Rates and Predictors of Perioperative Complications in Cytoreductive Nephrectomy: Analysis of the Registry for Metastatic Renal Cell Carcinoma

Eduard Roussel[a], *Riccardo Campi*[b,c], *Alessandro Larcher*[d], *Annelies Verbiest*[e], *Alessandro Antonelli*[f], *Carlotta Palumbo*[f], *Ithaar Derweesh*[g], *Fady Ghali*[g], *Aaron Bradshaw*[g], *Margaret F. Meagher*[g], *Matthias Heck*[h], *Thomas Amiel*[h], *Maximilian C. Kriegmair*[i], *Jose Rubio*[j], *Mireia Musquera*[k], *Maurizio D'Anna*[k], *Riccardo Autorino*[l], *Georgi Guruli*[l], *Alessandro Veccia*[l], *Estefania Linares-Espinos*[m], *Siska Van Bruwaene*[n], *Vital Hevia*[o], *Francesco Porpiglia*[p], *Enrico Checcucci*[p], *Andrea Minervini*[b,c], *Andrea Mari*[b,c], *Nicola Pavan*[q], *Francesco Claps*[p], *Michele Marchioni*[r,s], *Umberto Capitanio*[d], *Benoit Beuselinck*[e], *Maria C. Mir*[j,†,*], *Maarten Albersen*[a,†],

on behalf of the Young Academic Urologists Renal Cell Carcinoma Working Group

[a] *Department of Urology, University Hospitals Leuven, Leuven, Belgium;* [b] *Department of Urology, University of Florence, Careggi Hospital, Florence, Italy;* [c] *Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy;* [d] *Department of Urology, San Raffaele Scientific Institute, Milan, Italy;* [e] *Department of Medical Oncology, University Hospitals Leuven, Leuven, Belgium;* [f] *Department of Urology, Spedali Civili Hospital, University of Brescia, Brescia, Italy;* [g] *Department of Urology, University of California San Diego Cancer Center, Lousiana Jolla, CA, USA;* [h] *Department of Urology, Technical University of Munich, Munich, Germany;* [i] *Department of Urology, University Medical Centre Mannheim, Mannheim, Germany;* [j] *Department of Urology, Fundacion Instituto Valenciano Oncologia, Valencia, Spain;* [k] *Department of Urology, Hospital Clinic, Barcelona, Spain;* [l] *Department of Urology, VCU Medical Center, Richmond, VA, USA;* [m] *Department of Urology, Hospital La Paz, Madrid, Spain;* [n] *Department of Urology, AZ Groeninge, Kortrijk, Belgium;* [o] *Department of Urology, Hospital Ramon y Cajal, Madrid, Spain;* [p] *Department of Urology, University of Turin, San Luigi Gonzaga Hospital, Turin, Italy;* [q] *Urology Clinic, Department of Medical, Surgical and Health Science, University of Trieste, Trieste, Italy;* [r] *Department of Medical, Oral and Biotechnological Sciences, Laboratory of Biostatistics, "G. d'Annunzio" University of Chieti, Chieti, Italy;* [s] *Department of Urology, SS Annunziata Hospital, "G. D'Annunzio" University of Chieti, Chieti, Italy*

Article info

Article history:
Accepted April 22, 2020
Associate Editor:
Alberto Briganti

Keywords:
Metastatic renal cell carcinoma
Cytoreductive nephrectomy
Surgery
Complications
Morbidity
Mortality

Abstract

Background: Cytoreductive nephrectomy (CN) plays an important role in the treatment of a subgroup of metastatic renal cell carcinoma (mRCC) patients.
Objective: We aimed to evaluate morbidity associated with this procedure and identify potential predictors thereof to aid patient selection for this procedure and potentially improve patient outcomes.
Design, setting, and participants: Data from 736 mRCC patients undergoing CN at 14 institutions were retrospectively recorded in the Registry for Metastatic RCC (REMARCC).
Outcome measurements and statistical analysis: Logistic regression analysis was used to identify predictors for intraoperative, any-grade (AGCs), low-grade, and high-grade (HGCs) postoperative complications (according to the Clavien-Dindo classification) as well as 30-d readmission rates.

