Ann Surg Oncol (2022) 29:2484–2494
https://doi.org/10.1245/s10434-021-11133-4

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – UROLOGIC ONCOLOGY

Long-Term Oncological and Functional Outcomes After Robot-Assisted Partial Nephrectomy for Clinically Localized Renal Cell Carcinoma

Hugo Otaola-Arca, MD, PhD[1,2], Alfred Krebs, MD[1,2], Hugo Bermúdez, MD[1,2], Raúl Lyng, MD[1,2], Marcelo Orvieto, MD[1,2], Alberto Bustamante, MD[1,2], Conrado Stein, MD[1,2], Andrés Labra, MD[2,3], Marcela Schultz, MD[2,4], and Mario I. Fernández, MD[1,2]

[1]Department of Urology, Clínica Alemana de Santiago, Santiago, Chile; [2]Faculty of Medicine, Clínica Alemana-Universidad del Desarrollo, Santiago, Chile; [3]Department of Radiology, Clínica Alemana de Santiago, Santiago, Chile; [4]Department of Pathology, Clínica Alemana de Santiago, Santiago, Chile

ABSTRACT

Background. To evaluate long-term oncological and renal function outcomes in patients treated with robot-assisted partial nephrectomy (RAPN) for renal cell carcinoma (RCC).

Patients and Methods. Patients undergoing RAPN for clinically localized RCC between January 2014 and December 2019 at a tertiary robotic reference center were evaluated. Clinical course, pathologic characteristics, and long-term outcomes were obtained from our institutional review board-approved RCC database.

Results. A total of 234 patients were available for analysis. Median follow-up was 46 months (10.8–97.8 months), with 77 patients (32.9%) having at least 5-years of follow-up. Pathology revealed clear-cell RCC in 67.5% (n = 158). Among unfavorable factors, nuclear grades 3 or 4 were found in 67 (29.4%), lymphovascular invasion in 10 (4.3%), positive surgical margins in 22 (9.4%), necrosis in 21 (9%), and sarcomatoid pattern in 2 patients (0.9%). At 12 months, mean serum creatinine was 1.04 mg/dL and 12.9% of patients experienced upstaging in chronic kidney disease. Overall recurrence-free survival at 5-years was 97.8%. There were five local (2.1%) and two distant (0.9%) recurrences, none of them resulting in cancer-specific death. Median time to recurrence was 20 months (11–64 months). Warm ischemia time [hazard ratio (HR) = 1.14, p = 0.034] and sarcomatoid pattern (HR = 124.57, p = 0.001) were the only variables associated with local relapse.

Conclusions. Data from this large cohort demonstrate that patients undergoing RAPN have a low incidence of local and distant relapse, resulting in excellent long-term survival while preserving stable renal function in most patients.

Partial nephrectomy (PN) is considered the standard of care for T1 renal cell carcinoma (RCC) in patients eligible for surgery because of its adequate preservation of normal parenchyma while showing similar oncological results as radical nephrectomy (RN).[1] Nephron-sparing surgery can be performed either by an open, laparoscopic, or robot-assisted approach. The latter two offer lower morbidity than the open approach, with comparable short-term oncological outcomes among T1–T2a tumors.

Robot-assisted partial nephrectomy (RAPN) has been demonstrated to be similar to laparoscopic and open approaches in terms of warm ischemia time (WIT), perioperative complications, positive surgical margins (PSMs), and 5-year oncological and functional outcomes.[2,3] However, long-term outcomes published on RAPN are scarce.

Herein, we report the renal function and oncological outcomes of RAPN for RCC performed at a single tertiary robotic reference center, focusing on long-term results.

First Received: 16 June 2021
Accepted: 8 November 2021;
Published Online: 6 January 2022

M. I. Fernández, MD
e-mail: mfernandeza@alemana.cl

PATIENTS AND METHODS

Study Design and Patient Selection

RAPN for clinically localized RCC between January 2014 and December 2019 performed by five experienced surgeons at a single tertiary robotic reference center were registered. All surgeries were executed in the daVinci Si Surgical System (Intuitive Surgical, Sunnyvale, California, USA). Further inclusion criteria were pathological confirmation of RCC in the surgical specimen and follow-up of $\geq$ 12 months. Patients with metastatic RCC at initial diagnosis or benign tumors were excluded. The primary aim of the study was to assess the renal function and oncological outcomes after RAPN as well as its predictors. The secondary aim was to search for predictors of PSM and trifecta [as defined by warm ischemia time (WIT) $<$ 25 min, absence of Clavien–Dindo grade $\geq$ 2 complications within the first 90 postoperative days, and no PSM].[4]

The study was approved by the Institutional Review Board (2019-079), conforming to provisions of the Declaration of Helsinki.

Outcome Measurements

Variables of the study included clinical and tumor characteristics, intra- and perioperative data, pathological analysis, and follow-up information.

Clinical characteristics: age, gender, smoking history, comorbidities, body mass index (BMI), American Society of Anesthesiologists (ASA) score, preoperative renal function [serum creatinine level, estimated glomerular filtration rate (eGFR), and chronic kidney disease (CKD) stage], and prior personal history of RCC.

