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Sisto Perdonà , Claudio Simeone , Carlotta Palumbo ,
Umberto Capitanio , Ithaar Derweesh , Francesco Porpiglia ,
Riccardo Autorino

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Alessandro Antonelli¹, Alessandro Veccia^{1,2}, Nicola Pavan³, Carmen Mir⁴,
Alberto Breda⁵, Toshio Takagi⁶, Koon H. Rha⁷, Tobias Maurer⁸, Chao Zhang⁹,
Jean-Alexandre Long¹⁰, Cosimo De Nunzio¹¹, Estevão Lima¹², Matteo Ferro¹³,
Salvatore Micali¹⁴, Giuseppe Quarto¹⁵, Estefania Linares¹⁶, Antonio Celia¹⁷,
Luigi Schips¹⁸, Pierluigi Bove¹⁹, Alessandro Larcher²⁰, Cristian Fiori²¹,
Alexandre Mottrie²², Ahmet Bindayi²³, Carlo Trombetta³, Tommaso Silvestri³,
Joan Palou⁵, Oscar Rodriguez Faba⁵, Kazunari Tanabe⁶, Bo Yang⁹, Gaelle Fiard¹⁰,
Andrea Tubaro¹¹, Joao Nuno Torres¹², Ottavio De Cobelli¹³, Luigi Bevilacqua¹⁴,
Roberto Castellucci¹⁸, Andrew Tracey², Lance J. Hampton², Francesco Montorsi²⁰,
Sisto Perdonà¹⁵, Claudio Simeone¹, Carlotta Palumbo¹, Umberto Capitanio²⁰,
Ithaar Derweesh²³, Francesco Porpiglia²¹, Riccardo Autorino²

¹Urology Unit, ASST Spedali Civili Hospital, Brescia, Italy, Department of Medical and Surgical Specialties, Radiological Science, and Public Health, University of Brescia, Italy; ²Division of Urology, VCU Health, Richmond, VA, USA; ³Department of Urology, Cattinara Hospital, University of Trieste, Italy; ⁴Department of Urology, Instituto Valenciano de Oncología Foundation, Valencia, Spain; ⁵Department of Urology, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain; ⁶Department of Urology, Tokyo Women's Medical University, Tokyo, Japan; ⁷Department of Urology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; ⁸Department

of Urology, Medical Center rechts der Isar, Technical University of Munich, Munich, Germany; ⁹Department of Urology, Changhai Hospital, Shanghai, China; ¹⁰Department of Urology and Kidney Transplantation, Grenoble University Hospital, Grenoble, France; ¹¹Department of Urology, Hospital "Sant' Andrea", Sapienza University, Rome, Italy; ¹²Department of Urology, Hospital de Braga, Braga, Portugal; ¹³Department of Urology, European Institute of Oncology, Milan, Italy; ¹⁴Department of Urology, University of Modena and Reggio Emilia, Modena, Italy; ¹⁵Uro-Gynecological Department, Fondazione "G. Pascale" IRCCS, Naples, Italy; ¹⁶Department of Urology. Hospital Universitario La Paz. Madrid. Spain; ¹⁷Department of Urology, San Bassiano Hospital, Bassano Del Grappa, Italy; ¹⁸Department of Urology, SS. Annunziata Hospital, "G.D'Annunzio" University of Chieti, Chieti, Italy; ¹⁹Department of Urology, San Carlo di Nancy, Tor Vergata University, Rome, Italy; ²⁰Department of Urology and Division of Experimental Oncology, URI, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Milan, Italy; ²¹Department of Urology, San Luigi Gonzaga Hospital, University of Turin, Orbassano, Turin, Italy; ²²Department of Urology, OLV Ziekenhuis, Aalst, Belgium; ²³Department of Urology, UCSD Health System, La Jolla, CA, USA

Corresponding Author:

Riccardo Autorino, MD, PhD

Associate Professor of Urology

Division of Urology, VCU Medical Center

PO Box 980118, Richmond, VA 23298-0118

Phone: 804-828-5320; Fax: 804-828-2157

Email: ricautor@gmail.com

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ABSTRACT

Objectives. To analyze the outcomes of partial nephrectomy (PN) and radical nephrectomy (RN) in octogenarian patients.

Methods. The RESURGE (REnal SURgery in the Eldely) multi-institutional database was queried to identify patients ≥ 80 years old who had undergone a PN or RN for a renal tumor. Multivariable binary logistic regression estimated the association between type of surgery and occurrence of complications. Multivariable Cox regression model assessed the association between type of surgery and All-Causes Mortality.

