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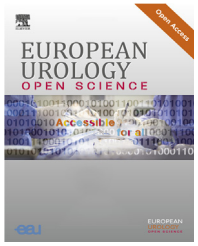

European Association of Urology

Brief Correspondence

Cytoreductive Nephrectomy Following Immune Checkpoint Inhibitor Therapy Is Safe and Facilitates Treatment-free Intervals

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Abstract

Patients with metastatic renal cell cancer (mRCC) who respond to upfront immune checkpoint inhibitor (ICI) combination therapies may be treated with cytoreductive nephrectomy (CN) to remove radiographically viable primary tumors. Early data for post-ICI CN suggested that ICI therapies induce desmoplastic reactions in some patients, increasing the risk of surgical complications and perioperative mortality. We evaluated perioperative outcomes for 75 consecutive patients treated with post-ICI CN at four institutions from 2017 to 2022. Our cohort of 75 patients had minimal or no residual metastatic disease but radiographically enhancing primary tumors after ICI and were treated with CN. Intraoperative complications were identified in 3/75 patients (4%) and 90-d postoperative complications in 19/75 (25%), including two patients (3%) with high-grade (Clavien ≥III) complications. One patient was readmitted within 30 d. No patients died within 90 d after surgery. Viable tumor was present in all but one specimen. Approximately half of the patients (36/75, 48%) remained off systemic therapy at last follow-up. These data suggest that CN following ICI therapy is safe and associated with low rates of major postoperative complications in appropriately selected patients at experienced centers. Post-ICI CN may facilitate observation without additional systemic therapy in patients without significant residual metastatic disease.

Patient summary: Current first-line treatment for patients with kidney cancer that has spread to other sites (metastatic cancer) is immunotherapy. For cases in which metastatic sites respond to this therapy but primary tumor is still detected in the kidney, surgical treatment of the tumor is feasible and has a low rate of complications, and may delay the need for further chemotherapy.

The treatment of metastatic renal cell carcinoma (mRCC) has changed dramatically over the past two decades. Combination treatments that include immune checkpoint inhibitors (ICIs) have emerged as first-line therapy for mRCC [1]. Current guidelines recommend considering upfront systemic treatments including ICI therapy for most patients with mRCC [2] because of significantly higher response rates to ICI treatment combinations. After a favorable response to upfront ICI therapy in metastatic sites, cytoreductive nephrectomy (CN) may be recommended, espe-

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cially for large and radiographically viable primary tumors. However, surgical outcomes have only been reported for a limited number of post-ICI CN cases, and data on how ICI therapy affects surgical complexity and complication rates for CN are conflicting [3–5]. The aim of this study was to evaluate perioperative outcomes for patients with mRCC who were treated with CN after ICI therapy at four high-volume institutions.

After institutional compliance review, data for consecutive patients with mRCC treated with upfront ICI followed by CN at four tertiary hospitals from 2017 to 2022 were evaluated. Decisions on systemic therapy and CN were made by institutional multidisciplinary teams. Patients were considered for post-ICI CN if there was a complete or near-complete response to ICI therapy at metastatic sites and the primary tumor was radiographically viable (enhancing), enlarging, or symptomatic. All patients in this series had a primary tumor as the largest site of residual disease after receiving ICI therapy. Outcomes analyzed included intraoperative complications, 90-d postoperative complications by Clavien-Dindo grade [6], length of hospitalization, 30-d hospital readmission, mortality within 90 d, and initiation of systemic therapy after CN.

We identified 75 patients with mRCC who were treated with ICI combination therapy followed by CN (Table 1). The median age was 63 yr (interquartile range [IQR] 56–68) and 24/75 of the patients (32%) were female. There were few comorbidities, with a median Charlson comorbidity index of 0 (IQR 0–1), and 87% had an Eastern Cooperative Oncology Group performance status of 0. Most patients were classified as having International mRCC Database Consortium intermediate risk (71%) with the clear cell RCC subtype (93%); 77% had T stage ≥pT3 and the median pathological tumor diameter was 8.4 cm (IQR 5.5–10.6). A total of 68 (90%) of patients received nivolumab/ipilimumab and seven (10%) received pembrolizumab/axitinib as preoperative therapy. The median time between systemic therapy initiation and CN was 97 d (IQR 56–259 days) and the median number of ICI cycles was 6 (IQR 4–11).

