

Risk factors for the development of postoperative complications in patients with metastatic kidney cancer treated with cytoreductive nephrectomy

Factores de riesgo para el desarrollo de complicaciones posquirúrgicas en pacientes con cáncer renal metastásico tratados con nefrectomía citorreductora

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Abstract

Background: The role of cytoreductive nephrectomy on the treatment of metastatic renal cell carcinoma (mRCC) is controversial due to its high complexity. **Objective:** To identify risk factors associated to postoperative complications in patients with mRCC after cytoreductive nephrectomy. **Method:** We conducted a retrospective, observational study in 67 patients who underwent cytoreductive nephrectomy for the management of mRCC. Demographic, perioperative and clinicopathologic characteristics were registered. Surgical complications were classified using the Clavien-Dindo system; major complications were those of grade 3 or higher. We performed a binary logistic regression analysis to identify risk factors associated with surgical complications. **Results:** Mean age was 56 years (37-83). Symptoms were present in 58 patients (89.7%). Weight loss was the predominant symptom (50.8%). Mean tumor diameter was 10.8 cm (4.6-22.5 cm). The rate of postoperative complications was 65%; 21 patients (31.4%) had major complications. Risk factors were estimated blood loss > 500 ml (OR 44.5, CI 95% 2.51-789, $p = 0.01$) and tumor diameter > 10 cm (OR 17.9, CI 95% 1.2-273, $p = 0.04$). **Conclusions:** Cytoreductive nephrectomy is a good option in highly selected patients with mRCC. Our major complication rate was 31.4%. Risk factors associated were blood loss and tumor diameter.

Keywords: Cytoreduction surgical procedures. Nephrectomy. Postoperative complications.

Resumen

Antecedentes: El papel de la nefrectomía citorreductora como tratamiento del carcinoma de células renales metastásico (CCRm) es controversial debido a su alta complejidad. **Objetivo:** Identificar factores de riesgo para complicaciones posquirúrgicas en pacientes con CCRm tratados con nefrectomía citorreductora. **Método:** Estudio retrospectivo, observacional, de 67 pacientes tratados con nefrectomía citorreductora por CCRm. Se registraron las características demográficas, perioperatorias y clinicopatológicas. Las complicaciones posquirúrgicas fueron clasificadas con el sistema Clavien-Dindo (mayores aquellas de grado 3 o superior). Se realizó un análisis de regresión logística binaria para identificar factores de riesgo para complicaciones. **Resultados:** La edad media fue de 56 years (rango: 37-83), y 58 pacientes (89.7%) presentaron síntomas,

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predominando la pérdida de peso (50.8%). El diámetro tumoral medio fue de 10.8 cm (rango: 4.6-22.5). Un 65% tuvo complicaciones posquirúrgicas; en el 31.4% fueron mayores. Los factores de riesgo asociados fueron el sangrado transoperatorio ≥ 500 ml (odds ratio [OR]: 44; intervalo de confianza del 95% [IC 95%]: 2.51-789; $p = 0.01$) y el diámetro tumoral > 10 cm (OR: 17.9; IC 95%: 1.2-273; $p = 0.04$). **Conclusiones:** La nefrectomía citoreductora es una opción de tratamiento para pacientes estrictamente seleccionados. Nuestra tasa de complicaciones mayores fue del 31.4%. Los factores de riesgo asociados fueron el sangrado transoperatorio y el diámetro tumoral.

Palabras clave: Citoreducción. Nefrectomía. Complicaciones posquirúrgicas

Introduction

Renal cell carcinoma (RCC) represents 90% of renal neoplasias, and approximately 3% of all malignant neoplasias in adults¹. In Mexico, RCC is the fifteenth most frequent neoplasia with a mortality rate of 3.3%. It is estimated that the prevalence between 2013-2018 was 8.28 cases per 10.000 people². The metastatic disease is diagnosed in 20-30% of cases, and the most frequent is lung metastasis, with a reported rate of 45%³.