Results. The study analyzed 585 patients (median age 83 years, IQR 81-84), 364 of whom (62.2%) underwent RN and 221 (37.8%) PN. Patients undergoing RN were older ($p=0.0084$), had larger tumor size ($p<0.0001$) and higher clinical stage ($p<0.001$). At multivariable analysis for complications, the only significant difference was found for lower risk of major postoperative complications for laparoscopic RN compared to open RN (OR: 0.42; $p=0.04$). The rate of significant ($>25\%$) decrease of eGFR in PN and RN was 18% vs 59% at 1 month, and 23% vs 65% at 6 months (p values <0.0001). After a median follow up time of 39 months, 161 patients (31%) died, of whom 105 (20%) due to renal cancer.

Conclusions. In this patient population both RN and PN carry a non-negligible risk of complications. When surgical removal is indicated, PN should be preferred, whenever technically feasible, as it can offer better preservation of renal function, without increasing the risk of complications. Moreover, a minimally invasive approach should be pursued, as it can translate into lower surgical morbidity.

Abbreviations: PN: Partial Nephrectomy; RN: Radical Nephrectomy; RESURGE: REnal SURGery in the Elderly; RCC: Renal Cell Carcinoma; AS: Active Surveillance; ACM: All-Causes Mortality; eGFR: estimated Glomerular Filtration Rate

Introduction

Renal Cell Carcinoma (RCC) has a peak in its incidence between the sixth and seventh decade, but older patients cover up to a third of new diagnoses¹, and their number is on the rise given prolonged life expectancy. Thus, urologists, oncologists and geriatricians will be increasingly facing with the complex issue of how to manage RCC in the “very” elderly. Especially in this setting, patients’ and tumor’s features needs to be considered to assess which management option offers the optimal trade-off between risks and benefits.

Despite general trend is in favour of partial nephrectomy (PN) and minimally invasive approaches², in many centers open radical nephrectomy (ORN) still represents the preferred surgical way in very elderly subjects³. Evidence supporting nephron-sparing and minimally invasive approaches for these subjects remains sparse, and studies adopted liberal definitions of “elderly” (as over 65, 70 or 75 years^{4,5})⁶. Only a handful number of small series focused their attention “octogenarians” or “oldest old”, as defined by the World Health Organization⁷.

The aim of this study was to provide a comprehensive comparison of surgical, functional and survival outcomes of PN versus RN in these “very elderly” (octogenarian) patients through the analysis of a multi-institutional international dataset (RESURGE: REnal SURGery in the Elderly).

Material and methods

Study design

The RESURGE project involves 23 Institutions from Europe, United States and Asia, with the objective to collect a large dataset on elderly patients undergoing surgery for RCC between 2000 and 2016. A data-sheet was shared and merged, reporting pre-, intra- and post-operative data, functional and survival follow up information^{8,9}. Institutional Review Board approval was obtained by each center.

The present study retrospectively analyzes the patients aged 80 years-old or more with complete data. Comorbidities were described by the Charlson-Romano score¹⁰; Glomerular Filtration Rate was estimated (eGFR) by the chronic kidney disease epidemiology collaboration (CKD-EPI) formula¹¹; the staging system was updated to the 2017 edition of the TNM classification¹²; post-operative complications were classified in agreement with the Clavien-Dindo system¹³. The indication to surgery, as well as the type of surgery (PN or RN) and approach were established at each Institution following surgeon's and patient's preferences. Follow up was conducted according to various schedules at each Institution and incomplete data were retrieved by registries consultation or phone interview. The causes of death were detailed as due to RCC or other reasons.

Statistical analysis

Categorical variables were described as numbers and proportions; continuous variables as medians and interquartile range (IQR). Patients submitted to PN vs RN

were compared by the Pearson's chi-square test and Kruskal-Wallis h test for categorical and continuous variables, respectively.

Multivariable binary logistic regression estimated the association between the type of surgery (PN or RN) and the occurrence of intra-, overall post-operative and major post-operative complications. Potential confounders (age, gender, BMI, Charlson score - 0 vs 1-2 vs ≥ 3 , open vs laparoscopic vs robotic approaches, pathological tumor size, R.E.N.A.L. score, pT - pT1 vs pT2 vs pT >2 , pN - pN0 vs pNx vs pN+, low vs high grading) were initially tested at univariate analysis and only those with a p significance <0.1 were included into final multivariable analysis.