Tumor characteristics: preoperative tumor size, clinical tumor, nodal stage (cT and cN), and R.E.N.A.L. nephrometry score [low (4–6 points); moderate (6–9 points); or high (10–12 points)]. An expert in uroradiology established tumor complexity according to computed tomography (CT) scan or magnetic resonance imaging (MRI) images.[5]

Perioperative data: operative time, estimated blood loss (EBL), blood transfusion rate, need for ischemia, WIT, the performance of regional lymphadenectomy, opening and suturing of the collecting system, use of intraoperative ultrasound, conversion to open or radical nephrectomy, intraoperative complications, length of hospital stay, postoperative renal function, and postoperative complications according to the Clavien–Dindo classification (with grade $\geq$ 3 considered as major complications).[6] Readmission and reoperation rates were also recorded, as well as trifecta.

Pathological analysis: tumor size, TNM stage according to the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (IUCC) system,[7] tumor type according to the 2004 World Health Organization (WHO) classification,[8] tumor features (necrosis, sarcomatoid pattern, lymphovascular or capsular invasion, Fuhrman nuclear grade),[9] and PSM (defined as the presence of tumor cells at the inked margin).

Follow-up: the institutional follow-up protocol included clinical examination, laboratory testing (complete blood count and serum creatinine level), and CT scan of the chest, abdomen, and pelvis at 3, 12, 24, 36, 48, and 60 months after surgery, and every 2 years thereafter.

eGFR rate was calculated using the Modification of Diet in Renal Disease (MDRD) formula. CKD stage was assigned based on the National Kidney Foundation's Kidney Disease Outcome Quality Initiative Classification (NKF-KDOQI).[10] Upstaging was defined as an increase from the baseline stage, except for a change from CKD stage I to II, which was regarded as clinically nonsignificant.[11]

Survival was calculated from date of surgery to December 2019. At this cutoff date, the national mortality registry was searched for any event affecting our cohort. Disease relapse was defined as any local recurrence (vascular, retroperitoneal, or renal fossa) or metastasis at a distant site on a CT scan (RCC was confirmed by biopsy in all these cases). Recurrences in the contralateral kidney were considered as asynchronous primary RCC. Study data were collected using REDCap electronic data capture tools hosted at our institution.

Statistical Analysis

Mean and standard deviation (SD), and median and interquartile range (IQR) were reported for variables with a normal and nonnormal distribution, when appropriate (according to Kolmogorov–Smirnov test with Lilliefors significance correction). Range (minimum–maximum) was also reported. Categorical variables were described by absolute numbers and proportions.

The cumulative incidence of local recurrence, distant metastasis, and deaths was calculated and plotted using the Kaplan–Meier method. Univariate competing-risks Cox regression was performed separately for local recurrence and distant metastasis. A multivariable competing-risks analysis could not be performed owing to the small number of events. Binary logistic regression models were used to identify the variables predicting upstaging of CKD at 12 months, PSM, and trifecta. All p-values were two-sided and statistical significance was defined as $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics v23 (IBM Corp., Armonk, NY).

RESULTS

Thirty-seven patients (out of 290) were excluded from the study because of a benign diagnosis on final pathology (Supplementary Fig. 1). Additionally, 19 patients were lost to follow-up within the first year and were also excluded. Hence, 234 patients were available for analysis. Median follow-up was 46 months (IQR 42.5 months), with 151 patients (64.5%) having ≥ 3 years follow-up.

Demographic and preoperative data are summarized in Table 1. Mean age at surgery was 57.4 ± 11.8 years. Most of the patients were ASA I–II (95.7%), and the median BMI was 27.4 ± 5.1 kg/m^2. Mean tumor size at preoperative imaging was 30 ± 21 mm (95.7% of neoplasms were staged as cT1). According to the R.E.N.A.L. score, almost two-thirds of patients (61.9%) had moderately or highly complex renal masses.

Perioperative data are listed in Table 2. Fourteen patients (6%) had intraoperative complications. Conversion rate to open partial nephrectomy and to robotic radical nephrectomy was 0.9% and 0.4%, respectively. Eleven patients (4.7%) had postoperative complications: Three (1.3%) were major complications requiring reintervention (urinary leakage in two cases and for an incisional hernia in one case; all were Clavien III). No Clavien IV or V complications occurred in our series. Readmission and reoperation rates were 2.1% and 1.3%, respectively.

Mean preoperative serum creatinine was 0.90 ± 0.1 mg/dL, and 24 patients (11.2%) had preoperative CKD stage ≥ III. Mean serum creatinine at 12 months was 1.04 ± 0.26 mg/dL, with a mean difference from preoperative value of + 0.08 [95% confidence interval (95% CI): 0.05–0.12; $p <$ 0.001] (Fig. 1). Univariate regression models revealed that been hypertense, baseline, and first postoperative day serum creatinine values were the only prognostic factors for upstaging CKD at 12 months. Nevertheless, none of them were significant on multivariate analysis (Supplementary Table 1).

Final pathology revealed clear-cell RCC (ccRCC) in 158 (67.5%), papillary RCC (pRCC) in 47 (20.1%), and chromophobe RCC (chRCC) in 28 patients (12%). Most tumors (178, 76.1%) were classified as pT1a. High nuclear grade tumors (grade 3–4) were found in 67 patients (29.4%), necrosis in 21 (9%), sarcomatoid pattern in 2 (0.9%), lymphovascular invasion in 10 (4.3%), and renal capsule invasion in 2 (0.9%). One patient had positive lymph nodes (0.4%), and 22 (9.4%) had a PSM, with a median size of 4.6 mm (IQR 5.0 mm) (Table 3).

