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Characteristics and Surgical Outcomes in Very Elderly Patients (≥75 years) with Renal Cell Carcinoma: Data from the Latin American Renal Cancer Group

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ABSTRACT

Background: The incidence of renal cell carcinoma (RCC) is increasing globally due to an aging population and widespread use of imaging studies. **Objective:** The aim of this study was to describe the characteristics and perioperative outcomes of RCC surgery in very elderly patients (VEP), ≥ 75 years of age. **Methods:** This is a retrospective comparative study of 3656 patients who underwent the treatment for RCC from 1990 to 2015 in 28 centers from eight Latin American countries. We compared baseline characteristics as well as clinical and perioperative outcomes according to age groups (<75 vs. ≥75 years). Surgical complications were classified with the Clavien-Dindo score. We performed logistic regression analysis to identify factors associated with perioperative complications. **Results:** There were 410 VEP patients (11.2%). On bivariate analysis, VEP had a lower body mass index ($p < 0.01$) and higher ASA score (ASA >2 in 26.3% vs. 12.4%, $p < 0.01$). There was no difference in performance status and clinical stage between the study groups. There were no differences in surgical margins, estimated blood loss

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(EBL), complication, and mortality rates (1.3% vs. 0.4%, p = 0.17). On multivariate regression analysis, age ≥75 years (odds ratio [OR] 2.33, p < 0.01), EBL ≥ 500 cc (OR 3.34, p < 0.01), and > pT2 stage (OR 1.63, p = 0.04) were independently associated with perioperative complications. **Conclusions:** Surgical resection of RCC was safe and successful in VEP. Age ≥75 years was independently associated with 30-day perioperative complications. However, the vast majority were low-grade complications. Age alone should not guide decision-making in these patients, and treatment must be tailored according to performance status and severity of comorbidities. (Rev Invest Clin. 2020;72(5):308-15)

Key words: Kidney cancer. Elderly. Nephrectomy. Latin America. Surgical Complications. Surgical outcomes.

INTRODUCTION

Genitourinary malignancies represent a significant public health problem, particularly in developing countries were up to 52% of all genitourinary cancer deaths occur[1]. In the most recent compilation of data on population-based cancer occurrence, the American Cancer Society estimated that kidney and renal pelvis tumors account for the 6th most common estimated new cancer cases in men (5%) and the 8th in women (3%) in the United States[2] The World Health Organization estimated that by 2018, from the total combined cancer data, kidney tumors were responsible for 403,262 (2.2%) estimated new cancer cases and 175,098 (1.8%) cancer deaths in the world. Furthermore, the worldwide age standardized rate (per 100,000 persons per year) for new cases of kidney cancer was 6.0 for men and 3.1 for women, while in low or medium human development index regions, it was 1.8 for men and 1.1 for women[3]. In addition, it has been recently demonstrated that over the most recent 10-year period, the greatest increase in renal cell carcinoma (RCC) incidence occurred in Central and South America, where the average annual percentage change ranged from 3.0% to 6.8% in men and 2.5% to 6.4% in women[4].

Due to increasing life expectancy, the number of incident cases of RCC will continue to grow and an increasing proportion of patients aged 75 or older will be ultimately diagnosed with renal cancer and will be considered for active treatment. Despite technological and pharmacological developments, surgery is the cornerstone for the management of most localized (T1/T2) and locally advanced (T3) tumors. Nonetheless, the benefit of this strategy is unclear for elder patients, particularly for frail individuals at higher risk of surgical complications. Guzzo et al. reported an overall complication rate of 22.6% and 0% mortality rate in a cohort of 115 patients >75 years of age who underwent laparoscopic renal surgery in the United States[5].

We have previously described our surgical experience in a small cohort of elderly patients with RCC showing that surgery appears to be safe in properly selected cases[6]. To the best of our knowledge, larger reports coming from Latin America are scarce. Therefore, our objective was to compare clinical characteristics and perioperative outcomes of patients 75 years or older with their younger counterparts treated surgically for RCC in Latin America.