In recent decades, treatment for metastatic RCC (mRCC) has evolved thanks to the rise of several therapeutic options. In the 1990s, systemic treatment was based on the administration of interleukin-2 and interferon alpha³. At this stage, the potential benefits of cytoreductive nephrectomy as part of the treatment for mRCC were established⁴. The theory states that cytoreductive nephrectomy acts by decreasing the tumor burden and removing new potential metastasis sources. Other mechanisms described are the elimination of proangiogenic factors and the alteration of the tumor microenvironment^{5,6}. Afterwards, the identification of new therapeutic goals allowed for the development of agents, such as the vascular endothelial growth factor, the platelet derived growth factor inhibitors, and others directed against the programmed cell death protein³, whose use improved oncological results, thus questioning the role of cytoreductive nephrectomy, as the new biological therapy options reduce the spectrum of patients that may benefit from aggressive surgical treatment^{7,8}. Additionally, the morbidity associated with the cytoreductive nephrectomy requires the careful selection of candidates for this procedure⁹.

Therefore, it is of the utmost importance to carefully consider patient and neoplasia characteristics in order to support decision making in handling¹⁰. For this purpose, there are prognostic models, such as the one put forth by International Metastatic RCC Database

Consortium (IMDC), and the model of Memorial Sloan Kettering Cancer Center, which allow to decide if patients with mRCC should undergo a cytoreductive nephrectomy, systemic therapy, or both^{6,11,12}.

The purpose of this study was to identify the risk factors for the development of complications following a cytoreductive nephrectomy in patients with mRCC.

Method

This is a retrolective, retrospective, and observational study taken from a database of 680 patients with RCC treated surgically in our institution, in which the demographic, clinical, surgical, histopathological, and oncological characteristics of 67 patients with mRCC treated with cytoreductive nephrectomy between March 1980 and December 2018. The following was recorded: Body Mass Index (BMI) and symptoms, such as hematuria, pain, palpable mass, and weight loss at the time of the mRCC diagnosis, as well as intraoperative bleeding and postsurgical complications, classified according to the Clavien-Dindo classification¹³. Other variables were also recorded, such as the American Society of Anesthesiologists (ASA)¹⁴ score and the presurgical glomerular filtration rate calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)¹⁵ formula. The histopathology report used the TNM system updated in 2018¹⁶ and it recorded other characteristics, such as the histological type, the differentiation degree (nuclear degree) and the surgical margins, as well as the presence of necrosis, rhabdoid differentiation or sarcomatoid differentiation¹⁷. The scores from performance status scale of the Eastern Cooperative Oncology Group (ECOG)¹⁸ and the Charlson Comorbidity Index (CCI)¹⁹ were calculated.

The statistical analysis was performed using SPSS, version 20.0. For the descriptive analysis, central trend measures were used, such as the mean or average, and for the dispersion measures, the standard deviation or the interquartile interval were used,

Table 1. Histopathological characteristics (n = 67)

Histological Type	
Clear cells	61 (92.4%)
Other	6 (7.6%)
Nuclear grade	
1-2	16 (26.7%)
3-4	44 (73.3%)
Differentiation	
Rhabdoid	4 (6.3%)
Sarcomatoid	15 (23.8%)
Necrosis	
Present	37 (56.9%)

according to the distribution of the variable studied. The distribution of variables was analyzed with the Shapiro-Wilk test. The bivariate analysis was performed with the Student t test for independent samples in parametric variables, and the non-parametric variable with the Mann-Whitney U test. The qualitative variables were analyzed with the ji square test of the Fisher's exact test. Independent risk factors were analyzed for perioperative complications with binary logistic regression. A value of $p \leq 0.05$ was considered statistically significant for a distribution of two tails.

Results

The ratio of men and women was 2:1, and the mean age at the time of the diagnosis was 56 (range: 37-83). In 58 patients (89.7%) symptoms were present at the time of the diagnosis, with the most common symptoms being weight loss (50.8%), while only 4 (6.3%) showed the classic RCC triad (hematuria, pain, and palpable mass). The mean glomerular filtration rate calculated using the CKD-EPI formula was 75 ml/min/1.73 m² (range: 20-125). 84.1% has a ECOG score ≤ 1 and 96.8% a score ≥ 5 for the CCI. The IMDC category classified 46 patients (68.7%) as intermediate risk, and 21 (31.3%) as high risk; no patient was classified as low risk.

