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Title: A comparison of perioperative, renal and oncologic outcomes in robotic-assisted versus open partial nephrectomy.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Introduction

Nephron-sparing partial nephrectomy (PN) is the gold standard treatment for small or solitary kidney cancers.[1-3] Historically, open PN (OPN) has been the standard of care. The introduction of minimally invasive surgery in recent decades has led to an increased uptake of robotic-assisted PN (RAPN) in centres with access to this technology. RAPN has demonstrated benefits over laparoscopic approaches such as comparable oncologic outcomes, reduced warm ischaemic times (WIT), a shorter learning curve and fewer complications.[4, 5] Although obvious advantages of the minimally invasive approach are avoiding a flank incision and reducing recovery time, the benefits of open surgery include lower or no organ ischaemia, purported easier access for larger and more complex tumours, and the ability to tackle multiple tumours in a single setting. This is achievable with similar oncologic and overall survival outcomes.[3, 5]

Australia has seen a steady increase in RAPN uptake since its introduction in 2010. Since the first reported series in 2014, subsequent Australian data on RAPN is lacking.[6] Accompanied by a paucity in worldwide literature comparing OPN to RAPN,[7] this has led to healthcare funding bodies refusing to subsidise costs of robotic surgery for patients in whom RAPN has been recommended, citing a lack of proven benefit over open surgery. In Australia, a resultant financial imbalance has left many patients out-of-pocket or seeking alternative treatments. It is evident, with more surgeons and centres offering RAPN, and given the financial implications for all stakeholders, that more data is needed to determine whether RAPN confers benefits over OPN.

In this study, we reviewed data from an Australian metropolitan urological practice and compared perioperative, pathological, oncological and renal functional outcomes in patients who have undergone RAPN versus OPN.

Patients and Methods

All patients received standard urological care where choice of surgical approach was based upon surgeons' preference and expertise.

All PNs managed at a metropolitan community practice between 2010 and 2016, were reviewed using a prospectively maintained RAPN database (HREC approval Peter MacCallum Cancer Centre Ethics Committee, Project 15/30) and retrospectively collected OPN database. Hospital ethics approval was obtained (HREC approval 10-23-01-17).

Surgical technique and surgeons' experience

RAPN technique was as previously described.[6] Surgeries were performed transperitoneally, except in posterior hilar tumours where a retroperitoneal approach was used. Renal vein clamping was reserved for central hilar tumours; whilst renal artery occlusion was universal during all other tumour excisions. The da Vinci *S* or *Si (Intuitive Surgical ®)* was used without the need for intra-operative fluorescence imaging.

A retroperitoneal flank incision was performed for all OPNs. Use of renal artery clamping depended upon surgeon preference. Cooling was not used in this cohort. The tumour was sharply excised, collecting system closed separately and larger vessels suture-ligated, before performing cortical reconstruction with interrupted mattress sutures. Choice of suture material and haemostatic agents varied with surgeon preference.

Our RAPN series represents all cases performed since transitioning from laparoscopic surgery, therefore includes the surgeons' learning curve. Open surgery was performed by established Urologists with 16 to 36-years experience.

Data Collection

Patient demographics and pre-operative variables are outlined in Table 1. These included age, gender, body mass index (BMI), pre-operative haemoglobin (Hb), serum creatinine (sCr) and estimated glomerular filtration rate (eGFR). Relevant medical history (e.g. hypertension and diabetes mellitus) was collected. Age-adjusted Charlson Comorbidity Index (CCI) scores and American Society of Anaesthesiologists (ASA) Physical Status Classification Scores, were recorded. Baseline tumour characteristics included tumour laterality, size, polarity, and R.E.N.A.L. nephrometry scores.[8]

Intraoperative and peri-operative variables collected (Table 2) were the use of arterial clamping, WIT, operation time, estimated blood loss (EBL), use of haemostatic agents, and complications; length of stay, immediate post-operative Hb levels, and 30-day Clavien-Dindo complications (distinguished as minor/grade 1–2) or major/grade 3–4).[9]

Pathological outcomes included malignant or benign resections, clinical stage, histological subtypes, Fuhrman nuclear grade classification, and surgical margin status (Table 3). These parameters were in accordance with the 7th Edition, 2010 Update World Health Organisation (WHO) and International Society of Urologic Pathologists (ISUP) grading system.[10] A positive surgical margin was defined as cancer cells at the level of the inked parenchymal excision surface.