Overall, six patients (2.6%) had disease relapse during follow-up (Tables 3 and 4). Four patients developed local recurrence in the surgical bed (only one of these patients had a PSM); two were treated with laparoscopic radical nephrectomy (one also received immunotherapy with nivolumab/ipilimumab), and the other two with a new RAPN. A complete answer was found in all four. On the other hand, one patient developed lung metastases and now has a complete response after two lines of immunotherapy (3 years of sunitinib followed by 1 year of nivolumab, which they are still receiving). Finally, one patient presented local recurrence in the surgical bed, regional lymph nodes, and pulmonary metastases simultaneously (at 10 months after RAPN). The latter patient progressed despite sequential treatment with resection of lung metastases, stereotactic body radiation therapy to the lung surgical bed, and nivolumab/ipilimumab. All patients with disease relapse are still alive.

Three deaths (1.3%) occurred during follow-up, none of them related to RCC (two patients died because of glioblastoma multiforme and one following melanoma) (Table 3). The 5-year cumulative incidence for both local and distant recurrence was 5.9% and 1.1%, respectively, and 2.9% for non-RCC death (Fig. 2). Univariate competing-risks regression revealed that WIT [per 1 min increment; hazard ratio (HR): 1.14; 95% CI 1.0–1.3; p = 0.03] and sarcomatoid pattern (HR: 124.57; 95% CI 7.6–2.0 × 10^3; p = 0.001) were associated with local recurrence (Supplementary Table 2); no predictive factor related to metastases' occurrence could be found.

Intraoperative complications, pathological tumor size, papillary type histology, and necrosis were associated with PSM on univariate competing-risks regression (Supplementary Table 3). However, only necrosis could be confirmed on multivariate analysis as predictors of PSM [odds ratio (OR) 5.49; 95% CI 1.62–18.59; p = 0.006].

Trifecta rate was 72.4%; several variables were found to be predictors on univariate analysis (Supplementary Table 4). However, only intermediate R.E.N.A.L. score (OR 0.34; 95% CI 0.12–0.89; p = 0.030), POD1 serum creatinine (per +1 mg/dL increment) (OR 0.076; 95% CI 0.01–0.56; p = 0.012), intraoperative complications (OR 0.16; 95% CI 0.042–0.56; p = 0.012), readmission < 30 days (OR 0.06; 95% CI 0.006–0.64; p = 0.020), and necrosis (OR 0.11; 95% CI 0.03–0.38; $p < 0.001$) predicted the occurrence of trifecta on multivariate analysis.

DISCUSSION

Our study confirmed the long-term functional and oncological safety of RAPN, with a low 5-year cumulative incidence of local recurrence (5.9%), distant metastasis (1.1%), and no RCC-specific mortality after a median follow-up of 46 months. Furthermore, other-cause mortality was low (2.9%).

TABLE 1. Demographic and preoperative data

Variable	Results
Patients (*n*)	234
Age (years), mean ± SD (range)	57.4 ± 11.8 (28–88)
Gender, *n* (%)	
Male	174 (74.4)
Female	60 (25.6)
Smoker, *n* (%)	
No	177 (75.6)
Yes	57 (24.4)
Hypertension, *n* (%)	
No	131 (56.0)
Yes	103 (44.0)
Diabetes, *n* (%)	
No	165 (70.5)
Yes	69 (29.5)
Body mass index (kg/m^2), median ± IQR (range)	27.4 ± 5.1 (17.9–42.9)
ASA score, *n* (%)	
I	60 (25.6)
II	164 (70.1)
III	10 (4.3)
Preoperative serum creatinine (mg/dL), mean ± SD (range)	0.9 ± 0.1 (0.4–1.9)
Preoperative eGFR (mL/min), mean ± SD (range)	76.5 ± 12.5 (35.8 to > 90)
Chronic kidney disease stage ≥ III, *n* (%)	
No	210 (89.7)
Yes	24 (10.3)
Family history of kidney cancer, *n* (%)	
No	227 (97.0)
Yes	7 (3.0)
Clinical tumor size (cm), median ± IQR (range)	30.0 ± 21.0 (5.0–98.0)
Bilateral, *n* (%)	
No	224 (95.7)
Yes	10 (4.3)
Multifocal, *n* (%)	
No	223 (95.3)
Yes	11 (4.7)
cT stage, *n* (%)	
cT1a	176 (75.2)
cT1b	48 (20.5)
cT2a	7 (3.0)
cT2b	0 (0.0)
cT3a	3 (1.3)
cN stage, *n* (%)	
cN0	234 (100.0)
cN1	0 (0.0)
R.E.N.A.L. score: complexity groups, *n* (%)[a]	
Low complexity: 4–6	95 (40.6)
Moderate complexity: 7–9	112 (47.9)

Table 1. (continued)

Variable	Results
High complexity: 10–12	21 (9.0)

ASA American Society of Anesthesiologists, *cN* clinical stage of the regional lymph nodes, *cT* clinical stage of the primary tumor, *eGFR* estimated glomerular filtration rate, *IQR* interquartile range, *SD* standard deviation

