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Outcomes of minimally invasive partial nephrectomy among very elderly patients: report from the RESURGE collaborative international database

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The aim of the study was to perform a comprehensive investigation of clinical outcomes of robot-assisted partial nephrectomy (RAPN) or laparoscopic partial nephrectomy (LPN) in elderly patients presenting with a renal mass.

The REnal SURGery in Elderly (RESURGE) collaborative database was queried to identify patients aged 75 or older diagnosed with cT1-2 renal mass and treated with RAPN or LPN. Study outcomes were: overall complications (OC); warm ischemia time (WIT) and 6-month estimated glomerular filtration rate (eGFR); positive surgical margins (PSM), disease recurrence (REC), cancer-specific mortality (CSM) and other-cause mortality (OCM). Descriptive statistics, Kaplan-Meier, smoothed Poisson plots and logistic and linear regression models (MVA) were used.

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Overall, 216 patients were included in this analysis. OC rate was 34%, most of them being of low Clavien grade. Median WIT was 17 minutes and median 6-month eGFR was 54 ml/min/1.73 m^2. PSM rate was 5%. After a median follow-up of 20 months, the 5-year rates of REC, CSM and OCM were 4, 4 and 5%, respectively. At MVA predicting perioperative morbidity, RAPN relative to LPN (odds ratio [OR] 0.33; p <0.0001) was associated with lower OC rate. At MVA predicting functional outcomes, RAPN relative to LPN was associated with shorter WIT (estimate [EST]-4.09; p <0.0001), and with higher 6-month eGFR (EST 6.03; p = 0.01).
In appropriately selected patients with small renal masses, minimally-invasive PN is associated with acceptable perioperative outcomes. The use of a robotic approach over a standard laparoscopic approach can be advantageous with respect to clinically relevant outcomes, and it should be preferred when available.

Key Words: kidney cancer ‹› robot-assisted partial nephrectomy ‹› laparoscopic partial nephrectomy ‹› minimally invasive surgery ‹› elderly

INTRODUCTION

Partial nephrectomy (PN) has become the standard of care for patients with small renal masses [1–4]. There is considerable evidence that PN provides comparable overall survival and oncological outcomes compared to radical nephrectomy (RN) [5–8], while reducing the risk of chronic kidney disease (CKD) and long-term cardiovascular aftermaths [9–13]. While open PN has historically been considered the gold standard, minimally invasive approaches offer the potential for improved post-operative recovery without compromising oncologic outcomes [14, 15].
Diagnoses of small renal masses for which PN may be indicated are rising, particularly among the elderly [16, 17]. Typically defined as those over the age of 75 years [3, 4], these patients have higher levels of comorbidity and higher risk of competing causes of mortality [18]. Pre-existing renal dysfunction or renal threatening conditions including diabetes and vascular disease are more common in these subjects and may provide increased impetus for nephron sparing surgery. In addition, the elderly are likely to have prolonged convalescence following surgery [19]. Thus, the improved pain control and post-operative convalescence associated with minimally-invasive surgery [20, 21, 22], namely laparoscopic or robot-assisted, may be particularly valuable in the elderly patient. However, there is a paucity of data with respect to outcomes of minimally invasive PN in these patients.
Therefore, the aim of this study was to perform a comprehensive analysis of surgical, functional and oncological outcomes of minimally invasive PN using a large multi-institutional dataset specifically devoted to elderly patients.

MATERIAL AND METHODS

Patient cohort

The REnal SURGery in Elderly (RESURGE) dataset is a cohort of older individuals (age ≥75 years at the time of surgery) who underwent partial or radical nephrectomy for a renal mass at one of 19 participating institutions between 1988 and 2017. Age 75 years was used to define 'elderly patients' in keeping with major guidelines [3, 4]. Research ethics board approval was obtained at all participating institutions prior to assembling the database.
In the present analysis, we examined elderly patients who underwent minimally invasive (laparoscopic or robot-assisted) PN for a clinically localized renal mass. We excluded patients with locally advanced (cT3-4), nodal involvement (cN1) or metastatic disease (cM1), urothelial pathology or inflammatory lesions, and those with multiple renal lesions. Thus, the cohort comprised patients treated for a solitary cT1-2cN0cM0 renal mass. Further, we excluded patients with missing data for relevant covariates including pre-operative estimated glomerular filtration rate (eGFR), tumour size, and R.E.N.A.L. nephrometry score [23].