Immediate post-operative change in sCr, and Day-1 and 6-month post-operative eGFR stage, were used to determine renal functional outcomes (Table 3). Patients were grouped into eGFR stages based on the K/DIGO 2012 Clinical Practice Guidelines using corresponding eGFR cut-offs of e60mL/min, <60mL/min, and <45 mL/min.[11-13]

Patients were stratified into low, intermediate or high risk of recurrence and underwent follow-up with cross-sectional imaging and serum biochemistry at corresponding intervals. Patients with less than 6 months of follow-up were excluded from oncological outcome evaluation.

Statistical analysis

Statistical analyses were performed using STATA/IC version 14.1 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). For continuous and categorical variables, Mann–Whitney U-tests and unpaired Student's t-tests, and Pearson's chi-square tests were used, respectively. Continuous parametric and non-parametric variables were reported using means ± standard deviations (SD), and medians and interquartile ranges (IQR), respectively. Categorical variables were reported as frequencies and proportions. A two-sided $p < 0.05$ was considered to indicate statistical significance. Regression analysis was performed on all variables studied.

Results

Between 2010 and 2016, 200 patients underwent PN (N=55 OPN and N=145 RAPN). 55 RAPNs were performed using the da Vinci *S*, and the remaining 90 via the da Vinci *Si* system. All patients were included in the analysis.

Baseline characteristics

No statistically significant difference between groups was demonstrated for tumour diameter and polarity, history of hypertension, diabetes, previous abdominal surgery and ASA or CCI (age-adjusted) scores (Table 1). Statistically significant differences in age (p=0.0001), median eGFR (p=0.004) and RENAL nephrometry scores (p=0.001) were noted, where lower age, lower median eGFR and higher RENAL scores were found in the RAPN group.

Intra- and peri-operative outcomes

Eight (14.8%) OPN patients underwent renal artery clamping with a median WIT of 16 minutes (range 11-30), versus 18 minutes (range 6-50 minutes) in the RAPN group. All except one RAPN patient required renal artery clamping; 6 (4.14%) RAPN cases exceeded a WIT of 30 minutes. The primary surgeon performed all OPN surgeries, whereas for RAPN cases, 26 (18%) had a portion of the operation performed by a supervised trainee.

EBL was significantly greater in the OPN group (median 700 vs 50ml, p=<0.0001), with statistically significant differences in pre- and post-operative Hb (p=0.0001). Correspondingly, more OPN patients required transfusion (10.9% vs 2.1%). 25.5% of OPN cases experienced complications versus 9.7% in RAPN. Two RAPN cases were converted to open surgery, one due to ureteric injury which required open repair, and the other due to poor access to an upper pole posterior tumour identified after mobilisation of the affected kidney. Operation duration was similar between groups (median 137.5 minutes OPN vs 145 minutes, p=0.16).

The incidence of Clavien-Dindo complications was significantly higher in OPN (p=0.015). Six (10.9%) OPN patients experienced major complications. Of these, three patients required ICU admission post-operatively; one had a spontaneous pneumothorax, the second had acute renal failure,

and the last one had a post-operative haemorrhage and haematoma. The remaining three patients experienced post-operative haematoma requiring readmission. Seven (4.8%) RAPN patients experienced major complications. One of these patients required ICU admission for a myocardial infarction, three required embolization for haematuria, one underwent nephrectomy as a result of post-operative bleeding, and two were readmitted to theatre for ureteric stent insertion for clot colic. Hospital stay was significantly shorter in the RAPN group (p=<0.0001), where median length of stay was 3 days, compared to 6 days in the OPN group.

Tumour histopathological data

There was no statistically significant difference between groups for tumour diameter, malignant potential, clinical stage, Fuhrman nuclear grade or histopathological diagnosis. Similar numbers of patients underwent pre-operative tumour biopsy (18.2% OPN vs 22.8% RAPN). Both groups demonstrated similar histological breakdown of malignant tumours, predominantly consisting of clear cell carcinoma, fewer papillary carcinomas, chromophobe carcinomas and one myxoid sarcoma in the RAPN group. The OPN group had a statistically significant higher number of positive tumour resection margins (10.9% OPN vs 3.4% RAPN, p=0.039).

Renal and oncological functional outcomes

sCr change at Day-1 post-op was greater in the OPN group (p=0.04). Interestingly, the groups showed no significant differences in eGFR grade at Day-1 and 6-months post-operatively. 27 patients were excluded from the 6-month eGFR analysis as, at the time of writing, their operations were less than 6 months prior. At 6 months post-operatively, 5.88% (N=3) of patients in the OPN group and 4.1% (N=5) of patients in the RAPN group had an eGFR of <45mL/min, whilst each group had >84% (84.31% OPN vs 86.89% RAPN) of patients with eGFRs of e60mL/min.