Following a similar design, multivariable Cox regression model assessed the association between the type of surgery and All-Causes Mortality (ACM), imputing time intervals as the period in months between surgery and death due to RCC or other causes or the last available control. All statistical analysis was performed with STATA®15 (StataCorp LLC, College Station, TX, USA).

Results

The study analyzed the data of 585 "octogenarian" patients (median age 83 years, IQR 81-84), 364 of whom (62.2%) underwent RN and 221 (37.8%) PN. Patients undergoing RN were older (83.1 vs 82.4 years, $p=0.0084$), had lower prevalence of hypertension (58% vs 70%, $p=0.005$), higher rate of baseline CKD stage III (47% vs 30%, $p=0.038$), larger clinical size (5.9 vs 3.5 cm, $p<0.0001$), higher clinical stage ($p<0.001$). Baseline eGFR and distribution of Charlson scores were similar between

groups. Moreover, pathological tumor size, pathological staging and grading were more advanced in the RN group (**Table 1**).

Peri-operative morbidity

PN had shorter operative time (150 [IQR 118-200] vs 170 [125-220] mins; $p=0.020$) and similar EBL (200 [100-400] vs 225 [100-400] ml; $p=0.1573$), whereas no difference was recorded for complications between the two study groups (**Table 2**).

At multivariable analysis for complications, the only significant difference was found for lower risk of major postoperative complications for laparoscopic RN compared to open RN (OR: 0.42; $p=0.04$) (**Table 3**). A detailed description of complications is summarized in **electronic supplementary table 1**.

Functional outcomes

Starting from similar baseline eGFR (RN median eGFR 60 ml/min, IQR 45-73; PN 60 ml/min, IQR 46-77, $p=0.3588$), the observed variations in eGFR after PN and RN were -3 (IQR -13, 0) vs -16 (IQR -26, -8) ml/min and -6 (-14, 0) vs -17 (-27, -8) ml/min, at 1 and 6 months respectively. The respective percentage variations were -3% (IQR -13%, 0%) vs -35% (IQR -42%, -13%) and -6% (IQR -14%, 0%) vs -31% (IQR -42%, -15%) (all p values <0.0001). The rate of significant ($>25\%$) decrease of eGFR in PN and RN was 18% vs 59% at 1 month, and 23% vs 65% at 6 months (all p values <0.0001).

Survival Analysis

After a median follow up time of 39 months (IQR 12-54), 161 patients (31%) died, 105 (20%) due to renal cancer and 59 (11%) for other causes. At univariate analysis ACM was associated to a Charlson index ≥ 3 (HR 1.6, $p=0.017$), type of surgery (RN referent, HR for PN 0.7, $p=0.033$) and a pT stage ≥ 3 (pT1-2 referent, HR for pT ≥ 3 1.5,

$p=0.066$). However, none of these factors reached statistical significance at multivariable analysis (**Table 4**).

Discussion

Current guidelines recommend PN over RN in resectable cT1 RCC, as better preservation of renal function protects from cardiovascular events¹⁴, and, according to more recent evidence, might even decrease cancer-specific mortality¹⁵. While the debate on which patients are really harmed by RN is ongoing¹⁶, several studies suggest that PN might be especially advantageous in more comorbid and frailer subjects¹⁷. However, in clinical practice RN seems to be still preferred to PN in the oldest patients. Population studies on large US datasets indeed show that PN for T1a RCC is done in 68% of 20-44 years subjects¹⁸, but only 28% in those over 65 years old¹⁹. These figures suggest that PN is generally disregarded in elderly patients likely because they are considered at higher risk for surgery-related complications. This translates into neglecting the potential advantages related to a better preservation of an already compromised baseline renal function.

