Median follow- up was 25.6 [19.6−30.2] months, median treatment-free survival was 22.4 [15.8−34.7] months. RFS at 12 months and at last follow-up were 84.6% and 53.8%. OS rate at last follow-up was 92.3%.

Conclusion: This series demonstrates the feasibility of partial nephrectomy following immune checkpoint inhibitor treatment, with acceptable morbidity rates and no major difficulties specifically attributable to the prior treatment. While the data suggest promising functional and oncological outcomes, further investigation is needed. The study underscores the importance of early re-evaluation of metastatic cases in multidisciplinary tumor boards.

Keywords: Kidney cancer; Partial nephrectomy; Immunotherapy; Immune checkpoint inhibitor; Delayed surgery

1. Introduction

Renal cell carcinoma (RCC) is the 14th most common cancer worldwide [1]. Although it is most often diagnosed incidentally at a localized stage, on imaging performed for other causes [2], it remains diagnosed at the metastatic stage in approximately 15% of the cases [1,3]. The management of these patients has considerably changed in recent years, leading to improvements in their overall [4]. Since the CARMENA trial [5], cytoreductive nephrectomy is no longer the standard of care for intermediate- or high-risk patients who now benefit from initial systemic treatment. With the introduction of immune checkpoint inhibitors (ICI), either combined with tyrosine kinase inhibitor (TKI) or dual ICI, the rate of complete radiological responses at the metastatic sites has increased. However, responses in the primary renal lesion are less frequently observed, renewing interest in surgical intervention for the primary lesion. The selection of patients eligible for nephrectomy and the true impact of this surgery on prognosis are still debated. Additionally, data on the complexity of these surgeries vary, with some authors reporting high levels of inflammation associated with immunotherapy (IO), suggesting more complicated procedures, whereas others have found no additional difficulties compared to patients who have not undergone systemic treatment [6,7].

Nevertheless, the extended survival of patients who are good responders to immunotherapy prompts consideration for nephron-sparing surgery whenever possible to achieve complete remission while preserving renal function.

Therefore, this study aims to describe the characteristics of patients eligible for delayed partial nephrectomy (PN) after immunotherapy, and to assess the feasibility, and functional and oncological outcomes of this surgical approach.

2. Materials and methods

2.2. Study population

Using the French Research Network on Kidney Cancer Database UroCCR (CNIL DR 2013-206; NCT03293563), we conducted a multicenter, retrospective study including all metastatic patients who underwent partial nephrectomy after a complete response to immune checkpoint inhibitors at metastatic sites.

2.3. Follow-up and outcomes

All preoperative, intraoperative, postoperative, and follow-up data were collected prospectively from the database after obtaining written consent.

Demographic data included patient age at surgery, sex, Body Mass Index (BMI), patient's general condition (assessed by the Eastern Cooperative Oncology Group [ECOG] performance status), history of hereditary syndrome, indication for nephron-sparing surgery (NSS), description of metastatic sites, systemic treatment molecules, treatment line, and duration of systemic therapy before surgery. The response to ICI therapy was assessed using enhanced CT scans, and the primary tumor response was evaluated based on the percentage of reduction in tumor size.

Tumor characteristics included the diameter and complexity according to the RENAL score on the CT scan before surgery (classified as low [4−6], moderate [7−9] or high [10−12]). The pathology report included the ISUP grade, tumor stage according to the 8th edition of the TNM classification system, and positive margin rate.

Morbidity was assessed in terms of the duration of surgery, estimated blood loss, blood transfusion rate, length of stay, and intra- and postoperative complications (considered minor if the Clavien-Dindo score was ≤ 2 and major if >2). The quality of the procedure was assessed using the Trifecta composite criteria [8] combining negative surgical margins, absence of perioperative complications, and a decrease in GFR of less than 10% postoperatively.

Functional outcomes were assessed by measuring the serum creatinine level, estimating the GFR according to the Modification of Diet in Renal Disease (MDRD) formula pre- and postoperatively (at 3 months), looking for acute kidney injury (AKI), postoperative de novo chronic kidney injury (CKD), and CKD upgrade.

Follow-up was conducted according to the French Urological Association guidelines [9], and oncological outcomes included recurrence-free survival (RFS), treatment-free survival (TFS) and overall survival (OS). OS was

defined as time between surgery and death of any cause. RFS was defined as time between surgery and diagnosis of local recurrence, metastatic progression, or death of any cause, whatever comes first. TFS was defined as time between discontinuation of IO and resumption of treatment due to revolution.

