Perioperative complications associated to nephrectomy in metastatic renal cell carcinoma

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Abstract

Background: Current evidence shows that cytoreductive nephrectomy (CN) could offer a survival benefit for patients with metastatic renal cell carcinoma (RCC). Nevertheless, due to a higher risk of perioperative complications this therapeutic strategy should be evaluated thoroughly. To identify perioperative mortality and morbidity predictors associated to CN, we analyzed metastatic RCC patients treated with surgery in our Institution. **Patients and methods:** We evaluated those patients with metastatic RCC treated with CN between 1980-2016 at our Institution. Univariate and binomial logistic regression analysis was used to assess predictors of adverse outcomes within a 30-day postoperative period. We defined a p value < 0.05 as statistically significant. **Results:** 46 patients with clinical stage IV RCC were included in this analysis; 32.6% had perioperative morbidity. Clavien-Dindo grade $\geq$ III complications occurred in 17.4%. Perioperative mortality was 15.2%. In multivariate analysis, age ≥ 65 years was an independent predictor of perioperative morbidity ($p = 0.001$). No factors were associated with perioperative mortality. **Conclusions:** Patients ≥ 65 years old with metastatic RCC, nephrectomy has a higher risk of complications and perioperative mortality. Therefore, the benefit of surgical therapy in this population should be evaluated thoroughly.

Key words: Carcinoma. Renal cell. Cytoreduction surgical procedures. Nephrectomy. Perioperative period. Postoperative complications.

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Introduction

Renal cell carcinoma (RCC) accounts for 3% of neoplasms in adults¹ and it is estimated that 30% of cases have metastatic disease at diagnosis². Currently, the National Comprehensive Cancer Network guidelines recommend cytoreductive nephrectomy (CN) in patients with potentially resectable metastatic RCC only when combined with systemic therapy, due to the overall survival benefit described in observational studies with this strategy³. However, there is still a lack of prospective clinical trials results that support this type of management⁴⁻⁶. On the other hand, CN is a complex surgery, with perioperative morbidity and mortality rates as high as 37% and 21%, respectively,^{4,7} and the potential benefit of CN should therefore be carefully weighed against the risk of serious complications prior to carrying out the procedure. Therefore, both perioperative prognosis and identifying the factors that determine these outcomes is necessary in order to define which patients with metastatic RCC can benefit from surgical treatment. With the purpose to identify the predictive factors of perioperative morbidity and mortality associated with CN, we analyzed patients with metastatic RCC surgically treated in our institution.

Material and methods

The information was obtained from our prospectively maintained database, and it included 592 adult patients who underwent nephrectomy for RCC in our institute between March 1980 and October 2016. Of the 74 cases with stage IV RCC undergoing nephrectomy, we included those with metastatic RCC that had complete perioperative information. A retrospective analysis was carried out, where the following variables were assessed: bleeding, blood transfusion, perioperative complications and mortality. Complications were categorized using the Clavien-Dindo classification⁸. Adverse effects were defined as bleeding > 1,000 mL, need for transfusion, perioperative complications and death within the first 30 days after surgery. A binomial logistic regression model was used for the multivariate analysis of adverse event predictors such as age, preoperative hemoglobin level, Eastern Cooperative Oncology Group (ECOG) performance status, Charlson comorbidity index, tumor size > 10 cm, and number and site of metastases. Univariate analysis was carried out using the chi-square test or Fisher's exact test, as appropriate. For the level of statistical significance, a p-value < 0.05 was established. The

statistical analysis was carried out with the support of the statistical program SPSS® v.22 (IBM Corporation, USA). Owing to the retrospective nature of the study, informed consent was not required. The researchers adhered to the precepts of the Declaration of Helsinki. In addition, the ethical guidelines in matters of research indicated by the Official Mexican Standard NOM 166-SSA1-1997 were followed.

Results

In the analysis, 46 patients with complete information were included, all at clinical stage IV.

Demographic and preoperative characteristics

Preoperative characteristics of the population are shown in [table 1](#). Median age at diagnosis was 55 years (range 40-77 years), with 64.7% of male patients. A total of 20 patients (40.35%) had an ECOG performance status of 0, and 91.3% of the population, a Charlson comorbidity index ≥ 5 . Most tumors were clear cell renal carcinomas, 63% were at clinical T-stage $\geq T3$; this information was absent in 6.5% of cases. The two most common sites of metastasis were the lung (76.1%) and lymph nodes (28.3%). On the other hand, only 63% of patients received systemic therapy with different pharmacological modalities (chemotherapy, immunotherapy or targeted therapy), depending on the historical moment surgery was performed at.