[a]R.E.N.A.L. score could not be collected in six patients

Laparoscopic PN has shown long-term oncological outcomes comparable to open surgery.[12,13] However, the robotic platform's added advantages have turned RAPN into the preferred technique for surgical treatment of localized kidney tumors in many centers, allowing experienced surgeons to perform nephron-sparing surgery even for complex masses.[14,15] Nevertheless, there are only a few previous reports on the long-term outcomes of RAPN. Among them, Kyllo et al.[16] reported excellent overall survival (OS) (96.8%) and cancer-specific survival (CSS) (99.2%) of RAPN after 2.4 years of follow-up. With longer follow-up, Bertolo et al.[3] reported a very low cumulative incidence of local recurrence (3.6% at 5 years, 4.1% at 7 years), distant metastases (3.2% at 5 years, 4.5% at 7 years), RCC-specific mortality (1.80% at 5 and 7 years), and other-cause mortality (6.4% at 5 years, 9.3% at 7 years). Similarly, Vartolomei et al.[17] reported rates of 5-year disease-free survival (DFS) of 90.9%, CSS of 97.5%, and OS of 95.1%. Finally, Andrade et al.[18] reported 5-year overall survival, cancer-free survival, and cancer-specific survival rates of 91.1%, 97.8%, and 97.8%, respectively. Our findings agree with these previous reports on oncological outcomes after RAPN.

Akin to other series on RAPN, unfavorable factors such as high nuclear grades, pT3 stage, necrosis, sarcomatoid pattern, and PSMs were present among patients with local or distant recurrences in our study (Table 4). However, lymphovascular invasion and renal capsule invasion were not present in any of our relapse cases. Univariate competing-risks regression analysis confirmed WIT and sarcomatoid pattern as the only prognostic factors for local recurrence, in agreement with other reports.[19,20] However, these variables failed to achieve statistical significance on multivariate analysis, likely due to the small number of events.

We found a slight increase in serum creatinine in the early postoperative period (0.17–0.38 mg/dL on average), which usually recovered at 1 month of follow-up. After accounting for age, gender, and race, our long-term follow-up data revealed an upstaging in CKD of 16.2% at 1 month, 12.9% at 12 months, and 9.8% at the last follow-up, according to the MDRD formula. Similarly, Bertolo et al.[3] reported CKD upstaging of 42.4% and 8.3% at 1 and 12 months, respectively.

In our sample, 94.8% had an eGFR $\geq$ 45 mL/min at 12 months (defined by some authors as the new baseline estimated glomerular filtration rate, NB-eGFR), strongly related to survival.[21] These data highlight that renal function can indeed deteriorate over time in a small proportion of patients undergoing nephron-sparing surgery, even though renal function preservation is superior than in RN.[22]

In the literature, a PSM is encountered in 0.1–10.7 of PNs.[23] They occur more frequently in cases in which surgery is imperative (solitary kidneys and bilateral tumors), and in patients with adverse pathological features (pT2a, pT3a, grade III–IV).[24,25] However, the potential negative impact of a PSM after PN on the oncological outcomes regardless of the surgical approach (open, laparoscopic, robotic) is still controversial.[2,26] In fact, several series have indicated that PSMs do not translate into a higher risk of metastases or decreased CSS.[23,27,28] On the other hand, patients with negative surgical margins are not necessarily spared from the risk of recurrence.[29] Still, in one study, local tumor bed recurrences were found in 16% of patients with PSMs compared with only 3% in those with negative margins.[24] Nevertheless, even if there seems to be a slightly higher risk of recurrence in patients with a PSM, RN or re-resection of the tumor bed would probably result in overtreatment in many cases.

In the present study, we found a PSM rate of 9.4%, with a median length of 4.6 mm. PSM was more frequent in those patients with intraoperative complications (18.2% versus 4.8%), pRCC (36.4% versus 17.9%), and necrosis (31.8% versus 5.8%). These patients with PSM had larger tumors (mean 37.1 versus 29.0 mm; mean differences: 8.1 mm). Among these 22 patients, only one developed local recurrence, and none of them presented distant metastasis nor RCC-related mortality on follow-up. Most patients with local tumor relapse (three out of five) had negative surgical margins; in one patient, the margin was not evaluable, and in another one, it was positive. Thus, our results align with those studies indicating that neither margin status nor margin size is associated with local or distant recurrence or mortality.