2.3. Data analysis

Data analysis was performed using the R software environment for statistical computing and graphics (version 4.0.0). Continuous variables were reported as median and interquartile range [IQR], whereas categorical variables were reported as frequencies and proportions. A univariate logistic regression analysis was performed to identify potential predictive factors for achieving ypT0 status, representing the absence of residual tumor cells in pathological evaluations.

3. Results

3.1. Patients' and surgeries' characteristics

Out of 93 patients in our database who underwent cytoreductive surgery in the context of ICI therapy, 13 underwent PN after IO between January 2019 and September 2023. The median age at surgery was 64 [50−68] and 10/13 patients (77%) were male. At diagnosis, the prognostic group according to the International Metastatic RCC Database Consortium (IMDC) [10] was favorable, intermediate, and poor for respectively 2/13 (15.4%), 7/13 (53.8%) and 4/13 (30.8%) patients. The median number of metastatic sites was 2 [1−3] and the median primary tumor size was 5.5 [3−7] cm. Most patients (11/13; 84.6%) received IO as first-line treatment with 4/13 patients (30.8%) treated using a combination ICI-TKI and 9/13 (69.2%) ICI in mono or dual therapy. The median duration of IO before surgery was 11.7 [7.7−14.9] months. The primary tumor site did not generally respond to treatment, since the median tumor size at surgery was 5.6 [5−6] cm corresponding to a median response of 0% [26.9 − -29.0]. The median RENAL score was 10 [8−10] (Table 1).

Three patients (23.1%) had an imperative indication for PN, 1 (7.7%) underwent open surgery, and the others underwent surgery using a minimally invasive approach. The median operating time was 180 min [167−268]. The median estimated blood loss was 400cc [300−937.5] and 2/13 patients (15.4%) presented intraoperative complications (a vena cava injury sutured without requiring conversion to open surgery and an injury to the gall bladder in a patient undergoing quadruple tumorectomy). The median length of stay was 3 days [3−6] and 4/13 patients (30.8%) developed postoperative complications, including 1/13 (7.7%) severe complication (urinary fistula requiring ureteral stenting and radiological drainage) (Table 2).

Table 1
Patients characteristics

	n=13
Age at surgery (years), median [IQR]	64 [50−68]
Sex, n (%)	
Male	10 (77)
Female	3 (23)
Hereditary syndrome, n (%)	0 (0)
BMI (kg/m2), median [IQR]	29.2 [27.2−31.3]
ECOG performance status at surgery, n (%)	
0	11 (84.6)
1	2 (15.4)
IMDC prognostic group, n (%)	
Favorable	2 (15.4)
Intermediate	7 (53.8)
Poor	4 (30.8)
Preoperative GFR (mL/min/1,73m2), median [IQR]	88.0 [72.4−96.7]
Tumor size at diagnosis (cm), median [IQR]	5.5 [3.0−7.0]
cT stage, n (%)	
cT1a	4 (30.8)
cT1b	5 (38.5)
cT2a	1 (7.7)
cT3a	3 (23.1)
Number of metastatic sites, median [IQR]	2 [1−3]
Metastatic sites at diagnosis, n (%)	
Lung	7 (53.8)
Bone	7 (53.8)
Lymph nodes	6 (46.2)
Liver	1 (7.7)
Pancreas	1 (7.7)
Treatment, n (%)	
Nivolumab + Ipilimumab	6 (46.2)
Nivolumab	3 (23.1)
Nivolumab + Ipilimumab + Cabozantinib	2 (15.4)
Pembrolizumab + Axitinib	1 (7.7)
Nivolumab + Axitinib	1 (7.7)
Treatment duration (months), median [IQR]	11,7 [7.7−14.9]
Line of treatment, n (%)	
First line	11 (84.6)
2nd line	1 (7.7)
3rd line	1 (7.7)
Tumor size at surgery (cm), median [IQR]	5.6 [5.0−6.0]
Tumor complexity at surgery, n (%)	
Low	0 (0)
Intermediate	6 (46.2)
High	7 (53.8)

Overall, while performing partial nephrectomy after immune checkpoint inhibitor therapy, no major difficulties specifically attributable to the prior immunotherapy treatment were generally encountered. The resection techniques employed were largely in line with those used in patients who did not receive prior systemic therapy, without the need for routinely implementing precautions unique to this cohort. According to the operative reports, there was no indication of increased surgical complexity, suggesting that the impact of immune checkpoint inhibitors did not significantly complicate the operative course. Post-surgery, IO was not reintroduced in 11/13 patients (84.6%), while 2/13 patients continued treatment for 2 and 14 months, respectively.