Median post-operative follow-up times were 29 months and 18 months, for OPN and RAPN, respectively. No tumour recurrences were seen in this cohort.

Discussion

Current guidelines do not support one PN surgical technique over another.[2] Nevertheless, the increasing availability of RAPN as a minimally invasive alternative to laparoscopic PN demands urgent need for direct comparison of outcomes between RAPN and the OPN standard of care. Australian data on RAPN outcomes is lacking, with no reported comparisons with OPN. Consistent with contemporary PN series, our cohort comprised predominantly of low to medium complexity (based on RENAL scores) and clinical stage T1-2 renal tumours. We report outcomes from consecutive patients over the same time period treated by multiple surgeons from a metropolitan practice therefore the data reflects 'real life' treatment outcomes in an Australian community setting.

The immediate appeal of robotic surgery for patients requiring PN is the greater ease of offering minimally invasive surgery for what is a complex laparoscopic procedure. The generic advantages of laparoscopic surgery can be expected in patients undergoing RAPN compared to OPN. A small meta-analysis by Wu et al. suggests reduced operative complications, EBL, and length of hospital stay in RAPN.[7] Recent studies reinforce these findings.[14-16] Similarly, our study demonstrated with statistical significance a benefit of RAPN over OPN in these peri-operative parameters.

The magnified three-dimensional vision and operative dexterity afforded by robotic surgery allows additional advantages during dissection and reconstruction. Increasingly, publications reflect upon the feasibility of nephron-sparing surgery for more complex tumours. In this series, despite a greater number of complex tumours seen in the robotic arm, these patients experienced less EBL and complications, and a lower positive margin rate. These findings suggest RAPN is at least equivalent to OPN and favours its potential for renal preservation in more complex tumours. Furthermore, there was no significant difference in operation time between groups (p= 0.16)[14, 17-19] despite our RAPN series accommodating the surgeons' learning curve (i.e. the first 50 cases),[6] suggesting early plateau of the RAPN learning gradient as proposed in earlier reports.[20]

Routine arterial clamping is frequently considered a drawback to RAPN due to associated renal ischaemia.[6, 21] This is in comparison to OPN where renal vessel clamping is not usually required. Interestingly, despite less use of arterial clamping in the OPN group (14.8% OPN vs 99.3% RAPN), the median WIT between groups was similar (p=0.95). Thus, when arterial clamping was required

during OPN, WIT was not significantly different from RAPN.

WIT cut-offs for maximum preservation of renal function and its impact on renal outcomes remains controversial.[22-24] This can be attributed to intrinsic deficiencies of sCr and eGFR as specific markers of renal ischaemic injury. sCr and eGFR are instead better indicators of CKD or CKD risk. Hence, their usefulness after PN is in inferring longer-term effects of ischaemia on kidney function.[12] Furthermore, factors such as age, smoking history, hypertension, diabetes mellitus, and intraoperative hypotension also affect post-operative eGFR.[13] CKD risk is reduced when eGFR is >60mL/min whilst an eGFR of <45mL/min has been found to have a 93% positive predictive value for CKD, with higher overall and cardiovascular mortality.[12] Majority of our cohort had a baseline and 6-month eGFR of e60mL/min (87.27% OPN; 89.66% RAPN) indicating low CKD risk and minimal renal functional impact. Despite significantly different rates of arterial clamping, post-operative eGFR stages were similar between groups, even when adjusted for age and RENAL scores. This supports earlier suggestions that a short WIT as a single parameter may not confer clinically significant detriment on renal function.[22-26] We found no statistical relationship between WIT and post-operative eGFR stage, further questioning the clinical importance of the 30-minute WIT cut-off.

We present the largest reported Australian PN series and first Australian series comparing RAPN to OPN. Study limitations include a retrospective design, non-randomisation, and differences in group size. Nonetheless, strong baseline cohort similarities can be said to reflect an Australian community practice demographic thus allowing a fair comparison. RAPN offers demonstrable advantages which may facilitate nephron-sparing surgery for more complex tumours. Worldwide, more data is needed to formulate surgical guidelines for enhancing patient selection for each approach. This could be gained from large multi-centred trials, which can also help to overcome surgeon experience bias. Additionally, cost-benefit data comparing RAPN to OPN in Australia are lacking, and previous analyses report mixed outcomes.[7, 27, 28] While this series confirms certain advantages in a robotic approach, further cost-benefit analysis can assist stakeholders involved in decision-making related to resource allocation for emerging technologies like robotic surgery.