Exposure

The primary exposure was surgical approach – robot-assisted partial nephrectomy versus pure laparoscopic nephrectomy.

Outcomes

The primary outcome was the rate of peri-operative complications. Secondary outcomes were functional and oncologic outcomes including warm ischemia time (WIT, in minutes), estimated glomerular filtration rate at 6 months post-operatively (eGFR, ml/min/1.73 m^2), positive surgical margins (PSM), disease recurrence (REC), cancer-specific mortality (CSM), and overall mortality (OM).

Covariates

To account for the potential confounding effect related to difference in treatment selection, relevant demographic and tumour-related data were collected. Demographic data included patient age (at the time of surgery), gender, pre-operative renal function (eGFR), the presence of a solitary kidney, and Charlson comorbidity index. Tumour related characteristics included radiographic tumour size (in mm) and R.E.N.A.L. nephrometry score [23]. Year of surgery was also collected.

Statistical analysis

Descriptive statistics were used to characterise the study cohort, stratified by surgical approach: counts and proportions were used for categorical data and medians and interquartile ranges (IQR) were used for continuous data. Multivariable logistic regression was used to assess the association between surgical approach and perioperative complications and PSM while accounting for the aforementioned covariates. These results were expressed as adjusted odds ratios (aOR) with associated 95% confidence intervals (95% CI). Similarly, multivariable linear regression was used to assess the association between surgical approach and WIT and 6-month eGFR, while accounting for the same set of covariates. These results were expressed using the estimate of the coefficient and the associated 95% CI. The Kaplan-Meier method

Table 1. *Baseline characteristics of 216 elderly patients treated with robot-assisted or laparoscopic partial nephrectomy*

	Overall (n = 216)	LPN (n = 98)	RAPN (n = 118)	p-value
Patient characteristics				
Age (years), median (IQR)	77 (76–80)	77 (76–79)	78 (76–80)	0.3
Gender, n (%)				0.7
Female	115 (53)	54 (55)	61 (52)	
Male	101 (47)	44 (45)	57 (48)	
Pre-op eGFR (ml/min/1.73 m^2), median (IQR)	65.3 (54.3–81.9)	64.0 (57.1–76.7)	67.0 (49.8–83.4)	0.5
Solitary kidney, n (%)				0.9
No	6 (3)	2 (2)	4 (3)	
Yes	210 (97)	96 (98)	114 (97)	
Charlson Comorbidity Index, n (%)				0.02
0	30 (14)	19 (19)	11 (9)	
1	30 (14)	11 (11)	19 (16)	
2	47 (22)	14 (14)	33 (28)	
3	58 (27)	35 (36)	23 (19)	
4	16 (7)	4 (4)	12 (10)	
≥5	35 (16)	15 (15)	20 (17)	
Tumor characteristics				
Radiographic tumor size (mm), median (IQR)	32 (23–40)	30 (22–38)	35 (26–42)	0.02
R.E.N.A.L. Category				0.3
1	106 (49)	53 (54)	53 (45)	
2	96 (44)	41 (42)	55 (47)	
3	14 (6)	4 (4)	10 (8)	
Other characteristics				
Year of surgery, n (%)				0.4
2000–2009	14 (6)	5 (5)	9 (8)	
2010–2014	121 (56)	52 (53)	69 (58)	
2015–2017	81 (38)	41 (42)	40 (34)	

LPN – laparoscopic partial nephrectomy; RAPN – robot-assisted partial nephrectomy; eGFR – estimated glomerluar filtration rate; IQR – interquartile range was used to characterise recurrence-free survival and smoothed Poisson plots were used to characterise cancer-specific and other-cause mortality. Owing to a lack of events, planned Cox proportional hazards models were not performed for these outcomes. All statistical tests were performed using the RStudio graphical interface v.0.98 for R software environment v.3.0.2 [24] with the following libraries, packages and scripts: Hmisc, plyr, stats, rms, and graphics. All tests were two-sided with a significance level set at $p < 0.05$.