TABLE 2. Perioperative data

Variable	Results
Operative time (min), median ± IQR (range)	120 ± 90 (50–330)
Estimated blood loss (mL), median ± IQR (range)	100 ± 250 (10–4.0)
Blood transfusion, *n* (%)	
No	232 (99.1)
Yes	2 (0.9)
Ischemia, *n* (%)	
No	21 (9.0)
Yes	213 (91.0)
Warm ischemia time (min) median ± IQR (range)	15 ± 107 (4–42)
Warm ischemia time < 25 min, *n* (%)	
No	38 (16.2)
Yes	196 (83.8)
Lymphadenectomy, *n* (%)	
No	227 (97.0)
Yes	7 (3.0)
Selective suture of an opened calyx, *n* (%)	
No	210 (89.7)
Yes	24 (10.3)
Use of intraoperative ultrasound, *n* (%)	
No	196 (83.8)
Yes	38 (16.2)
Conversion to open surgery, *n* (%)	
No	232 (99.1)
Yes	2 (0.9)
Conversion to radical nephrectomy, *n* (%)	
No	233 (99.6)
Yes	1 (0.4)
Intraoperative complications, *n* (%)	
No	220 (94.0)
Bleeding	10 (4.2)
Spleen lesion	2 (0.9)
Colonic lesion	2 (0.9)
Postoperative complications, *n* (%)	
No	223 (95.3)
Bleeding	8 (3.4)
Urinary leakage	2 (0.9)
Incisional hernia	1 (0.4)
Postoperative complications Clavien, *n* (%)	
Minor (Clavien I–II)	8 (3.4)
Major (Clavien III)	3 (1.3)
Length of stay (days), median ± IQR (range)	3 ± 1 (1–17)
Postoperative Hb (g/dL), mean ± SD (range)	
POD 0	12.9 ± 1.8 (8.9–23.4)
POD 1	12.5 ± 1.5 (6.6–15.8)
POD 2	11.7 ± 1.8 (7.5–15.1)
POD 3	11.2 ± 1.5 (7.8–14.3)
Achieved trifecta, *n* (%)[a]	
No	60 (27.4)

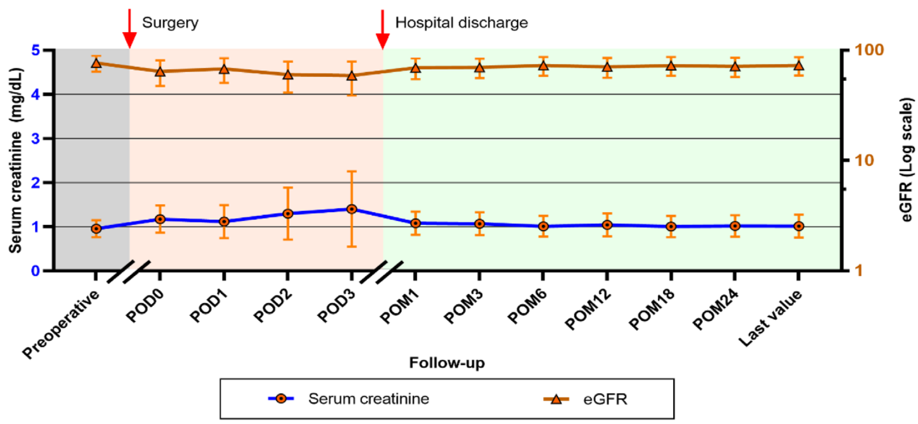
Table 2. (continued)

Variable	Results
Yes	159 (72.4)
Readmission ≤ 30 d, *n* (%)	
No	229 (97.9)
Yes	5 (2.1)
Reoperation ≤ 30 d, *n* (%)	
No	231 (98.7)
Yes	3 (1.3)

Hb hemoglobin, *IQR* interquartile range, *POD* postoperative day, *SD* standard deviation

[a]The trifecta could not be calculated in five cases due to the presence of a nonevaluable surgical margin

FIG. 1. Mean (standard deviation) serum creatinine and eGFR during follow-up. The chart represents the value of serum creatinine (blue) and eGFR (brown) at three timepoints: preoperative period (gray), during admission (beige), and after hospital discharge (green). The average value of serum creatinine of each moment and the differences concerning the preoperative value are shown below. *Last follow-up was at a median of 46 months



Follow-up time	Serum creatinine (mg/dL) Mean ± SD	Difference from preoperative value (mg/dL) Mean (95%CI)	*p* value	% CKD upstaging	% CKD downstaging
Preoperative	0.90 ± 0.10	Ref.			
POD0	1.18 ± 0.32	+ 0.20 (0.13 – 0.26)	<0.001	31.6	0.0
POD1	1.13 ± 0.38	+ 0.17 (0.12 – 0.21)	<0.001	23.2	1.7
POD2	1.30 ± 0.60	+ 0.31 (0.20 – 0.43)	<0.001	35.1	1.4
POD3	1.41 ± 0.86	+ 0.38 (0.16 – 0.59)	0.001	32.0	2.0
POM1	1.09 ± 0.27	+ 0.10 (0.06 – 0.14)	<0.001	16.2	0.0
POM3	1.07 ± 0.26	+ 0.06 (0.02 – 0.10)	0.003	10.3	2.9
POM6	1.01 ± 0.24	+ 0.06 (0.03 – 0.08)	<0.001	7.1	1.6
POM12	1.04 ± 0.26	+ 0.08 (0.05 – 0.12)	<0.001	12.9	3.6
POM18	1.00 ± 0.24	+ 0.06 (0.02 – 0.09)	0.002	11.9	2.8
POM24	1.02 ± 0.24	+ 0.05 (0.02 – 0.09)	0.001	9.4	3.1
Last follow-up	1.02 ± 0.26	+ 0.06 (0.03 – 0.08)	<0.001	9.8	2.9

95%CI = 95% confidence interval; CKD = chronic kidney disease; POD = postoperative day; POM = postoperative month; SD = standard deviation.