The present study gives an insight in a large, multi-institutional cohort of “oldest old” (octogenarian) patients, a population representing probably the contemporary frontier for surgery, being close to the limit of life expectancy in industrialized countries⁷. The analysis of this unique dataset allowed to have some interesting findings. First, PN or RN were both adopted as surgical approach at the participating Institutions, and minimally invasive approach was preferred in about 40% of cases. Not surprisingly, RN was preferred for larger (mean tumor size 5.9 cm) and higher stage (70% clinical

stage T2-4) tumors, whereas PN was mostly adopted for the so called small renal mass (SRM) (mean tumor size 3.5 cm and about 80% cT1 stage). Second, both RN and PN carry a non-negligible number of overall and major complications in this patient population. In this respect, our data are consistent with those of literature^{20,21,22} Nevertheless, our analysis also suggests that, despite being a potential more harmful procedure, PN might not carry a higher risk of complications over RN, and therefore it should not be discouraged solely based on the elderly age. Third, it is confirmed that PN offered a significant higher preservation of renal function keeping these subjects with borderline or impaired baseline function within safety limits with respect to end-stage CKD. Last, we found that despite advanced age, RCC represents a primary cause of death, confirming that elderly patients are often burdened by more aggressive and lethal tumors, as previously reported²³. ACM was not influenced by the type of surgery but comorbidities and tumor stage, confirming that PN provide equivalent survival as RN, but also indicating that within this age group no survival advantages should be expected²².

The available literature on kidney cancer surgery in octogenarian patients remains sparse, with only a handful number of studies specifically focusing on the “oldest old” (**Electronic supplementary table 2**). Hellenthal et al showed in a large cohort of patients extracted from Surveillance, Epidemiology, and End Results database that PN was less used for elderly patients and cancer mortality similar in two matched groups of ≤ 80 vs ≥ 80 years old. The latter group had however higher other causes mortality and was 1.31 folds likely to die for any causes and 2.54 times for RCC when submitted to RN⁶. More recently, May et al performed a multicenter analysis comparing

mortality of octogenarians with younger patients showing that cancer-specific mortality was related to age and tumor's features and not to the type of surgery²⁵. Tang et al retrospectively analyzed a group of 115 patients with a median age of 82 by comparing active surveillance (AS), PN and RN. No difference in overall survival or disease-specific survival among the three management strategies was found on univariable analysis, and multivariable analysis for overall survival found the Charlson comorbidity index as the only factor associated with worse survival. Therefore, the authors concluded that an “active treatment” (either PN or RN) might not provide a survival advantage compared with AS in this group of patients²⁶. The feasibility of laparoscopic approaches with acceptable complications rates in these patients was first showed by the studies of Pareek et al²⁰ and Thomas et al²¹. On the other hand, a multicenter analysis from 5 academic centers in France on 180 octogenarians mostly submitted to open RN (80% of sample) found that morbidity and mortality were significant²⁷. In this respect, our analysis shows that a minimally invasive approach for RN should be preferred, as it offer a lower risk (OR=0.42) of major complications, which especially in this group of patients might have a clinically significant impact.

The present study presents the largest cohort of octogenarians to date reported, and it offers a comprehensive analysis of surgical outcomes. We confirmed that PN and minimally invasive approaches are feasible with lower complications. This is a noteworthy advantage in this subset of patients burdened by risks specifically related to the hospitalization, as falls and fractures, delirium, etc. Moreover, this is the first study investigating changes in renal function in the oldest old showing that PN could avoid or delay end-stage CKD with its detrimental effects in such population⁵. Finally, we

confirmed that patient's comorbidity status and tumor's features rather than type of surgery have an impact on survival, probably because the functional advantages that are attributable to PN end up being diluted in subjects with shorter life expectancy. Nevertheless, octogenarian are patients to whom the best choice treatment still remains a dilemma. General conditions, changed physiology, life expectancy, medications, and patients' expectations make elderly suitable for other kind of treatments. In a significant portion of the aforementioned population, Active Surveillance (AS) represents a valid alternative treatment which is gaining more relevance. Literature evidences demonstrated that on carefully selected patients AS gives valuable results. Indeed, in a review on 17 studies including 36496 elderly, it was shown that AS presents a low rate of conversion to active treatment with mortality related more to comorbidities rather than RCC²⁷. Likewise, less invasive treatment as SRM ablation could be considered as an alternative in octogenarian. Among the few studies available, this procedure demonstrated to be safe and feasible without compromising survival outcomes. Moreover, the analysis of post-operative and functional outcomes revealed optimal results making percutaneous ablation an attractive form of treatment²⁸.