RESULTS

A total of 216 patients in the RESURGE database met inclusion and exclusion criteria and were included in the analysis. Of these, 98 patients (45%) underwent pure laparoscopic partial nephrectomy (LPN) and 118 (55%) underwent robotic-assisted laparoscopic nephrectomy (RAPN). While age at the time of surgery, gender, pre-operative eGFR, and the presence of a solitary kidney were similar between the two groups, patients treated with RAPN had higher levels of comorbidity (Table 1). Additionally, while R.E.N.A.L. category was similar, patients treated with RAPN had statistically significantly larger tumours though this is of marginal clinical significance (difference = 5 mm; Table 1). The year of surgery did not significantly differ according to surgical approach.

Perioperative complications occurred in 73 (34%) patients, 45 (46%) of those treated with LPN and 28 (24%) of those treated with RAPN (Table 2). Of these, the majority were Clavien-Dindo grade 1 or 2 (Table 3). At multivariable analysis, surgical approach was a significant predictor of peri-operative complications (RAPN vs. LPN OR 0.33, 95% CI 0.17–0.61; Table 4). No other predictors were identified among the covariates examined. Given the presence of missing information about Clavien grade in some cases, multivariable models were not built according to specific Clavien grade.

Among the secondary outcomes, the median duration of WIT was 19 minutes (IQR 15–25 minutes) among patients undergoing LPN and 16 minutes (IQR 13–19 minutes) among patients undergoing RAPN; median eGFR at 6 months post-operatively was 53 ml/min/1.73 m^2 (IQR 42-63 ml/min/1.73 m^2) and 55 ml/min/1.73 m^2 (44–70 ml/min/1.73 m^2) among patients treated with LPN and RAPN, respectively; PSM were found in 3 (3%) and 7 (6%) of patients treated with LPN and RAPN, respectively (Table 2). In multivariable models, surgical approach was a significant predictor of WIT with patients treated with RAPN having shorter WIT (estimate -4.09, 95% CI -5.99 to -2.18) and of 6-month eGFR (estimate 6.03, 95% CI 1.96–10.11) with patients treated with RAPN having higher 6-month eGFR (estimate 6.03, 95% CI 1.96 to 10.11). Conversely, PSM results were similar after either treatment modality (Table 3).

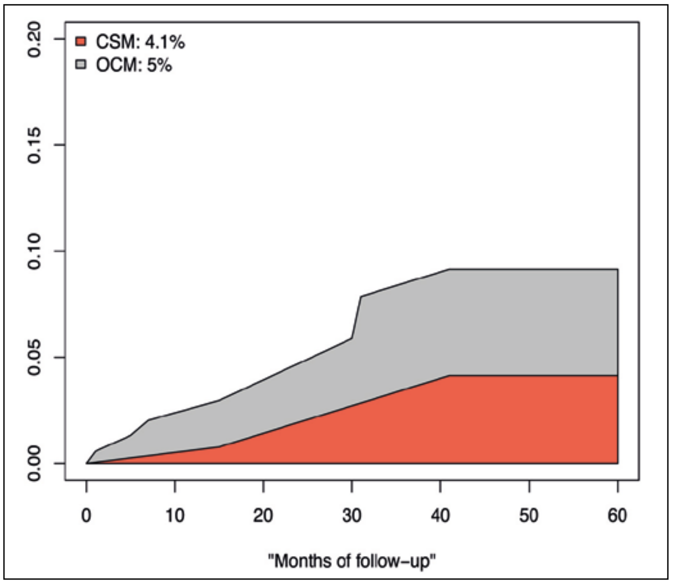

Figure 1. *Smoothed Poisson's plot estimating the competing risk of cancer-specific mortality (CSM) and other-cause mortality (OCM) in 216 elderly patients treated with robot-assisted or laparoscopic partial nephrectomy.*

Table 2. *Clinical outcomes of 216 elderly patients treated with robot-assisted or laparoscopic partial nephrectomy*