METHODS

This is a retrospective comparative study of the database of patients with renal tumors from the Latin American Renal Cancer Group (LARCG)[7]. It comprised data from 3656 patients who underwent surgery for RCC from 1990 to 2015 in 28 centers from eight Latin American countries. This study was approved by the corresponding Review Board of each institution. For this study, baseline characteristics as well as clinical and perioperative outcomes according to age groups (<75 years vs. ≥75 years) were compared. We arbitrarily defined very elderly patients (VEP) as those 75 years or older due to RCC epidemiology trends. Patients who did not undergo surgical treatment were excluded from this study. Variables analyzed included sex, age, renal function, comorbidities, eastern cooperative oncology group performance status, tumor stage, clinical stage (using the American Joint Committee on Cancer tumor-node-metastasis 8th edition staging system), type of surgery, estimated blood loss (EBL), length of hospital stay (LOS), and perioperative complications[8]. Surgical complications were classified according to the Clavien-Dindo classification[9]. Major complications were defined as Clavien-Dindo >II.

Table 1. Baseline characteristics between the study groups

	<75 year old (%)	≥75 (%)	p-value
Sex			0.99
Male	2121 (65.4)	268 (65.4)	
Female	1123 (34.6)	142 (34.6)	
BMI (kg/m^2)	28.1 ± 5.4	26.7 ± 4.2	0.01
Smoking status			0.01
Active smoker	228 (11.3)	25 (8.7)	
Ex-smoker	699 (34.7)	76 (26.7)	
Non-smoker	1087 (54)	184 (64.6)	
Hypertension			<0.01
Yes	436 (13.4)	91 (22.2)	
No	2810 (86.6)	319 (77.8)	
ECOG			0.12
ECOG 0-1	1822 (96.2)	246 (94.3)	
ECOG >1	71 (3.8)	15 (5.7)	
ASA			0.01
ASA 1-2	2263 (84.2)	232 (64.8)	
ASA >2	426 (15.8)	126 (35.2)	
Signs and symptoms at diagnosis			0.78
Yes	1667 (61.6)	218 (60.9)	
No	1037 (38.4)	140 (39.1)	
Clinical stage			0.57
CS I	1234 (60.5)	151 (59)	
CS II	324 (15.9)	42 (16.4)	
CS III	328 (16.1)	48 (18.8)	
CS IV	154 (7.5)	15 (5.8)	

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group.

Statistical analysis was performed using the SPSS 20.0 for IBM. For descriptive statistics, we used central tendency measures such as mean or median. Standard deviation or interquartile range and range were used as dispersion descriptive measures. Bivariate analysis was performed using paired samples test by t-test while non-parametric variables were compared with Mann–Whitney U-test. Proportions were compared using Chi-square test. Binary logistic regression analysis was performed to identify independent risk factors associated with perioperative outcomes and complications. Any $p \leq 0.05$ or 5% were considered as statistically significant for a two-tied distribution.

RESULTS

Baseline patient characteristics between the study groups are summarized in Table 1. Four-hundred and ten patients (11.2%) were ≥75 years old compared to 3246 (88.8%) patients who were <75 years old.

Table 2. Comparison of pathological characteristics between the study groups

	<75 year old (%)	≥75 (%)	p-value
Histology			0.01
Clear cell	1785 (55)	268 (65.4)	
Other	1461 (45)	142 (34.6)	
Fuhrman			0.95
Low grade	1359 (66.8)	184 (66.7)	
High grade	674 (33.2)	92 (33.3)	
pT stage			0.20
pT1-T2	2142 (79.8)	266 (76.9)	
pT3-T4	541 (20.2)	80 (23.1)	
pTumor size (cm)	5.0 ± 4.7	5.2 ± 4.5	0.33
Multifocality			0.42
Yes	130 (5.1)	23 (6.5)	
No	2477 (94.9)	331 (93.5)	
pN			0.78
pN0	1710 (94.5)	208 (95)	
pN1	99 (5.5)	11 (5.0)	
pM			0.99
pM0	1670 (90.8)	216 (90.8)	
pM1	170 (9.2)	22 (9.2)	

The median follow-up was 21.4 months. On bivariate analysis, patients <75 years had a higher body mass index and had more active smokers. On the other hand, older patients ≥75 years had more hypertension and a higher ASA score. There were no differences in signs and symptoms at diagnosis and performance status between the study groups.

There were no differences regarding clinical stage, pT stage, pathologic tumor size, Fuhrman grade, multifocality, pN, or pM between the study groups (Table 2). However, clear cell histology was far more frequent in the VEP (65.4% vs. 55%, p < 0.01). Tumor complexity assessment information was not the focus of our study and was not analyzed.