† These authors contributed equally to this work.
* Corresponding author. Department of Urology, Fundaction Instituto Valenciano Oncologia, Valencia, Spain.
E-mail address: mirmare@yahoo.es (M.C. Mir).

Results and limitations: Intraoperative complications were observed in 69 patients (10.9%). Thrombectomy (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.08–1.75, $p = 0.009$) and adjacent organ removal (OR 2.7, 95% CI 1.38–5.30) were significant predictors of intraoperative complications at multivariable analysis. Two hundred seventeen patients (29.5%) encountered AGCs, while 45 (6.1%) encountered an HGC, of whom 10 (1.4%) died. Twenty-four (3.3%) patients had multiple postoperative complications. Estimated blood loss (EBL; OR 1.49, 95% CI 1.08–2.05, $p = 0.01$) was a significant predictor of AGCs at multivariable analysis. CN case load (OR 0.13, 95% CI 0.03–0.59, $p = 0.009$) and EBL (OR 2.93, 95% CI 1.20–7.15, $p = 0.02$) were significant predictors solely for HGCs at multivariable analysis. Forty-one patients (11.5%) were readmitted within 30 d of surgery. No significant predictors were identified. Results were confirmed in a subanalysis focusing solely on patients treated in the contemporary targeted therapy era.

Conclusions: Morbidity associated with CN is not negligible. Predictors of high-grade postoperative morbidity are predominantly indicators of complex surgery. EBL is a strong predictor of postoperative complications. CN case load correlates with lower high-grade morbidity and highlights the benefit of centralization of complex surgery. However, risks and benefits should be balanced when considering CN in mRCC patients.

Patient summary: We studied patients with metastatic renal cancer to evaluate the outcomes associated with the surgical removal of the primary kidney tumor. We found that this procedure is often complex and adverse events are not uncommon. High intraoperative blood loss and a small number of cases performed at the treating center are associated with a higher rate of postoperative complications.

1. Introduction

Renal cell carcinoma (RCC) is the 14th most common malignancy in the world, accounting for 2% of all cancer diagnoses and cancer deaths. Overall, up to one-third of patients present with metastatic disease at diagnosis and another third will eventually develop metastases after initial treatment with curative intent [1,2].

Cytoreductive nephrectomy (CN) was established as the standard of care prior to the advent of vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) based on two prospective randomized controlled trials [3,4]. Furthermore, several retrospective, large studies during the VEGFR-TKI era fostered the continued use of CN [5]. Recently, the role of CN has been challenged by the CARMENA trial, showing no benefit of upfront CN prior to medical therapy (sunitinib) in patients with poor/intermediate International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk categories [6].

Nonetheless, there is a general consensus that certain selected subgroups of patients with low-volume, single-site metastases and few adverse IMDC criteria would still benefit from the continued use of upfront CN [7,8]. Additionally, the SURTIME trial concluded that deferred CN after VEGFR-TKI treatment appears to be safe [9]. Moreover, a considerable number of patients included in the sunitinib-only arm of the CARMENA trial (40/226, 17.7%) underwent secondary CN [6]. Current European Association of Urology guidelines recommend deferred CN as consolidative therapy in IMDC intermediate/poor-risk patients with sustained response on systemic therapy and good performance status [8,10]. The role of CN is even more controversial since the advent of immunotherapy, which has become the new backbone of systemic treatment in metastatic RCC (mRCC) patients. Ongoing trials will elucidate the optimal approach in future endeavors [11].

Notably, CN implies a certain risk of mortality and is associated with increased morbidity as per complication rates compared with non-CN [12]. However, most studies focus solely on survival outcomes. Thus, scarce data are available regarding morbidity of this often extensive surgery. Postoperative morbidity is of particular interest in the metastatic setting since significant postoperative morbidity might preclude or delay the use of subsequent systemic therapies. Therefore, our aim was to evaluate the morbidity associated with this procedure and elucidate predictive factors for complications. Altogether, this would facilitate decision making, and patient selection could be optimized.