	Overall	LPN	RAPN	p-value
Any complication, n (%)	73 (34)	45 (46)	28 (24)	0.001
Warm ischemia time (min), median (IQR)	17 (15–22)	19 (15–25)	16 (13–19)	<0.001
eGFR at 6 months (ml/min/1.73 m^2), median (IQR)	54 (43–66)	53 (42–63)	55 (44–70)	0.3
Positive surgical margins, n (%)	10 (5)	3 (3)	7 (6)	0.5

LPN – laparoscopic partial nephrectomy; RAPN – robot-assisted partial nephrectomy; eGFR – estimated glomerluar filtration rate; IQR – interquartile range

Patient age, and tumour complexity (R.E.N.A.L. category) were associated with increasing WIT while year of surgery was associated with decreasing WIT (Table 3). Similarly, higher pre-operative eGFR was associated with increasing post-operative eGFR (Table 3). Finally, patients treated more recently were less likely to have PSM (Table 3).
After a median follow-up of 20 months, 5-year recurrence rate was 4% (95% CI 0–7%). There were 4 (4%) recurrences among patients treated with LPN and 2 (2%) among patients treated with RAPN but owing to the paucity of events, stratified analyses were not performed. At 5 years, overall mortality was 9% with a cancer-specific mortality of 4% and other cause mortality of 5% (Figure 1). Again, owing to the paucity of events, stratified analyses were not performed.

DISCUSSION

The goal of PN, regardless of approach, is complete extirpation of the tumour while preserving renal function to the greatest degree possible and avoiding perioperative complications [25]. In this large, multi-institutional cohort of elderly patients undergoing minimally invasive PN, we demonstrate an acceptable safety profile for such an approach among the appropriately selected elderly patient. Further, using a robotic approach versus a standard laparoscopic approach seems to be beneficial with respect to perioperative complications, warm ischemia time and post-operative renal function.
As evidenced by the relatively high CCI scores, the patients included in this analysis have significant comorbidity. Previous work has demonstrated an interaction between patient comorbidity and the benefit of nephron sparing approaches to clinically-localized renal masses [26] – that is, while no difference in survival was demonstrated between patients treated with partial and radical nephrectomy when all patients are examined, PN is associated with improved survival in patients with significant comorbidity. Further, as the elderly are likely to have prolonged convalescence following surgery [19], improved pain control and post-operative convalescence associated with minimally-invasive surgical approaches [20, 21, 22] is likely to provide clinically meaningful benefit. Taken together, these data suggest that minimally-invasive PN may be the preferred approach to small renal masses in elderly and comorbid patients who are fit for surgery.
Previous observational studies comparing laparoscopic and robotic-assisted partial nephrectomy have

Table 3. *Grading of complications according to the Clavien-Dindo scale in 216 elderly patients treated with robot-assisted or laparoscopic partial nephrectomy*

	Overall	LPN	RAPN
Any complication, n (%)	73 (34)	45 (46)	28 (24)
Clavien-Dindo grade 1	17 (8)	11 (11)	6 (5)
Clavien-Dindo grade 2	20 (9)	9 (9)	11 (9)
Clavien-Dindo grade 3	12 (6)	3 (3)	9 (8)
Clavien-Dindo grade 4	2 (1)	2 (2)	0
Clavien-Dindo grade 5	1 (<1)	0	1 (1)
Grade missing	21 (10)	20 (20)	1 (1)

Table 4. *Multivariable analysis to identify predictors of complications, warm ischemia time, post-operative renal function, and positive surgical margins in 216 elderly patients treated with robot-assisted or laparoscopic partial nephrectomy*