Perioperative characteristics

Surgical details are summarized in [table 2](#). Lymphadenectomy was performed in 37% of cases. Mean surgical time was 253 minutes. Bleeding > 1,000 mL was reported in 41.3% of patients, with 54.3% requiring transfusion.

Complications

In total, 15 patients (32.6%) had some complication: intraoperative in 4 cases (8.7%) and postoperative in 11 (23.9%). Of these, in 17.4%, complications were Clavien-Dindo grade III or higher. The details are shown in [table 3](#).

In the univariate analysis, clinical stage $\geq T3$ was associated with the need for transfusion ($p = 0.007$) and risk of surgical bleeding > 1,000 mL ($p = 0.005$), whereas in the multivariate analysis it remained as an

Table 1. Clinical and demographic characteristics of 46 patients with clinical stage IV renal cancer

Clinical and demographic characteristics of 46 patients with clinical stage IV renal cancer	
	n = 46
Age years, median (range)	55 (40-77)
Age ≥ 65 years (%)	9 (19.6)
Males (%)	31 (64.7)
pT3-4 stage (%)	29 (61.7)
Hb, median (min-max)	11.97 (6.7-17)
Cr Cl (CKD-EPI), median (min-max)	76.52 (41-137)
Clinical T-stage (%)	
Tx	3 (6.5)
T1	10 (21.8)
T2	4 (8.7)
T3	22 (47.8)
T4	7 (15.2)
Tumor diameter (mean, cm)	10.94
Laterality (%)	
Left	29 (63)
Right	16 (34.8)
Bilateral	1 (2.2)
N1 (%)	13 (28.3)
Histology (%)	
Clear cell	42 (91.3)
Non-clear cell	4 (8.7)
Sarcomatoid pattern (%)	7 (15.2)
Fuhrman grade (%)	
1-2	9 (19.6)
3-4	29 (63)
Unknown	8 (17.4)
Charlson (%)	
≤ 2	3 (6.5)
3-4	1 (2.2)
≥ 5	42 (91.3)
Karnofsky < 80% (%)	3 (6.5)
ECOG (%)	
0	20 (40.35)
1	23 (50)
2	3 (6.5)
Systemic therapy (%)	29 (63%)
Targeted therapy	8 (17.4%)
Immunotherapy	7 (15.2%)
Immunotherapy + thalidomide	6 (13%)
Chemotherapy	5 (10.9%)
Other	1 (2.2%)

Cr Cl: creatinine clearance; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; Hb: hemoglobin; ECOG: Eastern Cooperative Oncology Group.

independent predictor only of the need for transfusion (odds ratio [OR]: 6.37; confidence Interval [CI] 95%: 1.37-29.57; $p = 0.018$), but not for the risk of bleeding.

Table 2. Surgical details of the 46 patients who underwent nephrectomy

Surgical details of the 46 patients who underwent nephrectomy	
Characteristics	n = 46 (%)
Surgical time, hours (%) (mean = 4.83 [2.5-9])	
< 2	0
2-3	3 (6.5)
3-4	14 (30.4)
4-6	17 (37)
> 6	5 (10.9)
Not reported	7 (15.2)
Lymphadenectomy - Yes (%)	17 (37)
Bleeding, mL (%)	
≤ 500	16 (34.8)
501-1,000	11 (23.9)
1,001-2,000	5 (10.9)
2,001-5,000	12 (26.1)
> 5,000	2 (4.3)
Transfusion - Yes (%)	25 (54.3)
Transfused units (%)	
0	21 (45.7)
1-2	7 (15.2)
3-4	3 (6.5)
> 4	1 (2.2)
Not reported	14 (30.4)
Required ICU (%)	13 (28.3)

ICU: intensive care unit.

Moreover, in another univariate analysis, age ≥ 65 years ($p < 0.001$) and the presence of liver metastases ($p = 0.01$) were associated with a higher risk of perioperative complications. However, in the multivariate analysis, only age ≥ 65 years remained as an independent risk factor (OR: 68.04; 95% CI: 6.13-754.22; $p = 0.001$) for developing any perioperative complication. No association was found with the remaining variables.