Our series demonstrates that RAPN is at least equivalent to the standard of care, OPN. RAPN's

distinct advantages are reduced operative complications, decreased blood loss, shorter hospital stays, and fewer positive surgical margins, in the context of similar operative times and more complex renal tumours. Despite universal clamping in RAPN, no significant difference in eGFR outcomes are demonstrated. Where available, RAPN is becoming increasingly mainstream for early stage renal cell carcinoma. Health funding models need to adapt accordingly to ensure patients are not denied minimally invasive surgery purely on financial grounds.

Background: To compare perioperative, renal and oncological outcomes after robotic-assisted partial nephrectomy (RAPN) versus open partial nephrectomy (OPN) for the treatment of renal tumours.

Methods: All partial nephrectomies performed at a metropolitan urology centre between 2010 to 2016 were analysed. Baseline data was collected for patient demographics, tumour characteristics (tumour size, laterality and polarity, RENAL scores), and perioperative variables (e.g. warm ischaemic time (WIT), operation time, estimated blood loss (EBL), length of stay). Tumour characteristics included malignancy, clinical stage, Fuhrman nuclear grade, and surgical margin status. Day-1 post-operative sCr, eGFR, and 6-month eGFR stage were used for assessing renal function.

Results: 200 patients underwent partial nephrectomy between 2010 to 2016 (N=200; 55 OPN vs 145 RAPN). Baseline data was similar between groups, except for lower age (p=0.0001) and higher RENAL scores (p=0.001) in the RAPN group. RAPN demonstrated significantly lower complication rates (p=0.015), lesser EBL (p=<0.0001), shorter hospital stays (p=<0.001), and reduced positive tumour resection margins (p=0.039). There was no significant difference in mean operation time between RAPN and OPN (137.2 (±48.0) OPN vs 146.07 (±35.91) RAPN; p=0.16). No statistical difference was shown for post-operative eGFR stage between groups at day-1 and 6-months post-surgery (p= 0.15 and p=0.861, respectively).

Conclusion: We present the largest reported Australian series on partial nephrectomy, confirming that a robotic-assisted approach is equivalent to OPN, with reduced complications, EBL, length of hospital stays, and fewer positive margins, even when resecting more complex tumours.

Keywords: kidney, partial nephrectomy, robotic surgery, complications, renal tumour

Tables

Table 1: Preoperative characteristics of patients and tumours stratified according to surgical approach

Preoperative Variable		OPN (N = 55)	RAPN (N = 145)	*p*-Value
Mean (SD) Age, years		64.64 (±11.67)	57.68 (±10.79)	0.0001
Gender, N (%)	Male	39 (70.91)	92 (63.45)	0.32
	Female	16 (29.09)	53 (36.55)	
Median(IQR), BMI		27.43 (7.59)	27.9 (6.7)	0.27
Median (IQR), Preoperative Haemoglobin (g/L)		142 (20)	142 (14)	0.28
Median (IQR), Preoperative Creatinine (µmol/L)		80 (31)	77 (18)	0.44
Median (IQR), Preoperative eGFR (mL/min/1.73m^2)		85 (21)	70 (15)	0.004*
Positive History of Hypertension, N (%)		29 (52.73)	69 (47.59)	0.516
Positive History of Diabetes Mellitus, N (%)		4 (7.27)	19 (13.10)	0.248
Previous Abdomen Surgery, N (%)		14 (25.45)	45 (31.03)	0.44
Median (IQR), Charlson Co-morbidity Index – Age Adjusted		4 (3)	4 (3)	0.32
ASA Physical Status Classification, N (%)	**1**	9 (16.36)	30 (20.83)	0.38
	2	31 (56.36)	79 (54.86)	
	3	14 (25.45)	35 (24.31)	
	4	1 (1.82)	0 (0.00)	
Baseline Tumour Characteristics		OPN (N = 55)	RAPN (N = 145)	*p*-Value
Affected Kidney, N (%)	**Right**	28 (50.91)	82 (56.55)	0.47
	Left	27 (49.09)	63 (43.45)	
Median (IQR) , Tumour Diameter (mm)		30 (16)	30 (18)	0.94
Tumour Polarity, N (%)	**Lower pole**	18 (32.73)	45 (31.03)	0.18
	Interpolar	16 (29.09)	61 (42.07)	
	Upper pole	21 (38.18)	39 (26.90)	
RENAL Nephrometry Score, N (%)	**Low (4-6)**	37 (67.27)	56 (38.62)	0.001*
	Medium (7-9)	16 (29.09)	74 (51.03)	
	High (10-12)	2 (3.64)	15 (10.34)	