Trifecta and pentafecta are combined outcomes reflecting surgeons' and patients' expectations after RAPN.[4,30] In our cohort, 72.4% achieved a trifecta outcome. Among the 60 patients who failed to reach this outcome, WIT > 25 min was found in 36.7% of the patients and a PSM in 35%. Additionally, 13.3% of cases did not meet the criteria due to the occurrence of complications (Clavien ≥ III). Based on these findings, we believe that achieving the trifecta remains a realistic goal after RAPN. Conversely, in our study, only 19.2% of patients met pentafecta criteria defined as achievement of the trifecta outcomes plus > 90% eGFR preservation at 12 months postoperatively and absence of CKD upstaging.[30] Therefore, we question whether pentafecta outcomes should be a reasonable expectation for renal surgery under the current state of the art.

TABLE 3. Pathological and oncological outcomes

Variable	Results
Tumor size at final pathology (cm), median ± IQR (range)	28 ± 24 (5–95)
pT stage, *n* (%)	
pT1a	178 (76.1)
pT1b	34 (14.5)
pT2	6 (2.5)
pT3	16 (6.8)
pN stage, *n* (%)	
pNx	227 (97.0)
pN0	6 (2.6)
pN1	1 (0.4)
Histological type, *n* (%)	
ccRCC	158 (67.5)
p1RCC	17 (7.3)
p2RCC	30 (12.8)
chRCC	28 (12.0)
tcRCC	1 (0.4)
Nuclear Fuhrman grade, *n* (%)[a]	
1	11 (4.8)
2	150 (65.8)
3	64 (28.1)
4	3 (1.3)
Necrosis, *n* (%)	
No	213 (91.0)
Yes	21 (9.0)
Sarcomatoid pattern, *n* (%)	
No	232 (99.1)
Yes	2 (0.9)
Lymphovascular invasion, *n* (%)	
No	224 (95.7)
Yes	10 (4.3)
Renal capsule invasion, *n* (%)	
No	232 (99.1)
Yes	2 (0.9)
Margin status, *n* (%)	
Negative	207 (88.5)
Positive	22 (9.4))
Not evaluable [b]	5 (2.1)
Size of positive surgical margin (mm), median ± IQR (range)	4.6 ± 5.0 (1.0–15.0)
Distance to negative surgical margin (mm), median ± IQR (range)	0.5 ± 0.5 (0.1–4.0)
Local recurrence, *n* (%)	
No	229 (97.9)
Yes	5 (2.1)
Distant metastasis, *n* (%)	
No	232 (99.1)
Yes	2 (0.9)
Mortality, *n* (%)	
Alive	231 (98.7)
Cancer-specific mortality	0 (0.0)

Table 3. (continued)

Variable	Results
Other cause mortality	3 (1.3)
Follow-up (months), median ± IQR (range)	46.0 ± 42.5 (10–97.7)

ccRCC clear cell renal cell carcinoma, *chRCC* chromophobe renal cell carcinoma, *IQR* interquartile range, *p1RCC* papillary type 1 renal cell carcinoma, *p2RCC* papillary type 2 renal cell carcinoma, *pN* pathological stage of the regional lymph nodes, *pT* pathological stage of the primary tumor, *tcRCC* tubule-cystic renal cell carcinoma.

[a]Nuclear grade could not be collected in six patients

[b]Margin status could not be evaluated by the pathologist due to tumor rupture during extraction

TABLE 4. Description of patients with local recurrence or distant metastases

Study ID	Local recurrence	Metastases	TNM	Nuclear grade	Histological type	Necrosis	Sarcomatoid pattern	PSM	Treatment	Status
#31	No	Lung	pT3a cN0M0	Grade III	ccRCC	No	No	No	Metastasis resection, SBRT and Nivolumab/ Ipilimumab	Progression, alive
#120	Surgical bed and regional lymph nodes	Lung	pT1a cN0M0	Grade II	ccRCC	No	No	No	1st line Sunitib (3 year) 2nd line Nivolumab	CR, alive
#148	Surgical bed	No	pT1a cN0M0	Grade III	ccRCC	Yes	No	NE	LRN	CR, alive
#206	Surgical bed	No	pT1b cN0M0	Grade II	p1RCC	No	No	No	RAPN	CR, alive
#221	Surgical bed	No	pT3a cN0M0	Grade IV	ccRCC	Yes	Yes	Yes	LRN + Nivolumab/ Ipilimumab	CR, alive
#233	Surgical bed	No	pT1a cN0M0	Grade III	p2RCC	No	No	No	RAPN	CR, alive

ccRCC clear cell renal cell carcinoma, *CR* complete response, *NE* not evaluable, *LRN* laparoscopic radical nephrectomy, *p1RCC* papillary type 1 renal cell carcinoma, *p2RCC* papillary type 2 renal cell carcinoma, *PSM* positive surgical margin, *RAPN* robot-assisted partial nephrectomy, *SBRT* stereotactic body radiotherapy

Our study bears some limitations, the first and most important being its retrospective nature. We used the Fuhrman classification for nuclear-grade categorization instead of the more recent International Society for Urological Pathology/World Health Organization (ISUP/WHO) classification. Additionally, the use of intraoperative hemostatic agents was left at the surgeons' discretion, which may have impacted the incidence of bleeding-related complications. Finally, we acknowledge that multivariate analysis for recurrence-free and cancer-specific survival could not be performed due to the low number of events in this study. Thus, we could not identify any significant predictor of adverse oncological outcomes, at least within the time frame of our patients' follow-up.