The histological characteristics of the tumors are shown in Table 1. The average tumor diameter reported by the imaging studies was 10.8 cm (range: 4.6-22.5). In 61 cases (92.4%) clear cell RCC was identified. 44 tumors (73.3%) were reported with nuclear degrees 3 and 4, and 20 with positive surgical margins (31.2%). Other histological characteristics, such as rhabdoid and sarcomatoid differentiation, were present in 4 (6.3%) and 15 (23.8%) cases,

Table 2. Postsurgical complications according to the Clavien-Dindo system (n = 67)

No complications	23 (34.3%)
I	1 (1.5%)
II	22 (32.8%)
III	2 (3%)
IV	14 (20.9%)
V	5 (7.5%)

Table 3. Risk factors for complications after 30 days

Variable	OR	IC 95%	p
Univariate Analysis			
Age ≥ 65 years	0.73	0.22-2.38	0.60
Bleeding ≥ 500 ml	16	3.7-68.9	<0.001
IMC ≥ 30 kg/m ²	0.62	0.17-2.26	0.47
Tumor diameter > 10 cm	8.15	1.82-36.5	0.01
Lymphadenectomy	2.5	0.77-8.1	0.13
Presurgical thrombocytopaenia	2.4	0.46-12.4	0.30
ASA > 2	1.2	0.37-3.9	0.76
Multivariate analysis			
Bleeding ≥ 500 ml	44.5	2.51-789	0.01
Tumor diameter > 10 cm*	17.9	1.2-273	0.04

ASA: score from the American Society of Anesthesiologists scale; CI 95%: confidence interval of 95%; BMI, Body Mass Index; OR: odds ratio.

*Measured by imaging studies

respectively. Additionally, 37 surgical samples (56.9%) had some degree of necrosis.

Postsurgical complications are described in Table 2. Twenty-three patients (34.3%) did not develop complications, 23 (34.3%) had minor complications, and 19 (30.2%) required intensive unit care. In total, 27 patients (45%) has transoperative bleeding > 1000 ml.

The univariate analysis (Table 3) to determine the risk factors for any complications after 30 days included the IMC ≥ 30 kg/m² (odds ratio [OR]: 0.62; confidence interval of 95% [IC 95%]: 0.17-2.26; $p = 0.47$), ASA score > 2 (OR: 1.2; IC 95%: 0.37-3.9; $p = 0.76$), presurgical hemoglobin ≤ 12 g/dl (OR: 1.73; IC 95%: 0.62-4.89; $p = 0.30$), presurgical thrombocytopenia (OR: 2.4; IC 95%: 0.46-12.4; $p = 0.30$), tumor diameter > 10 cm (OR: 8.15; IC 95%: 1.82-36.5; $p = 0.01$), lymphadenectomy (OR: 2.5; IC 95%: 0.77-8.1; $p = 0.13$), and transoperative bleeding ≥ 500 ml (OR: 16; IC 95%: 3.7-68.9; $p < 0.001$). In the multivariate analysis (Table 3), the independent risk factors to develop complications were transoperative bleeding > 500 ml (OR: 44.5; IC 95%: 2.51-789; $p = 0.01$) and tumor diameter > 10 cm (OR: 17.9; IC 95%: 1.2-273; $p = 0.04$).

Table 4. Morbidity of cytoreductive nephrectomy

Trial	Design, country, years	N	Age (years)	Perioperative morbidity (%)	Any complication (%)	Clavien Complications ≥ 3 (%)
Hernández, et al. (2020)	Observational retrospective, Mexico, 1980-2018	67	Mean: 56 (range: 37-83)	7.5	65.7	31.4
Blick, et al. ²⁵ (2010)	Retrospective cohort, multicentric, United Kingdom, 2003-2007	25	Mean: 63 (range: 30-85)	0	12	4
O'Malley, et al. ²⁴ (2011)	Retrospective cohort, United States of America, 2002-2010	65	Mean: 61 (range: 42-90)	2	48	8
Powles, et al. ²⁶ (2016)	Phase 2 clinical trial, prospective, United Kingdom, 2008-2012	65	Mean: 64 (IQR: 56-71)	1	22	3
Jackson, et al. ²⁷ (2015)	Transversal retrospective, United Kingdom, 2012	279	Mean: 62 (range: 19-95)	1.8	22.6	8

IQR: interquartile range.

