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ORIGINAL ARTICLE

Surgical treatment of renal-cell carcinoma in elderly people☆,☆☆

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Abstract

Objective: To describe the oncological characteristics and evolution of patients 65 years or older who underwent surgery for renal-cell carcinoma (RCC).

Methods: We reviewed our prospectively maintained database of patients with RCC treated surgically. Those ≥65 years old were selected. We analyzed clinical and pathological characteristics as well as oncological and functional outcomes. Overall survival (OS) was estimated with the Kaplan–Meier method. Multivariate Cox-proportional hazards model was used to determine predictors of OS.

Results: A total of 156 elderly patients with mean age 72.0 ± 5.5 years (range 65–92) and median follow-up of 33 months were included. Surgical approach was open radical nephrectomy in 114 (73.5%), laparoscopic radical nephrectomy in 13 (8.4%), open partial nephrectomy in 23 (14.2%) and laparoscopic partial nephrectomy in 6 (3.9%). Pathological stage was: Stage I, 71 (45.5%); Stage II, 27 (17.3%); Stage III, 48 (30.8%); and Stage IV, 10 (6.4%). Lastly, 51 (32.6%) patients died, 22 (43.1%) from cancer. The 5-year OS according to pathological stage was 77.6%, 71.9%, 45.1% and 11.7% for stage I, II, III and IV, respectively ($p < .001$). On multivariate analysis, pathological stage independently predicted OS (HR 1.96, 95% CI [1.36–2.84], $p = .0003$).

Conclusions: The surgical management of RCC appears to be safe in properly selected patients 65 years or older. Pathological stage predicts survival in this population.

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PALABRAS CLAVE
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Tratamiento quirúrgico del carcinoma de células renales en personas de edad avanzada

Resumen

Objetivo: Describir las características oncológicas y evolución de los pacientes con 65 años o más que son sometidos a cirugía por cáncer de células renales (CCR).

Métodos: Revisamos en nuestra base de datos a todos los pacientes con CCR tratados quirúrgicamente. Aquellos mayores de 65 años fueron seleccionados. Se analizaron las características clínicas y patológicas, así como los desenlaces oncológicos y funcionales. La supervivencia global (SG) fue estimada con el método de Kaplan–Meier. El análisis multivariado fue hecho con el modelo de Cox para determinar los predictores de SG.

Resultados: Se incluyeron un total de 156 pacientes ancianos con una edad media de 72,0 ± 5,5 años (rango 65–92) y una mediana de seguimiento de 33 meses. El abordaje quirúrgico fue nefrectomía radical abierta en 114 (73,5%) pacientes, nefrectomía radical laparoscópica en 13 (8,4%), nefrectomía parcial abierta en 23 (14,2%) y nefrectomía parcial laparoscópica en 6 (3,9%). El estadio patológico fue: estadio I 71 (45,5%), estadio II 27 (17,3%), estadio III 48 (30,8%) y estadio IV 10 (6,4%). Finalmente, 51 (32,6%) pacientes murieron, 22 (43,1%) por cáncer. La SG a 5 años de acuerdo al estadio patológico fue 77,6%, 71,9%, 45,1% y 11,7% para los estadios I, II, III y IV, respectivamente ($p < 0,001$). En el análisis multivariado el estadio patológico fue un factor independiente para predecir la SG (HR: 1,96, IC 95% [1,36–2,84], $p = 0,0003$).

Conclusiones: El tratamiento quirúrgico del CCR parece seguro en pacientes mayores de 65 años debidamente seleccionados. El estadio patológico predice la supervivencia en esta población.

Introduction

According to World Health Organization 2012 estimates, the incidence for kidney cancer was 337,800 new cases worldwide, of which 4500 were estimated to occur in Mexico and Central America.[1] Moreover, the estimated cumulative risk for age 75 of having kidney cancer was 0.7% for men and 0.3% for women worldwide, while in Mexico and Central America it was 0.5% and 0.3% respectively.[1] Recently, it has been demonstrated that over the most recent 10-year period, the incidence of RCC increased worldwide, most prominently in Latin American populations, where annual increases of over 3% were observed for both sexes.[2]

Due to the increase in age of the population, the number of cases of renal-cell carcinoma (RCC) continues to grow. Despite technological and pharmacological advances, surgical excision remains the standard of care for localized tumors. However, the benefit of this approach is unclear for elderly people particularly for those at higher risk for surgical complications. We and others have demonstrated that partial nephrectomy (PN) provides better functional outcomes,[3] especially in terms of cardiovascular events in geriatric population[4] while others support radical nephrectomy (RN) due to its lower complication rates.[5]

The reports on surgical outcomes for treating RCC in elderly people are limited, particularly from the region of Latin America. Thus, our objective was to describe the oncological characteristics as well as functional and oncological outcomes of 65-year-old patients or older who underwent surgery for RCC in a tertiary-care center in Mexico.