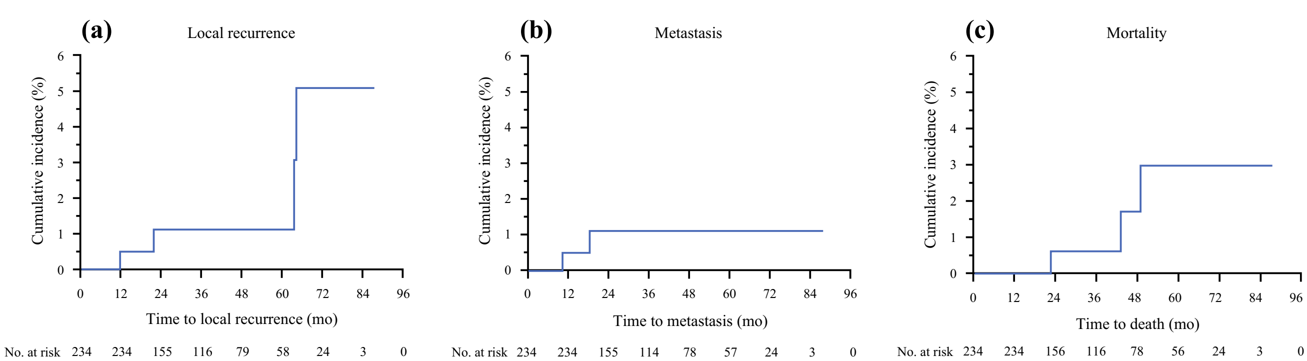


FIG. 2. Cumulative incidence curves for (A) renal cell carcinoma local recurrence (5.9% at 5 years), (B) metastasis (1.1% at 5 years), and (C) other cause mortality (2.9% at 5 years)

CONCLUSIONS

Data from this large group of patients confirm that RAPN achieves excellent long-term survival, with low morbidity and a low incidence of local and distant recurrences. Long-term renal function is preserved in most patients, with only a minor degree of deterioration in a small proportion.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1245/s10434-021-11133-4.

AUTHOR CONTRIBUTIONS Study concept and design: HO-A and MIF. Acquisition of data: HO-A, AK, and MIF. Analysis and interpretation of data: HO-A, AL, MIF, AK, and MS. Drafting of the manuscript: HO-A, AK, and MIF. Critical revision of the manuscript for important intellectual content: HO-A, MIF, AK, MO, CS, HB, AB, RL, and MS. Statistical analysis: HO-A. Obtaining funding: None. Administrative, technical, or material support: MIF and AB. Supervision: None.

FUNDING None.

DISCLOSURES The authors have nothing to disclose.