Our study is not devoid of limitations. The retrospective design carries inherent biases related to data collection and selection bias for the type of surgery. Such a bias has been widely debated into the literature, and only a randomized trial could account for it. Moreover, the fact that participating Institutions are academic and/or referral centers, which limits the reproducibility of these findings in other types of hospital settings. In addition, given the multicenter nature of the study, there is an intrinsic heterogeneity in surgical technique and expertise among the different institutions (and

surgeons) that is difficult to account for, and this should be taken into account when interpreting our study findings. The lack of control groups for AS and tumor ablation can be also regarded as an additional limitation, as these are two safe and effective management options in this patients population^{27,28}. Moreover, the median study follow-up is was just over 3 years, which in general might not be considered fully adequate when studying a population with kidney cancer. However, given the advanced age of these patients (and related limited life expectancy), we believe it is still meaningful to look at this time frame. Last, the lack of validated tools to assess frailty that should become mandatory in future studies in this subset of patients²⁹.

Conclusions

The management of renal mass in the octogenarian patient represents a challenging scenario. This multicenter analysis, based on “real life” data, allows to get some useful information that can be used for patient counseling and surgical decision-making. One should be aware that in this patient population both RN and PN can carry a non-negligible risk of complications, and therefore they should be reserved for larger tumors where more conservative approaches (AS; ablation) are suboptimal. When surgical removal is indicated, PN should be preferred over RN, whenever technically feasible, as it can offer better preservation of renal function, without increasing the risk of complications. Moreover, a minimally invasive approach should be pursued in this very frail population, as it can potentially translate into lower surgical morbidity.

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	RN (364)^a	PN (221)^a	p value
Patients' baseline features			
Age (years)	83.1±2.7	82.3±2.0	0.008
Female gender	181 (49.7)	122 (55.2)	0.199
BMI (kg/m ²)	25.4±3.8	25.7±3.6	0.145
Diabetes	82 (23.1)	41 (20.1)	0.410

Hypertension	206 (58.2)	142 (70.3)	0.005
Preoperative Hb (mg/dL)	12.3±2	12.8±1.9	0.006
Preoperative eGFR (mL/min)	58.7±19.7	60.4±20.3	0.358
CKD Stage III	55 (47)	17 (30.4)	0.038
Charlson group categories			0.652
0	51 (19.6)	33 (18.5)	
1-2	91 (35%)	70 (39.3)	
≥3	118 (45.4)	75 (42.2)	
Preoperative tumor's features			
R.E.N.A.L. Score (Complexity)			<0.001
4-6 (Low)	33 (17.7)	69 (48.6)	
7-10 (Intermediate)	120 (64.5)	69 (48.6)	
>10 (high)	33 (17.8)	4 (2.8)	
Clinical dimension (cm)	5.9±2.7	3.6±1.4	<0.001
cT stage			<0.001
1	108 (29.7)	171 (77.4)	
2	163 (44.8)	44 (19.9)	
3	75 (20.6)	5 (2.3)	
4	18 (4.9)	1 (0.4)	
cN stage			0.013
0	280 (90.6)	186 (97.4)	
1	26 (8.4)	4 (2.1)	
2	3 (1)	1 (0.5)	
RN= Radical Nephrectomy; PN= Partial Nephrectomy; BMI= Body Mass Index; CKD= Chronic Kidney Disease; eGFR= estimated Glomerular Filtration Rate; SD= Standard Deviation; ^a Number of patients; ^f SD, or no. (%)			

Table 1- Baseline comparison between patients who underwent radical nephrectomy (RN) and partial nephrectomy (PN)

	Total (n=585)	RN (n=364)	PN (n=221)	p value
Surgical outcomes^f				
Surgical technique				<0.001
Open	336 (57.5)	223 (61.3)	113 (51.1)	
Laparoscopic	177 (30.2)	135 (37.1)	42 (19.0)	
Robotic	67 (11.4)	4 (1.1)	63 (28.5)	
Missing	5 (0.9)	2 (0.5)	3 (1.4)	
Operative time (min)	-	178.8±75.8	162.6±66.9	0.020
EBL (mL)	-	352.3±296.7	300.2±337.7	0.158
Intraoperative complications	61 (10.4)	42 (11.5)	19 (8.6)	0.259
Post-operative complications	146 (25.0)	89 (24.5)	57 (25.8)	0.716
Major complications	32 (5.5)	21 (5.8)	11 (5.1)	0.690
Open	25 (4.3)	18 (8.0)	7 (6.2)	
Laparoscopic	5 (0.9)	3 (2.2)	2 (4.8)	
Robotic	2 (0.3)	0 (0.0)	2 (3.2)	
Pathological outcomes^f				
Tumor histology				<0.001
Benign	42 (7.2)	13 (3.6)	29 (13.1)	
Malignant	527 (90.1)	348 (95.6)	179 (81.0)	
Missing	16 (2.7)	3 (0.8)	13 (5.9)	
pT stage				<0.001
1	368 (62.9)	221 (60.7)	147 (66.5)	
2	54 (9.2)	49 (13.5)	5 (2.3)	
≥ 3	88 (15.0)	78 (21.4)	10 (4.5)	
Missing	75 (12.8)	16 (4.4)	59 (26.7)	
Grading				0.003
1-2	307 (52.5)	185 (50.8)	123 (55.6)	
3-4	205 (35.0)	149 (40.9)	56 (25.3)	
Missing	73 (12.5)	30 (8.3)	42 (19.0)	
Functional outcomes^f				
Pre-operative eGFR	-	58.7±19.7	60.4±20.3	<0.001
Post-operative eGFR at 6 th	-	39.6±12.8	51.6±19.2	<0.001