Materials and methods

We retrospectively analyzed our prospectively maintained database of 552 consecutive patients with renal tumors treated surgically (either with RN or PN) at our Institution. For this study we selected those aged 65 or older. The decision to perform RN or PN relied on tumor nephrometry score and surgeon's discretion. We excluded from this analysis patients with benign tumors or histology different from RCC as well as follow-up shorter than 3 months. The characteristics analyzed were gender, age, renal function, comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, tumor stage, type of surgery, estimated blood loss and complications. Perioperative 90-day mortality was assessed as well. For the evaluation of renal function the glomerular filtration rate (eGFR) was estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, considering normal 60 mL/min/1.73 m^2 or higher.[6] Any value below this cut-off point was considered chronic kidney disease (CKD), which was classified using the KDIGO categories.[7] Early surgical complications (within 30 days) were classified according to the Clavien–Dindo system.[8]

For the statistical analysis we used Student's *t* and Chi-square tests to compare means and proportions, respectively. Overall survival (OS) was analyzed with the Kaplan–Meier method and differences compared with the Mantel–Cox test. Univariate and multivariate Cox-proportional hazards model were used to determine the prognostic factors related to OS. The association between survival and each variable was summarized using hazard

ratios (HR) and 95% confidence interval (CI). A p value <0.05 was considered statistically significant (StatView for Windows; SAS Institute, Cary, NC).

Results

A total of 164 65-year-old patients or older with RCC were identified; 45.1% were women and 54.9% men. Eight patients (4.8%) died perioperatively and were included only in the surgical complications analysis. Thus, 156 patients with complete follow-up data were suitable for oncological and functional outcomes analysis.

Demographic characteristics

Mean age was 72.05 ± 5.57 (range 65–92). Median follow-up was 33 months (range 3–228). Regarding other comorbidities, only 22 (14.1%) patients were otherwise healthy, while 82 (52.6%) had hypertension, 66 (42.3%) overweight/obesity, 61 (39.1%) CKD, 55 (35.3%) diabetes, 47 (30.1%) dyslipidemia, and 28 (17.9%) other malignancies. Clinically, tumors were diagnosed due to a diversity of symptoms, including hematuria, back pain, palpable mass or fatigue, in 76 cases (48.7%). ECOG performance status was 0 in 107 (68.6%) and ≥1 in 49 (31.4%) patients.

Surgical outcome

Surgical approach was open radical nephrectomy in 114 (73.1%), laparoscopic radical nephrectomy in 13 (8.3%), open partial nephrectomy in 23 (14.7%), and laparoscopic partial nephrectomy in 6 cases (3.9%). Median estimated blood loss was 500 ml (range 50–4500 ml) with 53 patients (33.9%) receiving blood transfusion. Considering 8 perioperative mortality cases not included in other analyses, early surgical complications developed in 65 out of 164 patients (39.6%) including: 52 grade II, 1 grade IIIa, 1 grade IIIb, 3 grade IVa, and 8 grade V (Table 1).

Functional outcome

Renal function distribution of 156 patients was as follows: 61 (39.1%) had previous CKD, 53 (34%) developed newly onset postoperative CKD, and 42 (26.9%) maintained stable normal eGFR postoperatively.

Of those with previous CKD (61 patients, 39.1%), 32 experienced further impairment of renal function with 2 patients requiring temporary dialysis. Although the proportion of patients with worsened CKD was higher after RN in comparison to PN (54% vs. 45.4%), the difference was not significant ($p = 0.6$).

On the other hand, 53 patients (34%), with preoperative normal renal function developed newly onset postoperative CKD (30 grade 3a, 20 grade 3b, 2 grade 4 and 1 grade 5 of KDIGO classification) with 1 patient requiring temporary dialysis. As expected, this proportion of patients with ''de novo'' postoperative CKD was higher in those who underwent RN rather than PN (94.3% vs. 5.7%; $p = 0.0009$).