2. Patients and methods

2.1. Patient population

Institutional review board approval and data-sharing agreements were obtained at 14 North American and European institutions (Registry for Metastatic RCC—REMARCC project). Clinical records of patients undergoing nephrectomy for mRCC between 1980 and 2019 were recorded by each institution and collected in a purpose-built database. The primary endpoint of the study was the assessment of intra- and postoperative

complications as well as 30-d readmission rates. Surgical postoperative complications within 90 d were registered using the Clavien-Dindo classification (CDC); CDC3–5 was regarded a high-grade complication (HGC) [13]. Intraoperative complications were registered using the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0).

2.2. Data collection

Parameters related to demographics, clinical staging, surgery, histopathology, survival outcomes, and perioperative complications were analyzed for the entire cohort. We analyzed the following patient-specific characteristics: age, gender, European Cooperative Oncology Group performance status, Karnofsky performance score, IMDC prognostic criteria, preoperative creatinine, preoperative C-reactive protein, site of metastases, number of metastases, cT stage, and cN stage. We also analyzed the following surgery-specific characteristics: estimated intraoperative blood loss (EBL), resection of adjacent organs other than the adrenal gland, surgical approach (open vs minimally invasive), thrombectomy (according to level of extension), and CN case volume per center. Histopathology assessment entailed tumor classification, surgical margin status, lymph nodal status, and TNM staging according to the 2010 American Joint Committee on Cancer classification. Considering the timespan of the inclusion period, we subsequently performed a subanalysis on the patient cohort that underwent CN in the targeted therapy era (2006 and onward) and included the year of surgery as a parameter in the analysis.

2.3. Statistical analyses

In descriptive analyses, for continuous variables with non-normal distribution, data were presented as median and interquartile range (IQR). Categorical variables were compared using the chi-square test. Continuous variables were compared using the Mann-Whitney *U* test. Univariable logistic regression was used to assess the predictive factors for intra- and postoperative complications, as well as 30-d readmission rates. Significant factors were subsequently included in a multivariable logistic regression model, of which the area under the receiver operating characteristic curve (AUC) was used to evaluate the model. The assumption of linearity in these models was tested using quadratic terms. A p value of <0.05 was considered statistically significant. All analyses were performed using R (version 3.6.2).

3. Results

3.1. Baseline characteristics

A total of 736 cases (716 [97.3%] radical nephrectomy and 20 [2.7%] partial nephrectomy) were included in the analysis. Median follow-up was 16.5 mo (IQR 5.6–38.8). Only two out of 736 (0.3%) patients received presurgical systemic therapy. The baseline characteristics for our cohort are shown in Table 1. Baseline characteristics broken down by CN case load (high vs low) are shown in Supplementary Table S1.

Table 1 – Baseline characteristics of total CN cohort.

Patient characteristics	
Number of patients	*N* = 736
Age (yr) [a]	63 (55–70)
Gender, no. (%)	
Male	550 (74.7)
Female	186 (25.3)
ECOG PS, no. (%)	
0	187 (42.1)
1	125 (28.5)
2	90 (20.4)
3	37 (8.4)
4	3 (0.6)
Karnofsky performance score, no. (%)	
≥90	200 (65.6)
<90	105 (34.4)
IMDC risk categories, no. (%)	
Good	20 (4.2)
Intermediate	380 (80.5)
Poor	72 (15.3)
Metastatic volume, no. (%)	
Low (≤3 metastases)	236 (68.8)
High (>3 metastases)	107 (31.2)
Site of metastases, no. (%)	
Lung	434 (59.0)
Bone	206 (28.0)
Liver	82 (11.1)
Brain	43 (5.8)
Other	103 (14.0)
Clinical tumor stage, no. (%)	
cT1–2	268 (37.6)
cT3–4	445 (62.4)
cN0	379 (53.2)
cN1	282 (39.6)
cN2	51 (7.2)
Pathological tumor stage, no. (%)	
pT1–2	163 (22.9)
pT3–4	548 (77.1)
pN0/Nx	306 (42.8)
pN1	150 (21.0)
pN2	259 (36.2)
Primary tumor size (cm) [a]	9 (6.5–11)
Sarcomatoid features, no. (%)	122 (19.4)
Positive surgical margins, no. (%)	65 (10.3)
Histology, no. (%)	
Clear cell	531 (83.2)
Papillary	54 (8.5)
Chromophobe	10 (1.6)
Other	43 (6.7)
Approach, no. (%)	
Open	545 (77.1)
Minimally invasive	162 (22.9)
Estimated blood loss (ml) [a]	375 (112–800)
Thrombectomy, no. (%)	110 (17.3)
Adjacent organ removal, no. (%)	79 (12.5)
Length of stay (d) [a]	8 (6–11)