	Any complication, odds ratio (95% CI)	Warm ischemia time, estimate (95% CI)	eGFR at 6 months, estimate (95% CI)	Positive surgical margin[a], odds ratio (95% CI)
Approach, RAPN vs. LPN	0.33 (0.17–0.61)[b]	-4.09 [-5.99–(-2.18)][b]	6.03 (1.96–10.11)[b]	1.82 (0.46–8.94)
Age	0.91 (0.80–1.02)	0.35 (0.02–0.75)[b]	0.12 (-0.58–0.82)	–
Charlson comorbidity index	0.87 (0.73–1.01)	-0.18 (-0.76–0.39)	0.83 (-0.13–1.79)	–
Gender, female vs. male	1.06 (0.57–1.97)	-1.74 (-3.64–0.17)	3.72 (-0.37–7.81)	–
Pre-op GFR	0.99 (0.97–1.01)	-0.02 (-0.07-0.04)	0.74 (0.61–0.86)[b]	–
Solitary kidney, vs. not	2.60 (0.41–22.16)	-7.09 [-13.40–(-0.78)][b]	-12.1 (-35.23–11.02)	–
Tumor size	1.00 (0.98–1.03)	-0.02 (-0.10–0.06)	0.04 (-0.12–0.20)	0.98 (0.93–1.04)
R.E.N.A.L. Category				
1	Referent	Referent	Referent	–
2	1.86 (0.98–3.58)	0.71 (-1.27–2.69)	-5.14 [-9.36–(-0.92)]b	–
3	1.71 (0.38–6.70)	7.54 (2.92–12.17)[b]	0.69 (-7.54–8.91)	–
Year of surgery	0.92 (0.80–1.07)	-0.76 (-1.23–(-0.30))[b]	-1.13 (-2.49–0.24)	0.75 (0.58–0.95)[b]

[a]Restricted model due to limited number of events; [b] <0.05
eGFR – estimated glomerular filtration rate; CI – confidence interval; RAPN – robot-assisted partial nephrectomy; LPN – laparoscopic partial nephrectomy

been summarized in two systematic reviews and meta-analyses [27, 28]. These reviews have demonstrated that patients treated with RPN had a lower risk of positive surgical margin (risk ratio 0.53) than those treated with LPN [27]. Additionally, patients treated with RAPN had lower rates of conversion to open surgery, shorter WIT, and lower risk of any or major complications [27, 28]. Interestingly, in contrast to our findings, both reviews found that post-operative renal function was similar, regardless of surgical approach. Many of the studies evaluated in these reviews included temporally separated cohorts, with contemporaneous RPN cohorts being compared to historical LPN groups. In contrast, this analysis includes patients treated with these modalities in a concurrent fashion. Additionally, in contrast to comparisons relying upon administrative datasets, the prospectively collected data utilized in this analysis include details on tumour complexity, using the established R.E.N.A.L. nephrometry score [23], which is known to be associated with post-operative outcomes. [29–32]. Thus, as meta-analyses have demonstrated that patients undergoing RAPN have larger and more complex tumors [27], tumour complexity likely confounds the relationship between surgical approach and post-operative outcomes in analyses that fail to account for this tumour-related factor.

Despite the described high levels of comorbidity in this cohort, non-cancer related mortality was uncommon. This demonstrates an appropriate degree of patient screening and selection and these results should not necessarily be extrapolated to all elderly patients newly diagnosed with a small renal mass. Administrative analyses relying on Medicare beneficiaries have found that while, on average, surgical treatment (partial or radical nephrectomy) decreases cancer-specific mortality compared to non-surgical management, such a benefit was not observed when the cohort was restricted to patients aged 75 years and older [33]. Further, increasing age and comorbidity are associated with an increased risk of complications following PN [15, 34]. Therefore, a non-surgical (ablative) [34] or surveillance-based approach [35] may be more appropriate for patients with a small renal mass who are less fit for surgery.

Despite the strengths of this multi-institutional cohort including contemporaneously treated groups, detailed tumour characteristics, and meticulously collect outcome data, there are limitations. First, owing to the observational study design, study findings are likely affected by selection bias. Additionally, while the inclusion of many surgeons increases the generalizability of the findings, variation in the use of RAPN and LPN by individual surgeons introduces surgeon skill as another potential confounder. Last, a comparison to other management options such as active surveillance, kidney ablation or radical nephrectomy was outside the scope of the present analysis.

CONCLUSIONS

In appropriately selected elderly (over 75 years old) patients with small renal masses, minimally-invasive PN is associated with acceptable perioperative outcomes. Therefore, this therapeutic option should be considered also in this subset of patients on selective basis. Moreover, the use of a robotic approach over a standard laparoscopic approach is confirmed to be advantageous with respect to clinically relevant outcomes (complications, warm ischemia time and post-operative renal function), and therefore should be preferred when available.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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