Table 2
Characteristics and outcomes of surgeries

	n=13
Indication for nephron-sparing surgery, n (%)	
Imperative	3 (23.1)
Relative	1 (7.7)
Elective	9 (69.2)
Multiple tumorectomy, n (%)	1 (7.7)
Surgical approach, n (%)	
Open	1 (7.7)
Laparoscopic	1 (7.7)
Robot-assisted	11 (84.6)
Operating time (min), median [IQR]	180 [167−268]
Blood loss (mL), median [IQR]	400 [300−937.5]
Blood transfusion, n (%)	1 (7.7)
Intraoperative complications, n (%)	2 (15.4)
Postoperative complications, n (%)	4 (30.8)
Including severe (Clavien ≥3)	1 (7.7)
Length of stay (days), median [IQR]	3 [3−6]
Trifecta satisfied, n (%)	8 (61.5)

3.2. Pathological results

Regarding the final pathological results, all patients presented with clear cell renal cell carcinomas with Fuhrman grades of 2, 3, and 4 in three (37.5%), four (50%), and one (12.5%) patients, respectively (Table 3). None of the patients had positive surgical margins, and 5 out of 13 patients (38.5%) exhibited no residual tumor (ypT0). No predictive factors for achieving ypT0 were identified in the univariate analysis, with the duration of treatment ($P = 0.2$), response to treatment ($P = 0.4$), and type of treatment ($P = 0.3$) showing no significant association. Additionally, there was no difference in the primary tumor response on preoperative imaging between the ypT0 patients and those with residual tumors on pathology.

Table 3
Oncological results

	n=13
Negative surgical margins, n (%)	13 (100)
ypT0, n (%)	5 (38.5)
	n=8
Clear cell renal cell carcinoma, n (%)	8 (100)
Fuhrman grade, n (%)	
2	3 (37.5)
3	4 (50)
4	1 (12.5)
ypT stage, n (%)	
ypT1a	5 (62.5)
ypT1b	1 (12.5)
ypT2	1 (12.5)
ypT3a	1 (12.5)

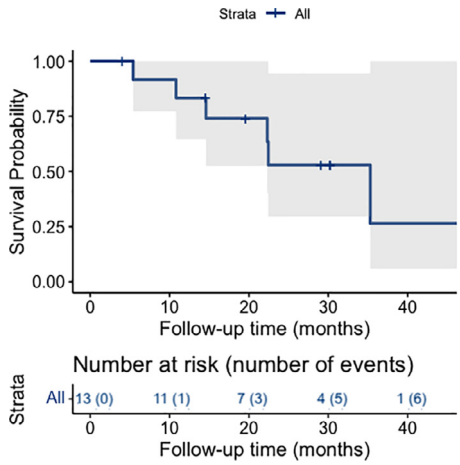

Fig. 1. Kaplan−Meier estimates of recurrence-free survival after delayed partial nephrectomy.

3.3. Functional results

Regarding functional results, 2/13 patients presented AKI postoperatively and only one presented a CKD upgrade (from stage 3B to 4). No de novo CKD was observed, and the median GFR at 3 months was 84.7 [66.6 −95.2] mL/min/1.73 m^2 with no significant difference from the median preoperative GFR of 88.0 [72.4−96.7] mL/min/ 1.73 m^2.

3.4. Oncological results

Finally, when looking at the oncological results, the median follow-up was 25.6 [19.6−30.2] months, and the overall survival at the last follow-up was 92.3%. One patient died 35.3 months after surgery from a cause unrelated to the kidney cancer. The recurrence-free survival at 12 months and at last follow up was 84.6% and 53.8%, respectively. Five patients experienced a disease recurrence at a median time of 14.6 [10.8−22.4] months and the median treatment-free survival was 22.4 [15.8−34.7] months (Figs. 1 and 2).

