



Open versus robot-assisted partial nephrectomy: A longitudinal comparison of 880 patients over 10 years

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Abstract

Background: Most comparisons between robot-assisted partial nephrectomy (RAPN) and open partial nephrectomy (OPN) indicate the superiority of RAPN, but the learning curve is often not considered.

Methods: All consecutive partial nephrectomies from the very first RAPN at a single tertiary referral centre ($n = 818$, 500 RAPN vs. 313 OPN) were retrospectively analyzed. Complications, success rates and surgical outcomes were compared. Inequalities between cohorts and the inherent learning curve were controlled by subgroup comparisons, regression analyses, and propensity score matching.

Results: Overall, RAPN had fewer complications, less blood loss, and shorter length of stay. However, an inherent learning curve caused higher complications for the first 4 years. Thereafter, perioperative outcomes clearly favoured RAPN, even for more complex tumours.

Conclusions: In one of the largest monocentric cohorts over more than 10 years, RAPN was found to be superior to OPN. However, not all advantages of RAPN are immediate because a learning curve must be passed.

KEYWORDS

minimally invasive surgery, nephrectomy, renal cell carcinoma, partial robot-assisted partial nephrectomy

1 | INTRODUCTION

Renal cell carcinoma (RCC) is the third most common malignancy of the urinary tract. Its incidence has increased in recent years due to improved imaging modalities and their wide application.¹ Although new therapeutic approaches have been developed, surgical removal of the tumor remains the gold standard of treatment.²

In this context, partial nephrectomy (PN) has proven to be oncologically equal to radical nephrectomy for small renal masses and locally advanced tumours.³ Since the first laparoscopic partial nephrectomy (LPN) in 1993 and the first robot-assisted partial nephrectomy (RAPN) in 2004, the standard approach for PN has been a matter of debate.^{4,5} Due to a shorter and steeper learning curve, RAPN was established much faster in urologic surgery.⁶ However,

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LPN also provides excellent results, even in complex and atypical situations. A lower morbidity of LPN compared to open partial nephrectomy (OPN) has been demonstrated with equal oncological outcomes.⁷⁻⁹ Nevertheless, OPN is still considered the gold standard according to the current guidelines.^{10,11}

To date, many studies have compared surgical outcomes of OPN with RAPN. RAPN has shown to be advantageous in terms of complications, estimated blood loss (EBL), and length of hospital stay, but it has a longer operating time and warm ischaemia time (WIT) in many cases.¹² Nonetheless, most studies cover shorter time spans,¹³ include limited patient numbers,¹⁴ or can only provide large patient cohorts in multicenter settings.¹⁵ As the effect of inherent learning is often not considered, it is difficult to draw direct conclusions for daily urologic practice in a 'real-world' setting. In addition, data are scarce regarding the question of how much time is needed to reach better outcomes with RAPN.

For this reason, we analyzed a large, single-center cohort of 813 PNs, including 500 RAPNs and 313 OPNs, over a time span of more than 10 years from 2007 to 2018. To show the impact of the inherent learning curve of RAPN on surgical outcomes, all consecutive partial nephrectomies from the very first RAPN in our department were included. As patients were not randomized but rather assigned to groups according to the surgeon's expertise, a regression analysis and propensity score matching were performed to outweigh selection bias.

2 | MATERIALS AND METHODS

All OPN and RAPN, including the very first case, at a tertiary referral center from 2007 to 2018 were retrospectively included. The operative standard for OPN was a retroperitoneal approach. However, four patients had anatomical abnormalities, such as a horseshoe kidney, for which a transperitoneal approach had to be chosen. All RAPNs were performed via a transperitoneal approach using a DaVinci® Si or S system (Intuitive Surgical). To preserve the maximum amount of nephron mass without impairing the oncological outcome, the tumors were enucleated, if possible, otherwise they were enucleoresected.¹⁶ All RAPNs were performed by seven trained robotic surgeons with experience in at least 50–100 radical prostatectomies, nephrectomies and pyeloplasties.