CN = cytoreductive nephrectomy; ECOG PS = Eastern Cooperative Oncology Group performance status, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.
[a] Data are shown as median (interquartile range).

3.2. Intraoperative complications: descriptive features and predictors

Intraoperative complications were observed in 69 patients (11%). Bleeding (25 cases, 36%; CTCAE grade not available), spleen laceration (13 cases, 19%; CTCAE grade 3), and vascular injury (11 cases, 16%; CTCAE grade 1) were the most frequently described, followed by diaphragm/pleural laceration (six cases, 9%; CTCAE grade 1), liver injury (five cases, 8%; CTCAE grade 1),and bowel injury (four cases, 6%; CTCAE grade 1).

Thrombectomy (odds ratio [OR] 1.38, 95% confidence interval [CI] 1.08–1.75, p = 0.009) and adjacent organ

Table 2 – Multivariable analysis of predictors of surgical morbidity and mortality: any-grade, low-grade, and high-grade postoperative complications; postoperative death due to a complication; and intraoperative complication.

Variables		Outcomes for perioperative complications: OR (95% CI)				
		AGC (CDC1–5)	LGC (CDC1–2)	HGC (CDC3-5)	Death (CDC5)	Intraoperative complication
Patient specific	Karnofsky performance score	–	–	0.97 (0.91–1.03)	–	–
	cT stage (cT1–2 vs cT3–4)	1.73 (0.86–3.51)	–	1.65 (0.33–12.38)	0.53 (0.048–12.43)	–
	cN stage (cN0 vs cN1–2)	–	–	–	–	1.44 (0.88–2.36)
	Number of metastases	–	0.99 (0.93–1.07)	–	–	–
Surgery specific	EBL (quantiles)	**1.49 (1.08–2.05)** [a]	**1.71 (1.15–2.55)** [a]	**2.93 (1.20–7.15)** [a]	6.23 (0.83–46.77)	–
	Adjacent organ removal	–	–	1.77 (0.36–8.62)	–	**2.71 (1.38–5.30)** [a]
	Thrombectomy	1.14 (0.76–1.71)	1.01 (0.57–1.78)	0.91 (0.41–1.99)	1.32 (0.62–2.81)	**1.38 (1.08–1.75)** [a]
	Positive surgical margin	–	–	–	2.13 (0.27–16.76)	–
	Surgical approach (MIS vs open)	0.59 (0.26–1.33)	0.96 (0.35–2.61)	–	–	–
	CN case load (quantiles)	–	–	**0.13 (0.03–0.59)** [a]	–	1.07 (0.49–2.26)

AGC = any-grade postoperative complication; CDC = Clavien-Dindo classification; CI = Confidence interval; CN = cytoreductive nephrectomy; EBL = estimated blood loss; HGC = high-grade postoperative complication; LGC = low-grade postoperative complication; MIS = minimally invasive surgery; OR = odds ratio; – = nonsignificant on univariable analysis.

[b] EBL is a complication in itself and so is not taken into account for the prediction of intraoperative complications.

[a] $p < 0.05$.

removal (OR 2.71, 95% CI 1.38–5.30, $p = 0.004$) remained significant predictors at multivariable analysis (Table 2). The AUC for this multivariable model was 0.66. Univariable analyses are shown in Supplementary Table S2.

3.3. *Postoperative complications: descriptive features*

Two hundred seventeen patients (29.5%) encountered any grade of postoperative complication (AGC), while 45 (6.1%) encountered an HGC, of whom 10 (1.4%) died (CDC5). Twenty-four patients (3.3%) had multiple postoperative complications. The median length of hospital stay was 8 d, 10 vs 7 d for the group that encountered AGCs versus the group that did not, respectively. The median EBL was 400 ml.