months				
eGFR variation	-	-17.0±13.9	-7.6±11.0	<0.001

RN= Radical Nephrectomy; PN= Partial Nephrectomy; EBL= Estimated Blood Loss; eGFR= estimated Glomerular Filtration Rate; SD= Standard Deviation; ^f SD, or no (%)

Table 2. Surgical outcomes

INTRAOPERATIVE COMPLICATION						
	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
Type of surgery[†]						
RN	Referent					
PN	0.72	0.40-1.27	0.261	0.67	0.29-1.54	0.357
Technique[‡]						
Open	Referent					
Laparoscopic	0.51	0.26-0.97	0.043	0.50	0.23-1.09	0.085
Robotic	0.20	0.04-0.85	0.03	0.28	0.06-1.31	0.107
Tumor features						
Clinical size	1.01	1.00-1.02	0.008	0.99	0.96-1.01	0.549
R.E.N.A.L. ≥10	2.12	1.09-4.12	0.027	1.39	0.66-2.94	0.380
cT1	Referent					
cT2	1.46	0.78-2.73	0.236	1.35	0.50-3.65	0.552
cT≥3	2.73	1.38-5.37	0.004	2.34	0.41-13.36	0.337
OVERALL POST-OPERATIVE COMPLICATIONS						
Type of surgery[†]						
RN	Referent					
PN	1.07	0.73-1.57	0.716	1.67	0.89-3.15	0.108
Technique[‡]						
Open	Referent					
Laparoscopic	0.57	0.37-0.89	0.013	0.73	0.42-1.26	0.270
Robotic	0.26	0.11-0.60	0.002	0.38	0.14-1.00	0.052
Tumor features						
Tumor size	1.01	1.00-1.01	0.004	1.01	0.99-1.03	0.107
cT1	Referent					
cT2	1.78	1.17-2.71	0.007	1.55	0.73-3.31	0.247
cT≥3	1.81	1.07-3.05	0.009	1.03	0.26-4.11	0.960
POST-OPERATIVE MAJOR COMPLICATIONS						
Type of surgery[†]						
RN	Referent					
PN	0.85	0.40-1.81	0.683	2.05	0.80-5.21	0.131
Technique[‡]						

Open	Referent					
Laparoscopic	0.36	0.13-0.96	0.042	0.42	0.15-1.14	0.04
Robotic	0.38	0.89-1.68	0.206	0.44	0.09-2.14	0.314
Tumor features						
Tumor size	1.01	1.00-1.02	0.007	1.02	0.99-1.04	0.106
cT1	Referent					
cT2	3.25	1.31-8.06	0.011	2.49	0.80-7.79	0.115
cT≥3	3.88	1.40-10.73	0.009	1.12	0.14-8.40	0.910

RN= Radical Nephrectomy; PN= Partial Nephrectomy; OR= Odds Ratio; CI= Confidence interval; † Radical Nephrectomy vs Partial Nephrectomy; ‡ Open vs Laparoscopic vs Robotic

Table 3. Univariate and multivariate analysis of the relationship between confounders and intraoperative, overall post-operative, and major post-operative complications.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Charlson ≥3	1.59	1.08-2.34	0.017	1.40	0.94-2.09	0.093
pT≥3	1.52	0.97-2.38	0.066	1.53	0.95-2.45	0.074
PN†	0.65	0.44-0.96	0.033	0.91	0.58-1.43	0.705

HR= Hazard Ratio; CI= Confidence Interval; PN= Partial Nephrectomy
† Radical Nephrectomy vs Partial Nephrectomy

Table 4. Comparison between univariate and multivariate analysis of the relationship between type of the surgery and ACM