Table 2. Operative outcomes: Intraoperative and perioperative variables

Intraoperative Variable		OPN (N = 55)	RAPN (N = 145)	*p*-Value
Artery Clamping, N (%)		8 (14.81)	144 (99.31)	<0.0001*
Median (IQR), Warm Ischaemic Time (WIT)		16 (9)	18 (6.5)	0.95
Mean (SD), Operation time (minutes)		137.2 (±48.0)	146.07 (±35.91)	0.16
Median (IQR), Estimated blood loss (EBL) (mls)		700 (350)	50 (150)	<0.0001*
Use of Haemostatic Agents, N (%)		33 (61.11)	136 (93.79)	<0.0001*
Intraoperative complication recorded, N (%)		14 (25.45)	14 (9.66)	0.003*
Perioperative Variable		OPN (N = 55)	RAPN (N = 145)	*p*-Value
Clavien-Dindo Complications, N (%)	**Minor (1 & 2)**	8 (14.55)	7 (4.83)	0.015*
	Major (3 & 4)	6 (10.91)	7 (4.83)	
Mean (SD), Day 1 Post-operative Hb		107.61 (±24.38)	123.38 (±12.44)	<0.0001*
Mean (SD) Decrease in Hb (post-pre)		31.86 (±23.18)	18.04 (±19.77)	0.0001*
Median (IQR), Length of stay (days)		6 (2)	3 (2)	<0.0001*

Table 3. Pathological, Oncological and Renal Functional Outcomes

Pathological Outcomes		**OPN (N = 55)**	**RAPN (N = 145)**	***p*-Value**
Malignant, N (%)		47 (85.45)	122 (84.14)	0.818
Clinical TNM Staging, N (%)	**1 & 2**	51 (96.23)	134 (95.04)	0.725
	3	2 (3.77)	7 (4.96)	
Histological Diagnosis, N (%)	**Clear Cell**	34 (61.82)	96 (66.21)	0.193
	Papillary	11 (20.00)	13 (8.97)	
	Chromophobe	1 (1.82)	10 (6.90)	
	Other	9 (16.36)	26 (17.93)	
Fuhrman Nuclear Grade for malignant tumours, N (%)	**1**	3 (6.67)	16 (14.41)	0.329
	2	33 (73.33)	79 (71.17)	
	3	9 (20.00)	16 (14.41)	
Positive Resection Margins, N (%)		6 (10.91)	5 (3.45)	0.039*
Oncological Outcomes		OPN (N = 51)	RAPN (N = 117)	*p*-Value
Median (IQR), Follow-up times (months)		29 (42)	18 (42.2)	<0.0001*
Tumour recurrence, N (%)		0 (0.00)	0 (0.00)	-
Post-operative Serum Creatinine (sCr)		OPN (N = 55)	RAPN (N = 145)	*p*-Value
Median (IQR), Day 1 Post-operative sCr (µmol/L)		80 (45)	76 (24)	0.13
Median (IQR), Change in sCr at Day 1 post-operative (µmol/L)		5 (23)	2 (13)	0.04*
Post-operative eGFR grade/stage		OPN (N = 51)	RAPN (N = 122)	*p*-Value
Day-1 post-op	**Grade 1-2: Normal to mildly reduced (e60)**	43 (78.18)	121 (83.45)	0.15
	Grade 3: Mildly to Moderately reduced (<60)	4 (7.27)	15 (10.34)	
	Grade 4-5: Moderately to Severely reduced (<45)	8 (14.55)	9 (6.90)	
Six months post-op[a]	**Grade 1-2: Normal to mildly reduced (e60)**	43 (84.31)	106 (86.89)	0.861
	Grade 3: Mildly to Moderately reduced (<60)	5 (9.80)	11 (9.02)	
	Grade 4-5: Moderately to Severely reduced (<45)	3 (5.88)	5 (4.10)	

[a]173 subjects had follow-up times which were **e** 6 months; 27 subjects have been excluded from the 6 month eGFR analysis (4 from the OPN group, and 23 from the RAPN group)

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