The nature of complications was vascular/lymphatic in 67 (30%), infectious in 42 (19%), cardiopulmonary in 39 (17%), gastrointestinal in 33 (15%), urological in 23 (10%), wound related in 13 (6%), and neurological in seven (3%) cases. Details per location are shown in Table 3.

3.4. *Predictors of postoperative complications*

At multivariable logistic regression analysis, EBL (OR per quantile: 1.49, 95% CI 1.08–2.05, $p = 0.02$; OR per 200 ml: 1.04, 95% CI 1.01–1.08, $p = 0.03$) emerged as a significant predictor of AGCs (Table 2). The AUC for this multivariable model was 0.69. Univariable analyses are shown in Supplementary Table S3.

EBL (OR per quantile: 1.71, 95% CI 1.15–2.55, $p = 0.01$; OR per 200 ml: 1.09, 95% CI 1.04–1.14, $p = 0.001$) emerged as a significant predictor of low-grade complications (LGCs; CDC1–2) at multivariable analysis (Table 2). The AUC for this multivariable model was 0.65. Univariable analyses are shown in Supplementary Table S4.

CN case load (OR per quantile: 0.13, 95% CI 0.03–0.59, $p = 0.009$; OR per 25 cases: 0.88, 95% CI 0.77–0.98, $p = 0.04$) and EBL (OR per quantile: 2.93, 95% CI 1.20–7.15, $p = 0.02$; OR per 200 ml: 1.06, 95% CI 1.02–1.08, $p = 0.007$) emerged as significant predictors of HGCs at multivariable analysis (Table 2). The AUC for this multivariable model was 0.82. Univariable analyses are shown in Supplementary Table S5.

No predictors of death related to major complications (CDC5) remained significant at multivariable analysis. Univariable analyses are shown in Supplementary Table S6.

3.5. *Thirty-day readmission rates*

Forty-one (11.5%) patients were readmitted within 30 d of surgery. No predictors for 30-dy readmission were identified.

3.6. *Subanalysis of targeted therapy era patient cohort*

A total of 560 patients were included in the subanalysis of patients who underwent CN in the targeted therapy era. Of them, 175 (31.3%) encountered AGCs, while 38 (6.89%) encountered an HGC, of whom seven (1.25%) died (CDC5). Intraoperative complications occurred in 66 (11.8%) patients. Results of the multivariable models are shown in Supplementary Table S7. Significant predictors of perioperative morbidity on multivariable analysis were identical to these in the total cohort, with the exception of adjacent organ removal as a predictor of intraoperative complications, which did not reach statistical significance ($p = 0.06$).

4. Discussion

The results of the CARMENA trial have recently shifted treatment paradigms in mRCC patients away from surgery by concluding that sunitinib alone is noninferior to CN followed by sunitinib [6]. It is abundantly clear that not every mRCC patient benefits from CN, although there is

Table 3 – Details of postoperative complications per location.

Site		Percentage of total	% High grade
Cardiopulmonary	35	4.8	2.9
Acute myocardial infarction	1	0.1	
Arrhythmia	10	1.4	
Pulmonary embolus	9	1.2	
Respiratory failure	6	0.8	
Pneumothorax	9	1.2	
Vascular/lymphatic	67	9.1	1.1
Lymphocele	10	1.4	
Postoperative bleeding	39	5.3	
Low hemoglobin	5	0.7	
Intra-abdominal hematoma	5	0.7	
Deep vein thrombosis	8	1.1	
Neurological	7	1.0	0
Nerve injury	3	0.4	
Cerebrovascular accident	2	0.3	
Severe mental confusion	2	0.3	
Gastrointestinal	33	4.5	0.5
Prolonged ileus	18	2.5	
Bowel obstruction	4	0.5	
Nausea/vomiting	3	0.4	
Enteric fistula	3	0.4	
Pancreatic injury	5	0.7	
Urological	23	3.1	0.8
Acute renal insufficiency	16	2.2	
Acute urinary retention	5	0.7	
Scrotal swelling/hematoma	2	0.3	
Wound/skin	13	1.8	0.1
Wound infection	5	0.7	
Dehiscence	3	0.4	
Hematoma	2	0.3	
Pressure skin ulcer	2	0.3	
Seroma	1	0.1	
Infection/metabolic	42	5.7	0.7
Malignant hyperthermia	2	0.3	
Sepsis	5	0.7	
Abscess	1	0.1	
Urinary tract infection	4	0.5	
Pneumonia	24	3.3	
Other infections	2	0.3	
Addisonian crisis	1	0.1	
Total	217	29.5	6.1