Discussion

The careful selection of candidates for cytoreductive nephrectomy is essential, always considering the risk-benefit assessment. Previously, we have published our experience with cytoreductive nephrectomy, and we found that an age of ≥ 65 is a factor for the development of complications and perioperative mortality in patients with mRCC²⁰.

There is a relationship between the symptoms at the time of the RCC diagnostic and the possibility that the disease is advanced, which represents a worse oncological outcome²¹.

Accordingly, 89.2% of our population presented symptoms, primarily weight loss in a little over half of the cases (50.8%). However, so far, the association with surgical outcomes in patients that undergo cytoreductive nephrectomy has been controversial.

It is worth noting the heterogeneity of the renal function in our population. However, this aspect was not a relevant risk factor for the development of any postsurgical complication.

The most common histological subtype was the clear cell carcinoma (92.4%), which is consistent with the figures previously reported in our country². In our series, nuclear degrees 3 and 4 were the most frequent which, according to the literature, is associated with metastatic disease up to 79% of cases¹⁷. 23.4%

of our patients had a sarcomatoid differentiation and this finding has also been associated with a worse prognosis²².

On the other hand, 39.1% of our patients underwent a lymphadenectomy, as certain evidence indicates that patients with suspicion of lymph node invasion could have better survival rate without increasing the risk of complications. Therefore, if this is technically feasible, it must be performed in patients with positive nodes suspicion^{8,23}. Other similar retrospective series have identified complication rates between 12% to 48%, including 17% of major complications, which highlights the relevance of the adequate preoperative selection²⁴⁻²⁷.

Jackson, et al.²⁷ studied tumor size ≥ 10 cm as an independent risk for transoperative bleeding of ≥ 1000 ml with subsequent transfusion requirements ($p = 0.021$), as well as major transoperative complications. Our study obtained similar results for complications 30 days after the cytoreductive surgery.

O'Malley, et al.²⁴ evaluated the morbidity associated with cytoreductive nephrectomy in a cohort of 65 patients collected retrospectively from Roswell Park Cancer Institute in New York, and they identified a complication rate of 48%, with a rate of major complication of 17%. As in other series, a lower percentage of major complications has been reported, as shown in Table 4. It is worth noting that, in our population,

66.6% of major complication were due to the need for intensive care unit treatment.

Our study has certain limitations derived from the retrospective nature and the number of patients included, which are situation that normally coincide with other published series. The last aspect has affected even prospective studies, which has been forced to prematurely interrupt research due to the difficulty to recruit patients^{8,9}.

However, our series is one of the few national series, and therefore, we consider that this information is relevant to make decisions in our country. On the other hand, the high cost of current medications for mRCC treatment, makes the cytoreductive surgery one of the treatment alternatives in health systems with budget limitations.

In conclusion, due to the high surgical morbidity and the wider availability of new biological therapies, the use of cytoreductive nephrectomy for treatment of patients of mRCC must be based on a strict selection, in such a way that only patients who will benefit from this approach undergo surgery. In our study, the transoperative bleeding ≥ 500 ml and the tumor diameter > 10 cm in imaging studies were associated with the development of any complication 30 after cytoreductive surgery. For these reasons, we recommend that these two factor be considered during the decision making process to handle patients with mRCC.

Ethical disclosures

Protection of People and Animals. The authors state that no experiments have been conducted in humans or animals for this research.

Data Confidentiality. The authors state that the protocols of their work center regarding the publication of patient data have been followed.

Right to privacy and informed consent. The authors state that no patient information appears in this article.

Conflicts of interest

The authors state that they do not have any conflicts of interest.

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