An open approach was used for CN in 53/75 patients (71%); 29/75 (39%) patients had tumor thrombus, including ten (13%) with upper-level inferior vena cava thrombus. The decision to perform open or minimally invasive CN was not standardized, but, in general, an open approach was favored for larger tumors, the presence of tumor thrombus, concern for locally advanced disease invading surrounding structures, a need to perform concurrent metastasectomy, or a need to perform regional lymph node dissection. The median operative time was 177 min (IQR 112–239) and median blood loss was 195 ml (Table 1). Three patients (4%) had an intraoperative complication: one cardiac arrhythmia requiring pharmaceutical intervention, one splenic injury requiring splenectomy, and one diaphragmatic injury requiring repair. Postoperatively, the median length of stay was 4 d (IQR 2–6 d). The 90-d overall complication rate was 19/75 (25%). Ten patients (13%) required a blood transfusion at any point postoperatively up to 90 d. Two patients (3%) had a high-grade (Clavien-Dindo ≥III) complication: one aspiration pneumonitis requiring intubation (Clavien IVa) and one upper gastrointestinal tract bleed requiring endoscopic intervention (Clavien IIIa). One patient was readmitted within 30 d; no mortalities occurred within 90 d (Table 1). The preoperative ICI duration (number of days receiving treatment) was not significantly associated with the odds of having a complication (odds ratio 1.00, 95% confidence interval 0.99–1.01; p = 0.7). Among patients who planned to restart ICI therapy after CN, the median time to restarting ICI therapy was 36 d (IQR 23–72 d) following surgery. The primary indications for restarting ICI therapy after surgery were a maintenance ICI regimen or disease progression. At last follow-up, approximately half of the patients (34/75, 48%) had not received additional systemic therapy after CN (Fig. 1).

Table 1 – Clinical and pathological characteristics of the study population (n = 75)

Parameter	Result
Median age, yr (interquartile range)	63 (56–68)
Female, *n* (%)	24 (32)
Median body mass index, kg/m^2 (interquartile range)	27.7 (24.4–32.2)
Median Charlson comorbidity index (interquartile range)	0 (0–1)
Eastern Cooperative Oncology Group performance status score ≥1, *n* (%)	10 (13)
Smoking history, *n* (%)	34 (45)
pT stage, *n* (%)	
ypT0	1 (1)
ypT1–T2	16 (21)
ypT3–T4	58 (77)
pN1 stage, *n* (%)	6 (8)
Primary tumor histology, *n* (%)	
Clear cell	69 (92)
Papillary	5 (7)
Unknown (complete response of primary tumor)	1 (1)
Tumor grade 3–4, *n* (%)	63 (84)
Median maximum pathological tumor size, cm (interquartile range)	8.4 (5.5–10.6)
Sarcomatoid dedifferentiation, *n* (%)	11 (15)
IMDC risk class, *n* (%)	
Favorable	6 (8)
Intermediate	53 (71)
1 risk factor	27 (36)
2 risk factors	26 (35)
Poor	9 (12)
Unknown	7 (9)
Nephrectomy approach, *n* (%)	
Open	54 (72)
Laparoscopic	20 (27)
Robot-assisted	1 (1)
Median operative time, min (interquartile range)	177 (112–239)
Median estimated blood loss, ml (interquartile range)	195 (100–400)
Thrombus, *n* (%)	29 (39)
Level 1 (renal vein)	19 (25)
Level 2 (infrahepatic inferior vena cava)	7 (9)
Level 3 (hepatic inferior vena cava)	2 (3)
Level 4 (suprahepatic/atrium)	1 (1)
Lymph node dissection, *n* (%)	38 (51)
Intraoperative complications, *n* (%)	3 (4)
90-d postoperative complications, *n* (%)	19 (25)
Clavien grade, *n* (%)	
I	8 (11)
II	9 (12)
IIIa (gastrointestinal bleed requiring upper endoscopy)	1 (1)
IIIb	0
IVa (aspiration requiring intubation)	1 (1)
IVb	0
V	0
Blood transfusion, *n* (%)	10 (13)
Median length of stay, d (interquartile range)	4 (2–6)
30-d readmission, *n* (%)	1 (1)

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.