general consensus that patients with low-volume, single-site metastases and few adverse IMDC criteria could benefit from the continued use of CN [7,8]. Moreover, deferred CN appears to be safe, and current guidelines recommend the use of deferred CN in IMDC intermediate-risk patients who have a sustained response to systemic therapy [8,9]. Furthermore, retrospective data indicate a survival benefit of CN in non–clear cell mRCC patients [5,14]. Additionally, a considerable number of patients will need a CN for local complications, such as bleeding or pain.

CN carries a higher morbidity and mortality rate than non-CN [12]. This study aimed to investigate the safety and morbidity of CN in mRCC patients in order to optimize patient selection for this procedure, since significant postoperative morbidity could preclude or delay the use of subsequent systemic therapies and thus impact the disease course significantly. Our study provided key findings that may better contextualize the current CN literature.

First, we demonstrate in a multicenter retrospective cohort study that the morbidity associated with CN is certainly not negligible, even at referral centers. Up to one-third of patients (29.5%) encountered any grade of adverse event during the postoperative course, and 6.1% encountered an HGC. The surgical mortality in this cohort was 1.4%. The reported rates of major postoperative complications in the literature range from 3% to 36%, and postoperative mortality rates range from 0% to 13% [15]. These results correlate with our findings. Unsurprisingly, having a postoperative complication was associated with an increased length of hospital stay. Intraoperative complications were registered in as much as one out of 10 (10.9%) patients, which correlates with the rates reported in the literature, ranging from 6% to 30% [15].

Postoperative complications were very diverse in nature, but the most frequent ones were vascular/lymphatic in nature, which is to be expected in complex procedures where extensive dissection is often warranted, leading to postoperative bleeding or the formation of lymphoceles. However, given the relatively high rate of postoperative lymphoceles, which is probably attributable to the performance of lymph node dissections and the lack of proven

oncological survival benefit thereof, surgeons might reconsider the performance of lymphadenectomy during CN.

Notably, surgical approach (minimally invasive vs open surgery) seems to correlate with AGCs and LGCs on univariable analysis but not with HGCs. This could be attributed to the fact that most LGCs are surgical site related, and these are expected to be lower in minimally invasive procedures than in open procedures. We did not differentiate between laparoscopic and robotic approaches since robotic systems were not available in all centers during the entirety of the study period. Additionally, in most centers, highly complex procedures are probably more likely to be performed as an open rather than a minimally invasive procedure.

Estimated intraoperative blood loss is a predictive factor for AGCs as well as HGCs in our study, but cannot be used as a preoperative patient selection tool. However, it could be considered a surrogate marker for other unmeasured disease parameters reflecting surgical complexity. Although it is evident that EBL is always kept to a minimum, it could warrant a more stringent postoperative follow-up for those patients who have experienced considerable blood loss during surgery. Additionally, intraoperative blood transfusion has previously been shown to be associated with unfavorable surgical morbidity [16].

Furthermore, CN case load at each center was strongly inversely correlated to high-grade postoperative morbidity, highlighting the impact of centralization of care on postoperative outcomes in complex surgical scenarios such as CN [17,18]. Trinh et al [19] have previously shown that a higher annual hospital volume and a greater number of beds were correlated with a lower number of deaths in patients who developed an adverse outcome during hospitalization for CN. In non-CN cases, hospital volume has been found to correlate with the rate of postoperative complications, blood transfusions, and length of stay after either radical or partial nephrectomy as well [20]. Most likely, the effect of CN case load is related to patient selection as well as surgical experience. Estimated intraoperative blood loss was significantly higher for centers with a higher CN load, which might reflect that more complex tumors are more likely to be treated in higher-volume centers. This could also explain why centers with a lower CN case load performed more minimally invasive surgeries, since more complex tumors are more likely to be treated with open surgery. Considering this, it is important to take into account the experience and surgical volume of a certain center with regard to CN and complex surgery in general. These findings could provide an argument for centralization of complex surgery such as CN and the creation of referral networks.