Other mid- and long-term complications included 2 cases of acute myocardial infarction, 1 stroke, 1 dementia, and 1 hyperparathyroidism. The frequency was higher for those who underwent RN vs. PN (41.7% vs. 13.8%; $p = 0.004$).

Table 1 Postoperative complications (Clavien–Dindo system).

	$N = 65$
Grade I	0
Grade II	
Chylous ascites	1
Thrombosis of left pampiniform plexus	1
Blood transfusion	50
Grade IIIa	
Gastrointestinal bleeding requiring endoscopy	1
Grade IIIb	
Ureteral injury during partial nephrectomy	1
Grade IVa	
Cardiac arrest	1
Pulmonary embolism	2
Grade IVb	0
Grade V	
Gastrointestinal bleeding	1
Disseminated intravascular coagulation	1
Myocardial infarction	1
Pulmonary embolism	1
Pneumonia	2
Sepsis	2

Oncological and survival analysis

Pathological stage distribution in 156 patients was: Stage I, 71 patients (45.5%); Stage II, 27 (17.3%); Stage III, 48 (30.8%); and Stage IV, 10 patients (6.4%). Mean tumor size was 6.9 ± 3.8 cm (1.8–23 cm), and only 41 (26%) patients had small renal masses (≤4 cm). During follow-up, 51 (32.6%) patients died, of whom 22 (14.1%) died from cancer. Other causes for mortality included cardiovascular disease (acute myocardial infarction, stroke, congestive heart failure) in 11 patients, other malignancies in 7, pneumonia in 6, CKD in 3, bleeding from pulmonary biopsy in 1, and trauma in 1.

Interestingly, the mean survival of patients dying of cancer was 31.3 ± 28.7 months, whereas for those dying of other causes was 56.8 ± 48.2 months ($p = 0.03$).

The 5-year OS for the entire cohort was 65%. When stratified according to pathological stage it was 77.6%, 71.9%, 45.1% and 11.7% for Stage I, II, III and IV, respectively ($p < 0.001$; Fig. 1). On univariate analysis, anemia, hypoalbuminemia, ECOG-PS, pathological stage, and nuclear grade were significantly associated to OS. However, on multivariate analysis (Table 2), only pathological stage remained as an independent predictor of OS (HR 1.96, 95% CI [1.36–2.84], $p = 0.0003$).

Discussion

As worldwide population ages, the frequency of several malignancies, including RCC, will continue to increase. Although surgical excision remains the standard of care for

Table 2 Univariate and multivariate analysis to predict OS in 156 elderly patients with RCC treated surgically.

	Univariate		Multivariate	
	HR [95% CI]	*p* value	HR [95% CI]	*p* value
Anemia	1.98 [1.13–3.49]	0.01	1.19 [0.58–2.41]	0.62
Hypoalbuminemia	2.38 [1.35–4.19]	0.002	1.49 [0.77–2.90]	0.23
ECOG performance status	2.80 [1.30–6.04]	0.008	1.77 [0.67–4.69]	0.24
Pathological stage	2.00 [1.49–2.70]	<0.0001	**1.96 [1.36–2.84]**	**0.0003**
Nuclear grade	1.54 [1.09–2.16]	0.01	1.13 [0.79–1.62]	0.47

OS, overall survival; RCC, renal-cell carcinoma; hazard ratio; CI, confidence interval.
In bold: statistically significant values.

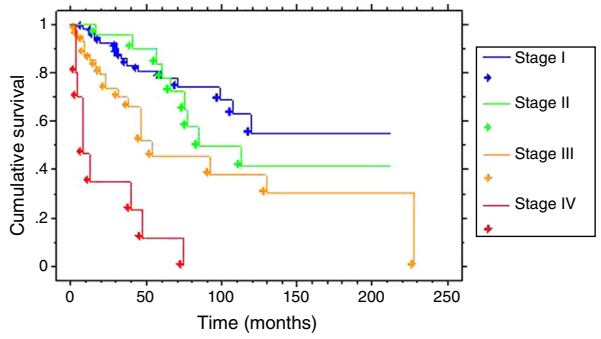

Figure 1 Meier curves for overall survival in 156 elderly patients with renal cell carcinoma according to pathological stage.