4. Discussion

Cytoreductive nephrectomy has been a cornerstone in the treatment of metastatic RCC (mRCC) for decades, based on the premise that complete removal of the primary tumor might eliminate a source of further metastases, enhance the body's immune response, and reduce tumor burden. However, the introduction of targeted therapies has posed challenges to this approach. The randomized phase 3 CARMENA trial [5], published in 2018, investigated the value of cytoreductive nephrectomy in mRCC patients eligible for systemic therapy with sunitinib. The trial concluded that sunitinib alone was not inferior to nephrectomy followed by sunitinib in intermediate-risk or poor-risk mRCC patients. These findings, coupled with the impact of

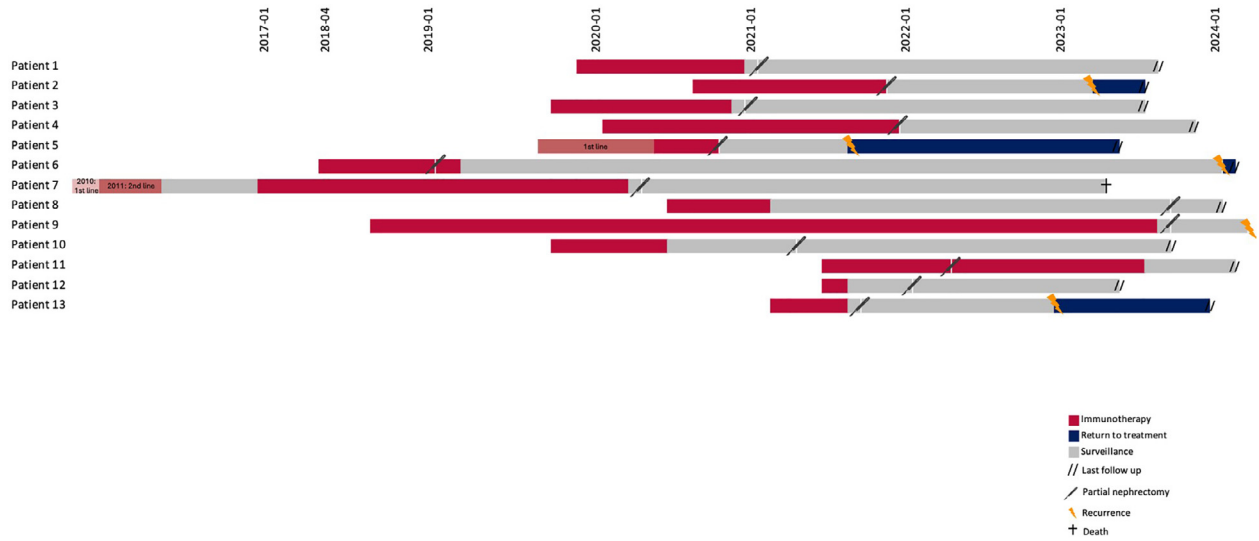

Fig. 2. Patients history and follow-up.

postoperative complications and surgery on quality of life, have shifted mRCC management away from surgery as the standard of care.

However, a post hoc analysis of the CARMENA trial identified a small subgroup of patients who underwent secondary nephrectomy after treatment with sunitinib, resulting in significantly higher overall survival (OS) [11]. The advent of Immune Checkpoint Inhibitors (ICIs) has revolutionized therapeutic approaches for mRCC. The CHECKMATE-214 [12] study demonstrated the superior efficacy of combining nivolumab and ipilimumab over sunitinib. Similarly, the KEYNOTE-426 [13] study reported considerable improvements in overall survival, progression-free survival, and objective response rate through the combination of pembrolizumab and Axitinib, as first-line treatment for mRCC, compared to sunitinib monotherapy. Therefore, immunotherapy-based combinations have resulted in complete responses at metastatic sites, though less frequently at renal lesions, rekindling interest in primary lesion surgery to achieve complete remission. The selection of candidates for delayed nephrectomy and its impact on prognosis remain subjects of debate. Additionally, surgery could be complicated by inflammation associated with immunotherapy [6,14].

Singla et al. [15] conducted a study assessing the pathological response and surgical outcomes in ten patients who underwent nephrectomy following ICI therapy, with a median postoperative follow-up of 180 days. The findings revealed a favorable pathological response to ICI therapy, with complete responses observed in both primary and metastatic lesions, enabling a high rate of negative surgical margins (100%) and immunotherapy discontinuation postoperatively in six patients. Importantly, the surgical procedures were generally well tolerated, with no significant surgical difficulties or major intraoperative complications reported.