The presence of an intravenous tumor thrombus is a known negative prognostic factor for oncological survival in RCC patients [21]. In mRCC patients undergoing CN, thrombectomy has been reported to be associated with a higher number of postoperative complications despite the use of cardiopulmonary bypass and venovenous bypass techniques [22]. However, thrombectomy did not remain a significant predictor of postoperative complications on multivariable analysis in our cohort. Both thrombectomy and removal of adjacent organs were, however, predictive for intraoperative complications. These are again markers of complex procedures in advanced cases. Patients with tumor thrombus or anatomically complex tumors invading adjacent organs are thus at a higher risk of intraoperative complications and should be counseled accordingly before undergoing surgery.

When performing a subanalysis on the patient cohort that underwent CN in the targeted therapy era, significant predictors of perioperative morbidity were identical to those in the total cohort. Only adjacent organ removal as a predictor of intraoperative complications did not reach statistical significance. When considering the year of surgery as a parameter in the logistic regression models, only intraoperative morbidity was impacted. There was a slightly higher rate of intraoperative complications in the more recent time period, which could indicate an increase in more complex cases or surgical risk taking over time. Overall, taking into account these analyses and the fact that most patients were treated in the contemporary targeted therapy era, predictors of surgical morbidity and mortality seem to remain constant over time.

Considering all this and taking into account the results of the CARMENA trial, it is of utmost importance for the clinician to outweigh risks and benefits of performing a CN at all time when selecting patients for this procedure, and patients should be well informed accordingly.

Limitations of our study are its retrospective nature and the inherent limits thereof. Additionally, no information was available on different surgeons and their preferences or experience within different centers. The CN case load is only a proxy for the surgical experience of the respective center and might not correspond to the surgical experience with non-CN. However, considering the timespan of this study, it can be assumed that nearly all cases underwent CN prior to the publication of the CARMENA trial and CN was probably routinely offered to mRCC patients presenting at the different institutions. Considering the predictive abilities of the models used, predictors should be interpreted as a whole, reflecting patients' predisposition to experiencing complications. These results should be validated in an external dataset.

5. Conclusions

Morbidity associated with CN is not negligible. Predictors of high-grade postoperative morbidity are predominantly indicators of complex surgery and should warrant increased vigilance toward postoperative complications. EBL is a strong predictor of both low- and high-grade complications. CN case load correlates with lower high-grade morbidity and highlights the benefit of centralization of complex surgery. However, risks and benefits should be balanced when considering CN in the contemporary management of mRCC patients.

***Author contributions*:** Maria C. Mir 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: Roussel, Campi, Mir, Albersen.
Acquisition of data: Roussel, Campi, Palumbo, Derweesh, Ghali, Bradshaw, Meagher, Heck, Amiel, Kriegmair, Rubio, Musquera, D'Anna, Autorino, Guruli, Veccia, Linares-Espinos, Van Bruwaene, Hevia, Porpiglia, Checcucci, Minervini, Mari, Pavan, Claps, Marchioni, Mir, Albersen.
Analysis and interpretation of data: Roussel, Larcher, Mir, Albersen.
Drafting of the manuscript: Roussel, Mir, Albersen.
Critical revision of the manuscript for important intellectual content: Verbiest, Beuselinck, Capitanio, Larcher, Campi, Palumbo, Derweesh, Ghali, Bradshaw, Meagher, Heck, Amiel, Kriegmair, Rubio, Musquera, D'Anna, Autorino, Guruli, Veccia, Linares-Espinos, Van Bruwaene, Hevia, Porpiglia, Checcucci, Minervini, Mari, Pavan, Claps, Marchioni, Mir, Albersen.
Statistical analysis: Roussel, Albersen.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Mir, Albersen.
Other: None.