REFERENCES

1. Ljungberg B, Albiges L, Bensalah K, et al. EAU guidelines on renal cell carcinoma. *Eur Urol*. Published online 2020. http://uroweb.org/guidelines/compilations-of-all-guidelines/
2. Porpiglia F, Mari A, Bertolo R, et al. Partial Nephrectomy in clinical T1b renal tumors: multicenter comparative study of open, laparoscopic and robot-assisted approach (the RECORd Project). *Urology*. 2016;89:45–51. https://doi.org/10.1016/j.urology.2015.08.049.
3. Bertolo R, Garisto J, Dagenais J, et al. Transperitoneal robot-assisted partial nephrectomy with minimum follow-up of 5 years: oncological and functional outcomes from a single institution. *Eur Urol Oncol*. 2019;2(2):207–13. https://doi.org/10.1016/j.euo.2018.06.012.
4. Hung AJ, Cai J, Simmons MN, Gill IS. "Trifecta" in partial nephrectomy. *J Urol*. 2013;189(1):36–42. https://doi.org/10.1016/j.juro.2012.09.042.
5. Kutikov A, Uzzo RG. The RENAL nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. *J Urol*. 2009;182(3):844–53. https://doi.org/10.1016/j.juro.2009.05.035.
6. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
7. Edge S, Byrd DR, Compton CC, Fritz AG, Greene F, Trotti A, eds. *AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual*. 7th ed. Springer; 2010. Accessed April 9, 2021. https://www.springer.com/gp/book/9780387884424
8. Lopez-Beltran A, Scarpelli M, Montironi R, Kirkali Z. 2004 WHO classification of the renal tumors of the adults. *Eur Urol*. 2006;49(5):798–805. https://doi.org/10.1016/j.eururo.2005.11.035.
9. Cornejo KM, Rice-Stitt T, Wu C-L. Updates in staging and reporting of genitourinary malignancies. *Arch Pathol Lab Med*. 2020;144(3):305–19. https://doi.org/10.5858/arpa.2019-0544-RA.
10. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139(2):137–47. https://doi.org/10.7326/0003-4819-139-2-200307150-00013.
11. Kim DK, Kim LHC, Raheem AA, et al. Comparison of trifecta and pentafecta outcomes between T1a and T1b renal masses following robot-assisted partial nephrectomy (RAPN) with minimum one year follow up: can RAPN for T1b renal masses be feasible? *PLoS ONE*. 2016. https://doi.org/10.1371/journal.pone.0151738.
12. Rassweiler J, Goezen AS. Laparoscopic partial nephrectomy in the era of robotic surgery: there is a role! *Minerva Urol E Nefrol Ital J Urol Nephrol*. 2018;70(1):6–8. https://doi.org/10.23736/S0393-2249.17.03039-9.
13. Mari A, Antonelli A, Bertolo R, et al. Predictive factors of overall and major postoperative complications after partial nephrectomy: results from a multicenter prospective study (The RECORd 1 project). *Eur J Surg Oncol*. 2017;43(4):823–30. https://doi.org/10.1016/j.ejso.2016.10.016.
14. Ghani KR, Sukumar S, Sammon JD, Rogers CG, Trinh Q-D, Menon M. Practice patterns and outcomes of open and minimally invasive partial nephrectomy since the introduction of robotic partial nephrectomy: results from the nationwide inpatient sample. *J Urol*. 2014;191(4):907–12. https://doi.org/10.1016/j.juro.2013.10.099.
15. Simhan J, Smaldone MC, Tsai KJ, et al. Perioperative outcomes of robotic and open partial nephrectomy for moderately and highly complex renal lesions. *J Urol*. 2012;187(6):2000–4. https://doi.org/10.1016/j.juro.2012.01.064.
16. Kyllo RL, Tanagho YS, Kaouk JH, et al. Prospective multi-center study of oncologic outcomes of robot-assisted partial nephrectomy for pT1 renal cell carcinoma. *BMC Urol*. 2012;12:11. https://doi.org/10.1186/1471-2490-12-11.
17. Vartolomei MD, Matei DV, Renne G, et al. Robot-assisted partial nephrectomy: 5-yr oncological outcomes at a single European tertiary cancer center. *Eur Urol Focus*. 2019;5(4):636–41. https://doi.org/10.1016/j.euf.2017.10.005.
18. Andrade HS, Zargar H, Caputo PA, et al. Five-year oncologic outcomes after transperitoneal robotic partial nephrectomy for renal cell carcinoma. *Eur Urol*. 2016;69(6):1149–54. https://doi.org/10.1016/j.eururo.2015.12.004.
19. Sun M, Shariat SF, Cheng C, et al. Prognostic factors and predictive models in renal cell carcinoma: a contemporary review. *Eur Urol*. 2011;60(4):644–61. https://doi.org/10.1016/j.eururo.2011.06.041.
20. Zhang L, Zha Z, Qu W, et al. Tumor necrosis as a prognostic variable for the clinical outcome in patients with renal cell carcinoma: a systematic review and meta-analysis. *BMC Cancer*. 2018;18(1):870. https://doi.org/10.1186/s12885-018-4773-z.
21. Lane BR, Demirjian S, Derweesh IH, et al. Survival and functional stability in chronic kidney disease due to surgical removal of nephrons: importance of the new baseline glomerular filtration rate. *Eur Urol*. 2015;68(6):996–1003. https://doi.org/10.1016/j.eururo.2015.04.043.
22. Deng H, Fan Y, Yuan F, et al. Partial nephrectomy provides equivalent oncologic outcomes and better renal function preservation than radical nephrectomy for pathological T3a renal cell carcinoma: a meta-analysis. *Int Braz J Urol*. 2021;47(1):46–60. https://doi.org/10.1590/S1677-5538.IBJU.2020.0167.
23. Rothberg MB, Paulucci DJ, Okhawere KE, et al. A multi-institutional analysis of the effect of positive surgical margins

following robot-assisted partial nephrectomy on oncologic outcomes. *J Endourol*. 2020;34(3):304–11. https://doi.org/10.1089/end.2019.0506.

24. Wood EL, Adibi M, Qiao W, et al. Local tumor bed recurrence following partial nephrectomy in patients with small renal masses. *J Urol*. 2018;199(2):393–400. https://doi.org/10.1016/j.juro.2017.09.072.
25. Bensalah K, Pantuck AJ, Rioux-Leclercq N, et al. Positive surgical margin appears to have negligible impact on survival of renal cell carcinomas treated by nephron-sparing surgery. *Eur Urol*. 2010;57(3):466–71. https://doi.org/10.1016/j.eururo.2009.03.048.
26. Tabayoyong W, Abouassaly R, Kiechle JE, et al. Variation in surgical margin status by surgical approach among patients undergoing partial nephrectomy for small renal masses. *J Urol*. 2015;194(6):1548–53. https://doi.org/10.1016/j.juro.2015.06.076.
27. Rothberg MB, Peak TC, Reynolds CR, Hemal AK. Long-term oncologic outcomes of positive surgical margins following robot-assisted partial nephrectomy. *Transl Androl Urol*. 2020;9(2):879–86. https://doi.org/10.21037/tau.2019.11.21.
28. Kang HW, Lee SK, Kim WT, et al. Surgical margin does not influence recurrence rate in pT1 clear cell renal cell carcinoma after partial nephrectomy: a multicenter study. *J Surg Oncol*. 2016;114(1):70–4. https://doi.org/10.1002/jso.24259.
29. Antic T, Taxy JB. Partial nephrectomy for renal tumors: lack of correlation between margin status and local recurrence. *Am J Clin Pathol*. 2015;143(5):645–51. https://doi.org/10.1309/AJCP7LKLZ8JSJQRG.
30. Kang M, Gong I-H, Park HJ, et al. Predictive factors for achieving superior pentafecta outcomes following robot-assisted partial nephrectomy in patients with localized renal cell carcinoma. *J Endourol*. 2017;31(12):1231–6. https://doi.org/10.1089/end.2017.0369.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.