The laparoscopic approach (44.4% vs. 37.4%, p < 0.02) and radical nephrectomy (72.2% vs. 57.9%, p < 0.01) were far more commonly performed in VEP. Surgical and perioperative characteristics are listed in Table 3. There were no differences in surgical margin status, lymph node dissection, EBL, and complication rates. Major complication rates, defined as Clavien-Dindo Grade >II, were also similar between the study groups (5.0% vs. 4.2% in VEP, p = 0.59). Perioperative mortality was also similar between the study groups (0.4% vs. 1.4% in VEP, p = 0.85). LOS was slightly longer in older patients (4 ± 4 vs. 4 ± 3 days, p < 0.01). Subgroup analysis among patients treated with partial nephrectomy was performed, and no differences were observed with regard to total complication rates between the study groups (p = 0.99, Table 4). No perioperative deaths were registered among those 75 years or older who underwent partial nephrectomy.

On our multivariate logistic regression analysis, EBL ≥500 cc (odds ratio [OR] 3.34, CI 2.23-4.99), age ≥ 75 years (OR 2.33, CI 1.29-4.21), open surgery (OR 2.52, CI 1.70-3.77), and > pT2 stage (OR 1.63,

Table 3. Surgical and perioperative characteristics between the study groups

	<75 year old (%)	≥75 (%)	p-value
Surgical approach			0.02
Laparoscopic	1164 (37.4)	176 (44.5)	
RALP	24 (0.7)	4 (1.0)	
Open	1927 (61.9)	216 (54.5)	
Primary tumor treatment			0.01
Radical nephrectomy	1878 (57.9)	296 (72.2)	
Partial nephrectomy	1368 (42.1)	114 (27.8)	
Surgical time (min)	174 ± 88	164 ± 75	0.01
EBL (mL)	455 ± 675	416 ± 473	0.37
Surgical margins			0.77
Positive	102 (3.4)	12 (3.1)	
Negative	2885 (96.6)	371 (96.9)	
Blood transfusion			0.28
Yes	455 (17.5)	66 (19.9)	
No	2140 (82.5)	265 (80.1)	
Lymphadenectomy			0.06
Yes	532 (19.1)	47 (12.9)	
No	2250 (80.9)	318 (87.1)	
Clavien-Dindo			0.17
None	572 (43.7)	96 (44.7)	
Clavien I-II	670 (51.2)	110 (51.2)	
Clavien III-IV	61 (4.7)	6 (2.8)	
Clavien V	5 (0.4)	3 (1.3)	
Length of stay (days)	4 ± 3	4 ± 4	0.01

EBL: estimated blood loss.

CI 1.02-2.59, p < 0.04) were associated with 30-day perioperative complications following surgical treatment for RCC (Table 5).

DISCUSSION

In the past decade, an increase in the incidence of RCC has been detected in most countries, particularly in Latin American populations for both men and women[4]. This is probably due to the widespread use of abdominal imaging studies for other diagnostic purposes. Nevertheless, while mortality trends have been steady or declining in high-income countries, they have remained unchanged or even increased in Latin America[4].

Although the treatment of choice for localized renal masses should be individualized, surgical resection (including nephron-sparing surgery [NSS]) is still considered the standard of care for organ-confined disease[10]. In experienced hands, NSS is an excellent alternative for patients with small renal masses (SRM), with oncological equivalence and better preservation

Table 4. Comparison of complication rates following partial nephrectomy between the study groups

Clavien-Dindo	<75 year old (%)	≥75 (%)	p-value
None	200 (45.1)	20 (45.5)	0.99
Clavien I-II	222 (50.1)	22 (50.0)	
Clavien III-IV	20 (4.6)	2 (4.5)	
Clavien V	1 (0.2)	0 (0)	

Table 5. Independent risk factors for 30-day perioperative complications following primary treatment

Variable	OR	CI	p-value
Univariate			
Age ≥75 years	1.05	0.77-1.42	0.75
EBL ≥500	5.33	4.07-6.97	0.01
BMI ≥30 kg/m^2	1.44	1.04-1.98	0.03
Partial nephrectomy*	0.85	0.68-1.05	0.13
> pT2 stage	1.89	1.44-2.47	0.01
Open Surgery**	1.67	1.34-2.08	0.01
Multivariate			
Age ≥75 years	2.33	1.29-4.21	0.01
EBL ≥500	3.34	2.23-4.98	<0.01
BMI ≥30 kg/m^2	1.50	0.97-2.3	0.07
> pT2 stage	1.63	1.02-2.59	0.04
Open surgery**	2.52	1.70-3.77	<0.01

*Radical nephrectomy.
**Minimally invasive surgery.
EBL: estimated blood loss; OR: odds ratio; BMI: body mass index.

of renal function when compared to radical nephrectomy[11].