Pignot et al. [6] examined the oncological outcomes and surgical safety of delayed nephrectomy after optimalICI therapy response to ICI in 30 patients, with a median follow-up of 19.5 months. The study demonstrated promising progression-free survival rates of 96.7% and 78.3%, and overall survival rates of 100% and 86.1% at one and two years, respectively, following delayed nephrectomy, highlighting the potential benefits of this approach in achieving good oncological outcomes. Nevertheless, they emphasized that more than 63% of surgeries encountered challenges, such as inflammatory changes, fibrosis, and technical difficulties due to desmoplastic reactions, stressing the importance of careful patient selection and surgical planning in this setting.

Shapiro et al. [14] presented a study involving 75 patients who underwent cytoreductive nephrectomy after combination ICI therapy, all of which were radical nephrectomies predominantly performed as open procedures. The study observed limited morbidity and concluded that the preoperative duration of ICI therapy did not significantly correlate with the odds of complications. While inflammatory reactions were present, this technical complexity did not significantly increase the complication rate. Approximately half of the study's patients did not resume systemic therapy following post-ICI cytoreductive nephrectomy. These findings underscore the potential advantages of delayed cytoreductive nephrectomy in mRCC management, particularly after a complete response to ICI therapy. The management of metastatic renal cell carcinoma, especially after a complete response to ICI therapy.

Similarly, Graafland et al.'s series of 21 delayed nephrectomies [16] reported a high rate of surgical difficulties due to fibrosis (71%), as mentioned in operative reports. Nevertheless, they did not experience an increased risk of major surgical complications (with four intraoperative complications and three postoperative minor complications).

Finally, Yip et al. [17] published the largest cohort of 113 patients undergoing surgery post-ICIs treatment. The findings indicated a low rate of major complications and favorable survival outcomes (82% OS and 47% PFS at 3 years), underscoring the feasibility and safety of these surgeries. However, factors such as Memorial Sloan Kettering Cancer Center risk factors and pathological T stage were identified as predictors of a higher complication rate, emphasizing the importance of individualized patient management and risk assessment in the perioperative setting.

All these data underline the importance of treating these patients in expert centers and early multidisciplinary tumor board reviews, ideally within a year, of patients showing a response at metastatic sites, regardless of the primary lesion's response.

European [18] and American [19] guidelines recommend partial nephrectomy whenever possible for patients treated at a localized stage. Numerous studies have shown that oncological control achieved with partial nephrectomy is equivalent to that radical nephrectomy, with no significant differences observed in terms of overall survival and recurrence-free survival [20,21]. Partial nephrectomy also better preserves renal parenchyma, limiting postoperative renal function deterioration and reducing the risk of cardiovascular events [22,23] even in the metastatic setting [24]. Moreover, the robot-assisted minimally invasive laparoscopic approach, that is now widely used and can potentially be combined with new technologies such as 3D model guidance, demonstrated a significant reduction of post-operative morbidity [20,25,26]. Finally, a prospective study demonstrated that kidney preservation positively impacts psychological well-being and quality of life [27]. These points, along with prolonged survival for good responders to ICIs, prompt consideration of nephron-sparing surgery, as for patients treated at a localized stage.

Little is known regarding post-ICI PN. The first case report, published in 2022 by Mebroukine et al. [7] highlighted the feasibility of the procedure without major intraoperative difficulties. Among the previously cited series of delayed nephrectomies following ICI, only 6 out of 250 were NSS. Our study outlines our experience with delayed PN following complete response to IO in patients with metastatic kidney cancer, contributing to the existing literature with a larger cohort. These data demonstrate that this treatment strategy can be both safe and beneficial in carefully selected patients. Despite challenging tumor characteristics, surgical outcomes have been favorable, with most cases conducted using minimally invasive approaches. The intraoperative complication rate was acceptable, with only two patients experiencing complications that were successfully managed during surgery. Postoperative complications were also satisfactory, with only one severe complication requiring additional intervention. Thus, the morbidity and the high rate of trifecta satisfaction are comparable to series of partial nephrectomies performed at a localized stage [26,28,29], demonstrating the feasibility and safety of the procedure in this context. Oncological outcomes align with those reported in the literature [6,17,30], suggesting sustained disease control in the majority of cases with prolonged treatment-free survival. Characteristics from our cohort indicate that patients tend to be young with elective indications for partial nephrectomy. This suggests that delayed nephron-sparing surgery rather than radical nephrectomy after IO should not be reserved for imperative situations but offered to selected patients for prolonged remission without treatment while preserving renal function.