***Financial disclosures*:** Maria C. Mir certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor*:** None.

References

[1] Hsieh JJ, Purdue MP, Signoretti S, et al. Renal cell carcinoma. Nat Rev Dis Prim 2017;3:17009.
[2] Capitanio U, Bensalah K, Bex A, et al. Epidemiology of renal cell carcinoma. Eur Urol 2019;75:74–84.
[3] Flanigan R. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 2001;345:1655–9.
[4] Mickisch GHJ, Garin A, Van Poppel H, De Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet 2001;358:966–70.
[5] Bhindi B, Abel EJ, Albiges L, et al. Systematic review of the role of cytoreductive nephrectomy in the targeted therapy era and beyond: an individualized approach to metastatic renal cell carcinoma. Eur Urol 2019;75:111–28.
[6] Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 2018;379:417–27.
[7] Kuusk T, Szabados B, Liu WK, Powles T, Bex A. Cytoreductive nephrectomy in the current treatment algorithm. Ther Adv Med Oncol 2019;11:1758835919879026.
[8] Bex A, Albiges L, Ljungberg B, et al. Updated European Association of Urology guidelines for cytoreductive nephrectomy in patients with synchronous metastatic clear-cell renal cell carcinoma. Eur Urol 2018;74:805–9.
[9] Bex A, Mulders P, Jewett M, et al. Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: the SURTIME randomized clinical trial. JAMA Oncol 2019;5:164–70.
[10] de Bruijn R, Wimalasingham A, Szabados B, et al. Deferred cytoreductive nephrectomy following presurgical vascular endothelial growth factor receptor-targeted therapy in patients with primary metastatic clear cell renal cell carcinoma: a pooled analysis of prospective trial data. Eur Urol Oncol 2020;3(2):168–73, Apr.
[11] Albiges L, Powles T, Staehler M, et al. Updated European Association of Urology guidelines on renal cell carcinoma: immune checkpoint inhibition is the new backbone in first-line treatment of metastatic clear-cell renal cell carcinoma. Eur Urol 2019;76:151–6.
[12] Abdollah F, Sun M, Thuret R, et al. Mortality and morbidity after cytoreductive nephrectomy for metastatic renal cell carcinoma: a population-based study. Ann Surg Oncol 2011;18:2988–96.
[13] Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
[14] Graham J, Wells C, Donskov F, et al. Cytoreductive nephrectomy in metastatic papillary renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). J Clin Oncol 2018;36:581.
[15] Larcher A, Wallis CJD, Bex A, et al. Individualised indications for cytoreductive nephrectomy: which criteria define the optimal candidates? Eur Urol Oncol 2019;2:365–78.
[16] Gershman B, Moreira DM, Boorjian SA, et al. Comprehensive characterization of the perioperative morbidity of cytoreductive nephrectomy. Eur Urol 2016;69:84–91.
[17] Williams SB, Ray-Zack MD, Hudgins HK, et al. Impact of centralizing care for genitourinary malignancies to high-volume providers: a systematic review. Eur Urol Oncol 2019;2:265–73.
[18] Freifeld Y, Woldu SL, Singla N, et al. Impact of hospital case volume on outcomes following radical nephrectomy and inferior vena cava thrombectomy. Eur Urol Oncol 2019;2:691–8.
[19] Trinh Q-D, Bianchi M, Hansen J, et al. In-hospital mortality and failure to rescue after cytoreductive nephrectomy. Eur Urol 2013;63:1107–14.
[20] Maxine S, Marco B, Quoc-Dien T, et al. Hospital volume is a determinant of postoperative complications, blood transfusion and length of stay after radical or partial nephrectomy. J Urol 2012;187:405–10.
[21] Wagner B, Patard J-J, Méjean A, et al. Prognostic value of renal vein and inferior vena cava involvement in renal cell carcinoma. Eur Urol 2009;55:452–60.
[22] Goetzl MA, Goluboff ET, Murphy AM, et al. A contemporary evaluation of cytoreductive nephrectomy with tumor thrombus: morbidity and long-term survival. Urol Oncol Semin Orig Investig 2004;22:182–7.