Active surveillance (AS) for SRM has gained popularity worldwide since large cohorts have demonstrated that adherent patients have low risk of metastasis (1–2%) at a median of 2-year follow-up[12]. These results are encouraging and AS must be considered an alternative in the VEP that is a poor surgical candidate.

Nonetheless, the optimal treatment option in the VEP is debatable, to say the least. An adequate general and geriatric evaluation by a multidisciplinary team may provide additional insight for deciding the optimal treatment in this patient population[13]. A large retrospective study of 537 patients demonstrated that active treatment in patients aged ≥75 years with clinical T1 renal cancer was not associated with improved overall survival and that nephrectomy accelerated renal dysfunction[14]. A recent study of 115 octogenarian patients observed no differences in survival between AS, NSS, and radical nephrectomy for SRM[15]. However, AS may be inadequate in healthy elderly patients and surgical resection should always be considered in selected individuals because at least 20% of SRM are considered to be potentially aggressive cancers[16].

Despite the previous findings, the surgical modality of choice (RN vs. NSS) for localized renal masses in

elderly patient is still unclear. In this study, we observed that while patients 75 years or older had higher ASA scores (ASA >2) and larger tumors, they did not have higher 30-day total complication rate. A recent study where a propensity score analysis of surgical, functional, and oncologic outcomes was performed between 613 patients over 75 years of age compared to matched controls who underwent partial versus radical nephrectomy, found that partial nephrectomy in elderly patients with localized tumors did not compromise oncologic outcomes and allowed better functional preservation compared to radical nephrectomy during a 3-year follow-up. However, they reported a higher overall complication rate in the partial nephrectomy group (33% vs. 25%, p = 0.01)[17]. In our study, partial nephrectomy was performed less commonly in older patients and, on subgroup analysis, there were no differences in complication rates between the study groups. Moreover, long-term renal function was not analyzed in our database. The laparoscopic approach was more common in this subgroup, with no differences in EBL and blood transfusion rates. Surgical time was shorter in VEP, and a possible explanation for this is that more patients underwent radical nephrectomy. On the other hand, LOS was slightly higher in VEP (p < 0.01). Interestingly, in our bivariate analysis, VEP did not have greater perioperative complications; however, in our sparse multivariate model, the variables associated with 30-day perioperative complications (Clavien-Dindo Grade I-V) following surgery were EBL ≥500 cc, open surgery, age ≥75 years, and > pT2 stage. Of greater importance, in our multivariate logistic regression analysis, age ≥75 years was not associated (OR 1.22, CI 0.60-2.48, p = 0.59) with greater major complications (Clavien-Dindo >II).

The main limitations of this study are its retrospective nature and the missing data that are intrinsic to multicenter databases such as LARCG. LARCG, however, is the first Latin American effort to create a multinational patient database for patients with RCC, and we believe that these results are clinically useful in our population. Larger prospective studies should be conducted to further address this issue.

The higher perioperative complication rates and the fact that renal function benefit after NSS is seen throughout many years of follow-up may make this surgical approach for elderly patient unappealing to some surgeons, and this is possibly the reason more of these patients were treated with radical nephrectomy in our cohort. However, our data suggest that there is no difference in perioperative complication rates of NSS between the study groups. An et al. reported similar perioperative outcomes and further demonstrated that NSS was associated with better preservation of renal function and equivalent overall and cancer-specific survival between modalities[18]. Thus, in countries, where there is limited experience with minimally invasive ablative techniques or if clinical follow-up may be a concern, we recommend surgical resection (NSS in experienced hands) as primary treatment in physically fit elderly patients.

Surgical resection of RCC is safe and successful in properly selected VEPs. Age ≥75 years was an independent risk factor associated with any 30-day perioperative complications following surgical treatment for RCC. However, perioperative outcomes, most importantly major complication and mortality rates, are similar to their younger counterparts. Age alone should not guide decision making in these patients, and treatment must be tailored according to performance status and severity of other comorbidities.

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These results were presented at the American Urological Association's (AUA) 2018 Annual Meeting in San Francisco, California.

This is a retrospective study of a large database of patients from Latin America. This study was IRB approved at each institution.

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