Patient age, gender, body mass index (BMI), ASA (American Society of Anaesthesiologists) score and number of prior abdominal surgeries were obtained. Tumor laterality, size, growth pattern (endo- vs. exophytic), complexity and preoperative aspects and dimensions used for an anatomical (PADUA) score served as tumor characteristics.¹⁷ Surgical results included operating time, EBL, frequency and duration of WIT, and postoperative complications according to Clavien Dindo within 30 days after surgery. Final pathologic results with positive surgical margins (PSMs) were reviewed. The Trifecta rate was defined as absence of PSMs, WIT \leq 25 min, and absence of any postoperative complications. The margin, ischaemia and complications

(MIC) rate was defined as absence of PSMs, WIT \leq 20 min, and absence of major postoperative complications \geq Clavien Dindo grade 3.^{6,18}

As the primary outcome, complication and success rates (Trifecta and MIC) were analyzed. Comparison of operating time, EBL, WIT, off-clamp excisions, PSMs, transfusion rates and length of stay served as secondary outcomes.

OPN and RAPN cohorts were compared, including all cases over the whole period and as time-dependent subgroup analyses from 2007 to 2012 and 2013 to 2018. To analyze whether results changed over time within groups, OPN cases from 2007 to 2012 were compared with OPN cases from 2013 to 2018, likewise for RAPN. The time when the overall complication rate per year of OPN exceeded RAPN was estimated via a linear regression analysis. Further uni- and multi-variate regression analyses were conducted to compare the influences of the surgical approach, PADUA score, and patient-specific characteristics on primary outcomes. A propensity score matching for PADUA score, tumour size and number of prior abdominal surgeries with a tolerance rate of 0.05 rendered a comparison of matched OPN and RAPN cohorts possible.

Demographic and perioperative data were analyzed with descriptive statistics. Categorical variables were reported as frequencies and proportions, and continuous data were reported as the median and range. Fisher's exact and Mann-Whitney U-tests were used to compare between independent groups, McNemar and Wilcoxon ranksum tests for dependent samples, and propensity score for matched data. Covariates were included in the multiple regression analysis only if the respective effect was significant in the univariate analysis. Statistical analyses were performed with SPSS version 25 (IBM). All tests were two-sided, and p -values <0.05 were considered significant. This study was approved by the Ethical Review Board of Saarland (reference Bu 67/19), and all patients provided written consent.

3 | RESULTS

3.1 | Overall comparison

A total of 813 partial nephrectomies were included from 2007 to 2018, with 500 RAPN and 313 OPN. The annual total caseload increased from 42 in 2008 to 118 in 2017, mostly because RAPNs were increasingly performed, from 4 procedures in 2008 to 88 in 2017 (see Figure 1).

Overall, patient demographics only differed regarding the number of prior abdominal surgeries (OPN $>$ RAPN, $p < 0.001$; see Table 1). As for tumor characteristics, tumours for OPN were larger (4.2 vs. 3 cm, $p < 0.001$) and more complex: 60.9% of all tumours for OPN, but only 33.7% for RAPN, were considered as high-risk (PADUA ≥ 10 ; $p < 0.001$).

Concerning primary outcomes, RAPN had fewer postoperative complications, with 20% minor and 4.4% major complications ($p < 0.001$; see Table 1). Trifecta fulfilment was not different between

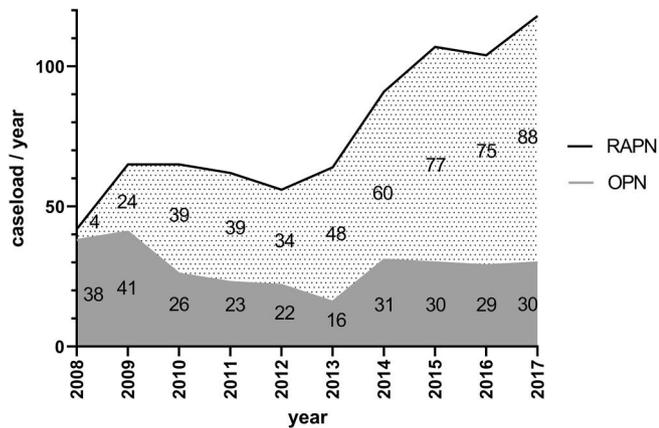


FIGURE 1 Annual caseload of open (grey area) and robot-assisted partial nephrectomies (dotted area) from 2008 to 2017, including the annual number of cases per group. OPN, open partial nephrectomy; RAPN, robot-assisted partial nephrectomy

OPN and RAPN, whereas MIC was fulfilled more often with OPN (70.6% vs. 63%, $p < 0.05$).

As for secondary outcomes, EBL was lower in RAPN (200 vs. 300 ml, $p < 0.001$), and operating time was significantly longer (157 vs. 188 min, $p < 0.001$). The rate of off-clamp excisions did not differ, but WIT was significantly longer for RAPN (15 vs. 13 min, $p < 0.01$), and 6%–7% of cases had PSMs. Patients were discharged earlier after RAPN (6 vs. 10 days, $p < 0.001$) with lower yet not significantly different transfusion rates (8.8% vs. 12.8%).