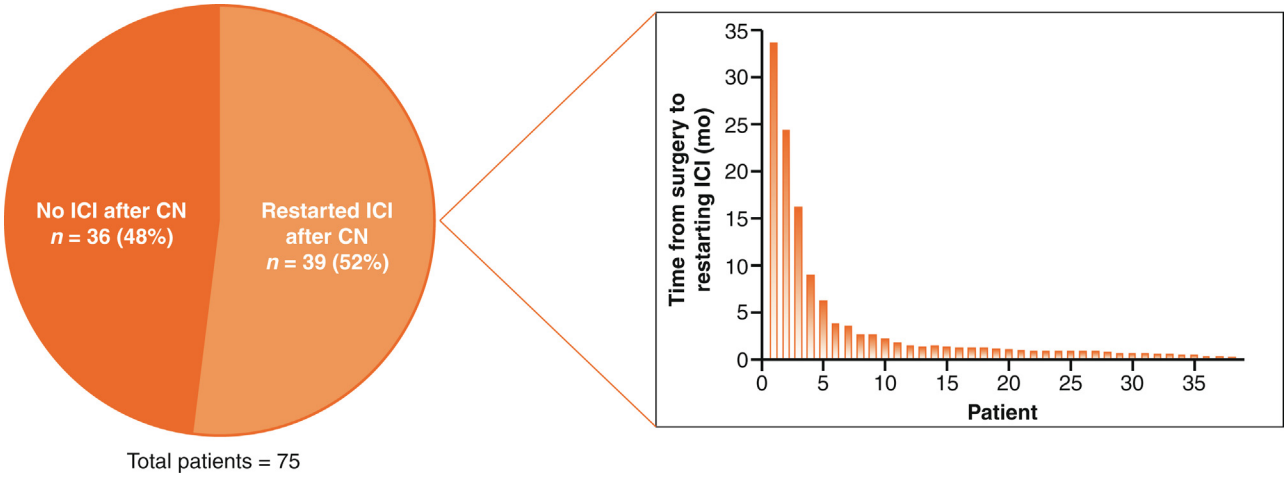

Fig. 1 – Proportion of patients who did (39/75, 52%) and did not restart (36/75, 48%) immune checkpoint inhibitor therapy (ICI) after cytoreductive nephrectomy (CN) at last follow-up. The bar chart shows the time from CN surgery to restarting ICI therapy for the 39 patients in the former group.

For patients who respond well to ICI at metastatic sites, CN has two potential benefits: (1) removal of large tumors that might be a cause of current or future symptoms; and (2) removal of the remaining site of disease to allow discontinuation of systemic therapy. However, in order for these potential benefits to become tangible, surgery must be associated with a minimal risk of morbidity. A systematic review by Bhindi et al [7] revealed that for patients undergoing deferred CN during the targeted therapy era, the rate of perioperative mortality was 1–5% and the incidence of complications was 22–27% for any-grade complications and 3–25% for high-grade complications. Approximately 40% of patients in the current study had tumor thrombus, which is associated with higher rates of perioperative complications and death. Importantly, the current study had no mortalities reported at 90 d, a total complication rate of 25%, and a major complication rate of 3%, which compares favorably to prior studies of upfront CN, CN following targeted therapies, and post-ICI CN [3–5,8,9]. Improvements in surgical and perioperative techniques in recent years may have contributed to these favorable outcomes. However, it is also likely that a subset of the healthiest patients were selected for surgery after ICI treatment, leading to observational bias. We did not observe that the number of times a patient received ICI therapy was associated a higher risk of postoperative complications. Previous reports have described a significant inflammatory reaction related to ICI therapy, adding to the surgical complexity [4]. We have also encountered this inflammatory reaction in many patients undergoing CN after ICI, which can distort the normal surgical planes and add to surgical complexity. In our series, however, this technical complexity did not result in a significant increase in the complication rate or blood loss in comparison to historical CN series, which may be because the surgeries were performed at high-volume CN centers. Although the optimal timing for CN has not been proven in high-quality studies, these data provide continued evidence of the safety of deferred CN in patients who respond to upfront systemic therapy. The decision on when to perform upfront CN versus deferred CN after initial ICI therapy should be based on multiple factors, including a multidisciplinary review and a detailed discussion with the patient about the risks and benefits of each approach. Post-ICI CN is not appropriate for all patients, and patient selection for this strategy is critical to reduce perioperative morbidity and improve oncological outcomes.

All but one patient had viable tumor on post-ICI pathology, consistent with prior reports [3,5]. This observation is not surprising, as patients with large primary tumors that appeared radiographically viable were selected for surgery. The impact of post-ICI CN on survival outcomes remains unknown without high-quality data for CN in combination with modern systemic therapies. However, there is a rationale for consolidative CN to remove viable tumors until systemic therapies reliably produce complete responses in all sites of disease. In a subset of patients treated with ICI, systemic therapy may be discontinued, allowing patients to have intervals free of systemic treatment [10]. For patients with mRCC treated with systemic therapy and their primary tumor in place who have a complete response to treatment, post-ICI CN frequently renders patients radiographically cancer free and facilitates discontinuation of systemic therapy. In the current study, approximately half of the patients did not resume systemic therapy after post-ICI CN, which theoretically reduces the risk of systemic therapy–related adverse events and the cost of treatment. Although these data are promising, it is unclear how durable a complete response to ICI therapy will be after discontinuing therapy. The impact of post-ICI CN should be investigated in a prospective study to better define the potential benefit of surgery in this setting.

Author contributions: Daniel D. Shapiro had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Shapiro, Karam, Spiess, Abel.
Acquisition of data: Shapiro, Karam, Zemp, Master, Sexton, Ghasemzadeh, Schmeusser, Davaro, Patil, Surena Matin, Spiess, Abel.
Analysis and interpretation of data: Shapiro, Abel.

Drafting of the manuscript: Shapiro, Abel.
Critical revision of the manuscript for important intellectual content: Shapiro, Karam, Zemp, Master, Sexton, Ghasemzadeh, Schmeusser, Davaro, Patil, Surena Matin, Spiess, Abel.
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