To guide patient selection and implement cytoreductive partial nephrectomy in clinical practice, we offer insights grounded in our experience and supported by existing literature. Like the localized setting, the decision between partial nephrectomy and radical nephrectomy in metastatic scenarios should consider several factors, such as the tumor's size and complexity, assessed by the RENAL and PADUA scores, which predicts surgical complexity, and the volume of healthy kidney tissue to be preserved. Other considerations include the patient's overall comorbidity burden, frailty, age, and baseline renal function. In the metastatic context, assessing the initial tumor extent and response to treatment is critical for determining the surgical approach. For patients responding well to immune checkpoint inhibitors at metastatic sites, PN can effectively reduce tumor burden and facilitate systemic therapy discontinuation, provided that surgical morbidity is minimized. Robotic surgical approaches have been shown to significantly lower complication rates, expanding PN indications in metastatic settings. While acknowledging morbidity risks and potential delays in systemic therapy reintroduction, the primary aim remains to cease treatment post-surgery. Optimal decision-making between delayed PN and RN should involve a multidisciplinary review and thorough patient discussions about the risks and benefits, focusing on the duration of complete response rather than systemic therapy duration, with surgery considered after six to twelve months of sustained response.

It is noteworthy that a significant number of patients showed no pathological evidence of disease. In fact, 38.5% of patients had ypT0 stage disease, which is significantly higher than that in previous series. Among patients with residual disease in the primary tumor, only one exhibited a pT3a stage, suggesting the oncological safety of a conservative strategy [31]. This may be attributed to the selection of patients who exhibited complete responses at the metastatic sites and whose renal tumors were accessible to nephron-sparing surgery. No predictive factors for complete response were identified in our univariate analysis (including primary tumor's response to treatment), likely due to the small sample size. However, four of the five patients treated with a combination of nivolumab and ipilimumab were ypT0. Notably, one patient who presented with a ypT0 pathological analysis later developed pulmonary and bone metastatic recurrence 60 months after the delayed PN. This mismatch between radiological and pathological

response highlights the difficulty of evaluating RECIST radiological criteria using conventional imaging, and therefore the need to develop and evaluate new techniques.

This study offers insights from our initial experience in managing patients who demonstrated favorable ICI responses. Nonetheless, it is important to acknowledge several limitations in our study. The small sample size (13 patients) may not fully capture the diverse mRCC patient population, limiting the generalizability of our findings. The retrospective nature of our study may introduce selection bias, as included patients already showed a favorable response to immunotherapy. Additionally, while adequate for preliminary analyses, the follow-up period may not fully account for long-term outcomes beyond the observed timeframe. Variability in surgical techniques and institutional practices may also have contributed to outcome heterogeneity. Consequently, our findings require validation through larger, prospective studies. The ongoing PROBE [32] (NCT04510597) and Cyto-KIK [33] (NCT04322955) trials are poised to provide such data. The PROBE trial, a randomized controlled study, aims to compare overall survival in mRCC patients receiving ICI-based combination therapies, with or without subsequent cytoreductive nephrectomy. Meanwhile, the Cyto-KIK trial is evaluating whether preoperative administration of ICIs alongside Cabozantinib before cytoreductive nephrectomy can optimize surgical outcomes and reduce tumor burden. These trials are expected to clarify the potential of integrating ICIs with surgical intervention, ultimately guiding clinical practice in the management of metastatic RCC.

5. Conclusion

This first series of partial nephrectomies following systemic treatment with immune checkpoint inhibitors demonstrates the feasibility of this surgical approach, with acceptable morbidity rates and no major difficulties specifically attributable to the prior treatment. While the data suggest promising functional and oncological outcomes, including the potential for prolonged remission, these findings warrant further investigation. Ultimately, the results underscore the importance of early re-evaluation of metastatic patient cases in multidisciplinary tumor boards

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Gaëlle Margue: Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Clément Klein:** Writing – review & editing, Formal analysis, Data curation. **Bastien Parier:** Data curation. **Laurence Albiges:** Data curation. **Géraldine Pignot:** Data curation. **Gwenaëlle Gravis:** Data curation. **Pierre Bigot:** Data curation. **Nathalie Baize:** Data curation. **Alexandre Ingels:** Data curation. **Charlotte Joly:** Data curation. **François Audenet:** Data curation. **Yann Vano:** Data curation. **Thibaut Waeckel:** Data curation. **Romain Levard:** Data curation. **Philippe Barthelemy:** Data curation. **Damien Ambrosetti:** Data curation. **Virginie Verkarre:** Data curation. **Mokrane Yacoub:** Data curation. **Marine Gross-Goupil:** Writing – review & editing, Methodology, Data curation. **Jean-Christophe Bernhard:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Data availability

Requests for specific data will be considered by the UroCCR scientific committee following publication of the manuscript for researchers who provide a methodologically sound proposal.