the vast majority of cases, there is a therapeutic dilemma in the elderly population since this subgroup is at higher risk of surgical complications. Moreover, previous comorbidities, performance status, and other family/social conditions could preclude surgical management. In those unfit for surgery, active surveillance or minimally invasive (ablative) therapy[12] could be good alternatives with acceptable outcomes.[9] At our institution, despite acceptable results, only few patients have been treated with radiofrequency ablation because of limited availability.[10] In the current series, only 26% of patients had small renal masses (SRM) amenable for minimally invasive/ablative therapy. Recently, the role of renal-mass biopsy,[11] active surveillance, and focal therapy[12] for the management of SRM has been discussed, highlighting the accuracy of 100% of biopsy for differentiating between malignancy and benignity.[11]

To our knowledge, this is the first report on surgical management of RCC in elderly people from a Latin American country. In line with other multi-institutional investigations, the proportion of patients who were symptomatic at diagnosis was 48.7%. Verhoest and colleagues described that 47.1% of patients with RCC aged $\geq$60 to $\leq$80 were symptomatic.[13] As expected, only 14.1% of our patients had no previous comorbidities while the rest had a diversity of other diseases, including hypertension, obesity/overweight, CKD, diabetes, dyslipidemia, and other malignancies. Of them, almost 40% had previous CKD, which is of paramount relevance when considering that preoperative eGFR predicts the risk of surgical complications in geriatric patients.[14]

The frequency of early postoperative complications in our series was similar to other ones. Berger and colleagues[14] described 38.8% of surgical complications, including 3.3% of grade V complications using the Clavien–Dindo grading system. On multivariate analysis, they found that ECOG-PS and preoperative renal function were independent predictors of postoperative complications in octagenarians.[14]

Although newly onset impairment of renal function was more frequent after RN, the vast majority of our patients developing CKD had Grade 3a and 3b CKD. This is in line with a recent series by Chung and coworkers who found that 70.2% of RN patients developed Stage III CKD in comparison to 25.4% of PN patients, without difference in the frequency of Stage IV CKD.[15] To date, the role of surgically induced CKD (CKD-S) on OS is controversial. In our series, 34% of patients experienced newly onset CKD; however, according to a recent investigation by Lane et al., CKD-S has lower impact on OS than CKD due to medical causes.[16]

During follow-up, in our series 32.6% of patients died and 14.1% died from cancer. Interestingly, survival of those dying from cancer was significantly shorter than that of those who died from other causes. Moreover, on multivariate analysis, only pathological stage independently predicted OS. This could be related to a recent finding published by members of the CORONA Project who found that older patients displayed a higher cancer-specific mortality in comparison with younger individuals despite a lower proportion of advanced tumors.[17] This phenomenon could be attributed to a more aggressive tumor behavior in geriatric population, suggesting that the decision for elderly patients to undertake surgical treatment should be based not only on patient's age, but taking into account tumor characteristics, comorbidities, performance status, and geriatric parameters.

Our study has certain drawbacks relative to retrospective investigations and limited number of patients. Although the inclusion of comorbidity index would be helpful, this parameter is not of paramount relevance. Rather, a meticulous preoperative geriatric assessment using validated instruments could be more useful and should be integrated as part of standard evaluation to improve the decision process in the elderly population. Currently, the laparoscopic approach is the standard of care for the management of renal tumors; however, our series includes a large number of open surgeries, reflecting the time span analyzed. The strengths of our investigation include a thorough evaluation of renal function (before and after surgery), the use of a standardized complication system (Clavien–Dindo) and performance status.

Conclusion

Elderly patients with RCC tend to have multiple comorbidities. Although the surgical management of RCC appears to be safe in properly selected patients aged 65 or older, this subgroup has higher risk of perioperative mortality and complications. Patients dying from cancer had shorter survival than those dying from other causes. Pathological stage remained an independent predictor of overall survival in this population.

Conflict of interest

Francisco Rodríguez-Covarrubias declares receiving fees as speaker for MSD and Ferring, not related to the content of this article. Ricardo A. Castillejos-Molina declares receiving fees as speaker for Lilly Icos not related to the content of this article. Mariano Sotomayor-de-Zavaleta declares receiving fees as advisor board member and speaker for Lilly-Icos, not related to the content of this article. The rest of the authors have nothing to disclose.

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