Perioperative mortality

Perioperative mortality was 7 patients (15.2%). All of them had a Charlson comorbidity index ≥ 8; six had clinical stage ≥ T3, as well as bleeding higher than 2,000 mL. Two died due to hypovolemic shock, one due to acute myocardial infarction on postoperative day 19, one due to pulmonary thromboembolism, one due to congestive heart failure (this patient had comorbidities such as antiphospholipid syndrome, Budd-Chiari syndrome and pulmonary arterial hypertension) and two more died from septic shock (nosocomial pneumonia and urosepsis).

In the univariate analysis, age ≥ 65 years ($p = 0.02$), the presence of liver metastases ($p = 0.03$) and surgical

Table 3. Perioperative complications of the 46 patients who underwent nephrectomy

Perioperative complications of the 46 patients who underwent nephrectomy*	
Perioperative complication (%)	15 (32.6)
1 complication (%)	6 (13)
≥ 2 complications (%)	9 (19.6)
Intraoperative complication (%)	4 (8.7)
Hypovolemic shock	2 (4.3)
PTE	1 (2.2)
Cardiorespiratory arrest	1 (2.2)
Pneumothorax	1 (2.2)
Diaphragmatic injury	1 (2.2)
Intestinal ischemia	1 (2.2)
Postoperative complication (%)	11 (23.9)
Acute tubular necrosis	3 (6.5)
Septic shock	2 (4.3)
Urosepsis	2 (4.3)
Pneumonia	1 (2.2)
Hypercalcemia	1 (2.2)
Urinary fistula	1 (2.2)
Hematoma	1 (2.2)
Hypovolemic shock	2 (4.3)
Deep vein thrombosis	1 (2.2)
Acute myocardial infarction	1 (2.2)
Atrial fibrillation	1 (2.2)
Clavien-Dindo (%)	
I	4 (8.7)
II	3 (6.5)
III	1 (2.2)
IV	0
V	7 (15.2)

*Complications numbers are not additive, since a single patient may have experienced more than one complication.
PTE: pulmonary thromboembolism.

bleeding > 1,000 mL ($p = 0.01$) were associated with perioperative mortality. However, this association was not maintained independently in the multivariate analysis.

Discussion

In this work, we present nephrectomy surgical morbidity and mortality during the first 30 days in patients with metastatic RCC. We observed that the main predictor of adverse effects in our population is advanced age.

Current evidence indicates that CN is associated with better oncological prognosis, with morbidity figures ranging from 27.8% to 37%^{4,9}, and mortality ranging from 1.9% to 4.8%^{5,10}. According to observations reported by Kader, mortality can reach 21% in people older than 75 years⁷. In our population, the rate of perioperative complications was 32.6%, which is similar to that reported in other series⁴. Clavien-Dindo categories ≥ 3 occurred in 17.4%, which is a higher figure than those

described in the literature¹¹. The main factor in our analysis was age ≥ 65 years, which is expected if we consider that these patients have lower functional reserve and higher difficulty to recover after a surgical intervention⁵. In addition, the degree of local invasion (T3 or T4), regardless of the presence of distant metastasis, stood out as the only predictor of blood transfusions, reinforcing the observations previously described by Takagi¹². Of note, other patient characteristics such as ECOG performance status, Charlson index, body mass index or renal function were not associated with complications, which reinforces the fact that it is advanced age and tumor characteristics that favor surgical morbidity.

The results of our work should be interpreted within the context of the limitations of a retrospective study. We consider relevant highlighting that most patients had multiple comorbidities, to the point that more than 90% of them had a Charlson index > 5 points. Another limitation of the present study is that only 63% of patients received adjuvant systemic therapy. This variability was due to the historical context of the series and to the evolution in the indications and different modalities of systemic therapy over the years. These results are similar to those reported in a recent analysis by the National Cancer Database, which found that up to 61% of patients with metastatic RCC do not receive adjuvant systemic therapy after CN¹³.

Conclusion

There is still no consensus on the benefit of CN in patients with metastatic RCC. In our study, we found that age ≥ 65 years was independently associated with higher risk of perioperative morbidity. On the other hand, the degree of local invasion (clinical stage T3/T4) increased the risk of transfusions. These findings suggest that assessment of those patients with these characteristics should be extremely careful in order to determine if the benefit of CN is greater than the morbidity it may entail.

Conflict of interests

There are no conflicts of interest involving the authors.

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