Approval of the research protocol by an Institutional Reviewer Board

UroCCR (NCT03293563) has received the approval of the Committee for the Protection of Individuals ("Comité de Protection des Personnes Sud-Ouest et Outre-mer III"; decision number DC 2012/108). It is IRB-approved and obtained the CNIL authorization number DR-2013-206

Informed Consent

All patients received oral and written information about the objectives and methodology of the project and written consent was obtained.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209–49.

[2] Turner RM, Morgan TM, Jacobs BL. Epidemiology of the small renal mass and the treatment disconnect phenomenon. Urol Clin North Am 2017;44(2):147–54.

[3] Padala SA, Barsouk A, Thandra KC, Saginala K, Mohammed A, Vakiti A, et al. Epidemiology of renal cell carcinoma. World J Oncol 2020;11(3):79–87.

[4] Demasure S, Spriet I, Debruyne PR, Laenen A, Wynendaele W, Baldewijns M, et al. Overall survival improvement in patients with metastatic clear-cell renal cell carcinoma between 2000 and 2020: a retrospective cohort study. Acta Oncologica 2022;61(1):22–9.

[5] Méjean A, Ravaud A, Thezenas S, Colas S, Beauval JB, Bensalah K, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 2018;379(5):417–27.

[6] Pignot G, Thiery-Vuillemin A, Albigès L, Walz J, Lang H, Balssa L, et al. Oncological outcomes of delayed nephrectomy after optimal

response to immune checkpoint inhibitors for metastatic renal cell carcinoma. Eur Urol Oncol 2022;5(5):577–84.
[7] Mebroukine S, Yacoub M, Michiels C, Ravaud A, Gross-Goupil M, Bernhard JC. Feasibility of robotic-assisted partial nephrectomy for complete remission of metastatic renal cell carcinoma after long exposure to immune checkpoint inhibitors (UroCCR-106). J Surg Case Rep 2022;2022(12):rjac560.
[8] Hung AJ, Cai J, Simmons MN, Gill IS. Trifecta" in partial nephrectomy. J Urol. 2013;189(1):36–42.
[9] Bigot P, Barthelemy P, Boissier R, Khene ZE, Pettenati C, Bernhard JC, et al. French AFU cancer committee guidelines - update 2022-2024: management of kidney cancer. Progrès en Urologie 2022;32 (15):1195–274.
[10] Heng DYC, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009;27(34):5794–9.
[11] Méjean A, Ravaud A, Thezenas S, Chevreau C, Bensalah K, Geoffrois L, et al. Sunitinib alone or after nephrectomy for patients with metastatic renal cell carcinoma: is there still a role for cytoreductive nephrectomy? Eur Urol 2021;80(4):417–24.
[12] Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378(14):1277–90.
[13] Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380(12):1116–27.
[14] Shapiro DD, Karam JA, Zemp L, Master VA, Sexton WJ, Ghasemzadeh A, et al. Cytoreductive nephrectomy following immune checkpoint inhibitor therapy is safe and facilitates treatment-free intervals. Eur Urol Open Sci 2023;50:43–6.
[15] Singla N, Elias R, Ghandour RA, Freifeld Y, Bowman IA, Rapoport L, et al. Pathologic response and surgical outcomes in patients undergoing nephrectomy following receipt of immune checkpoint inhibitors for renal cell carcinoma. Urol Oncol: Sem Org Invest 2019;37 (12):924–31.
[16] Graafland NM, Szabados B, Tanabalan C, Kuusk T, Mumtaz F, Barod R, et al. Surgical safety of deferred cytoreductive nephrectomy following pretreatment with immune checkpoint inhibitor−based dual combination therapy. Eur Urol Oncol 2022;5(3):373–4.
[17] Yip W, Ghoreifi A, Gerald T, Lee R, Howard J, Asghar A, et al. Perioperative complications and oncologic outcomes of nephrectomy following immune checkpoint inhibitor therapy: a multicenter collaborative study. Eur Urol Oncol 2023;6(6):604–10.
[18] Ljungberg B, Albiges L, Abu-Ghanem Y, Bedke J, Capitanio U, Dabestani S, et al. European association of urology guidelines on renal cell carcinoma: the 2022 update. European Urology 2022;82 (4):399–410.
[19] Campbell SC, Clark PE, Chang SS, Karam JA, Souter L, Uzzo RG. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA guideline: part I. J Urol 2021;206(2):199–208.
[20] Ingels A, Bensalah K, Beauval JB, Paparel P, Rouprêt M, Lang H, et al. Comparison of open and robotic-assisted partial nephrectomy approaches using multicentric data (UroCCR-47 study). Sci Rep 2022;12(1):18981.
[21] Kunath F, Schmidt S, Krabbe LM, Miernik A, Dahm P, Cleves A, et al. Partial nephrectomy versus radical nephrectomy for clinical localised renal masses. Cochrane Database Syst Rev 2017;5(5): CD012045.
[22] Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. Eur Urol 2014;65(2):372–7.
[23] Miller DC, Schonlau M, Litwin MS, Lai J, Saigal CS. Urologic Diseases in America Project. Renal and cardiovascular morbidity after partial or radical nephrectomy. Cancer 2008;112(3):511–20.
[24] Babaian KN, Merrill MM, Matin S, Tamboli P, Tannir NM, Jonasch E, et al. Partial nephrectomy in the setting of metastatic renal cell carcinoma. J Urol 2014;192(1):36–42.
[25] Michiels C, Khene ZE, Prudhomme T, Boulenger de Hauteclocque A, Cornelis FH, Percot M, et al. 3D-Image guided robotic-assisted partial nephrectomy: a multi-institutional propensity score-matched analysis (UroCCR study 51). World J Urol 2023;41(2):303–13.
[26] Margue G, Ingels A, Bensalah K, Doumerc N, Vaessen C, Roupret M, et al. Late complications and 5 years outcomes of robotic partial nephrectomy in France: prospective assessment in the French Kidney Cancer Research Network (UroCCR 10). World J Urol 2023;41 (8):2281–8.
[27] Gratzke C, Seitz M, Bayrle F, Schlenker B, Bastian PJ, Haseke N, et al. Quality of life and perioperative outcomes after retroperitoneoscopic radical nephrectomy (RN), open RN and nephron-sparing surgery in patients with renal cell carcinoma. BJU Int 2009;104(4):470–5.
[28] Simhan J, Smaldone MC, Tsai KJ, Canter DJ, Li T, Kutikov A, et al. Objective measures of renal mass anatomic complexity predict rates of major complications following partial nephrectomy. Eur Urol 2011;60(4):724–30.
[29] Klein C, Margue G, Champy C, Parier B, Waeckel T, Bensalah K, et al. Can simplified PADUA renal (SPARE) Nephrometry scoring system help predict renal function outcomes after robot-assisted partial nephrectomy? (UroCCR study 93). Minerva Urol Nephrol 2023;75(5):569–76.
[30] Gunenc D, Issa W, Gerald T, Zhou Q, Zhang S, Ibezue IC, et al. Pathological response and outcomes in patients with metastatic renal cell carcinoma (mRCC) receiving immunotherapy-based therapies and undergoing deferred cytoreductive nephrectomy (CN). Clin Genitour Cancer 2024;22(5):102177. https://doi.org/10.1016/j.clgc.2024.102177.
[31] Boulenger de Hauteclocque A, Ferrer L, Ambrosetti D, Ricard S, Bigot P, Bensalah K, et al. Machine-learning approach for prediction of pT3a upstaging and outcomes of localized renal cell carcinoma (UroCCR-15). BJU Int 2023;132(2):160–9.
[32] Bell H, Cotta BH, Salami SS, Kim H, Vaishampayan U. PROBE'ing the Role of Cytoreductive Nephrectomy in Advanced Renal Cancer. Kidney Cancer J 2022;6(1):3–9.
[33] Isali I, Braun A, Bukavina L, Psutka SP. Role of cytoreductive surgery in the era of immunotherapy. Curr Opin Urol 2022;32(6):618–26.