3.2 | Propensity score matched analysis

By propensity score matching for the number of prior abdominal surgeries, tumor size and PADUA score, 216 OPNs were matched with 216 RAPNs in a 1:1 fashion. The mean tumour size was 4 cm, and the PADUA score was 10, with 56.5% (OPN) and 52.3% (RAPN) high-risk tumours (see Table S1). With regard to the overall comparison, differences in EBL were no longer significant after propensity score matching (OPN 300 vs. RAPN 250 ml), and all other primary and secondary outcomes remained unchanged (see Table S1).

3.3 | Regression analysis

In the multivariate regression analysis, the surgical approach had a significant impact on complications in favour of RAPN (see Table 2). Higher patient age, ASA score and number of prior abdominal surgeries also increased the risk for complications (for all OR 1.03–1.48, $p < 0.05$). The PADUA score did not have any impact on complications.

Concerning success rates, the MIC rate was impacted by the surgical approach, and RAPN had a lower odds ratio for fulfilling MIC (0.61, $p < 0.01$). Higher PADUA scores had a negative impact on MIC rates (OR 0.9, $p < 0.05$). As patient-related factors, ASA, BMI and the

number of prior abdominal surgeries had a significant effect on Trifecta or MIC fulfilment, regardless of the surgical approach (OR 0.71–0.97, $p < 0.05$, see Table 2).

3.4 | Inherent learning curve

Patient demographics did not change over time when comparing cases from 2007 to 2012 with 2013 to 2018 only within RAPN and only within OPN groups (see Table S2). Tumor size increased from 3.9 to 4.3 cm for OPN ($p < 0.01$). PADUA score did not change for RAPN, but more mid- (34.2% vs. 21%) and high-risk tumours (34.5% vs. 17.5%) were treated ($p < 0.01$).

While the surgical outcomes remained unchanged for OPN, operating time significantly decreased for RAPN (172 vs. 152 min, $p < 0.001$). More tumors were excised off-clamp in 2013–2018 (8.4% vs. 17.9%, $p < 0.01$). WIT decreased by 5 min ($p < 0.001$), and patients were discharged 1 day earlier ($p < 0.001$) with higher MIC rates (54% vs. 66.4%, $p < 0.05$; see Table S2).

3.5 | Time-dependent comparison

When comparing RAPN versus OPN from 2007 to 2012 and 2013 to 2018, the PADUA score and tumor size significantly differed within both periods ($p < 0.001$). The number of prior abdominal surgeries was higher in OPN from 2013 to 2018 ($p < 0.001$).

Concerning primary outcomes, RAPN was not superior in terms of complication rates from 2007 to 2012, but it was superior from 2013 to 2018 ($p < 0.001$; see Table 3). When stratifying by year of surgery, the overall complication rate significantly decreased from 50% in 2008 to 20.5% in 2017 for RAPN ($p < 0.01$), and it did not significantly increase from 28.9% to 46.7% for OPN, respectively (see Figure 2). A linear regression model indicated that the annual complication rate for RAPN (Spearman's rho -0.73 , $p < 0.05$) fell below the corresponding complication rate for OPN in 2010 (rho 0.43; n.s.). While MIC was reached significantly more often from 2007 to 2012 with OPN (69% vs. 54.5%, $p < 0.05$), the success rates were no longer different afterwards (see Table 3).

As for secondary outcomes, the operating time was shorter for OPN ($p < 0.001$). Although EBL was already lower with RAPN from 2007 to 2012, this difference became significant in 2013–2018 (200 vs. 300 ml, $p < 0.001$). Correspondingly, blood transfusions were less frequent with RAPN than OPN ($p < 0.05$). The number of off-clamp excisions and WIT were no longer different from 2013 to 2018. Patients were always discharged earlier after RAPN ($p < 0.001$).

4 | DISCUSSION

In this study, a longitudinal, single-center comparison of 500 robot-assisted versus 313 open partial nephrectomies from 2007 to 2018 was conducted. Of note, we included the very first RAPN at our



	OPN	RPN	p-value
Patient demographics			
Age (year)	65 (21; 88)	63 (24; 93)	n.s.
Gender male	194 (62%)	327 (65.4%)	n.s.
BMI (kg/m ²)	26.9 (17.1; 50.1)	27.6 (18; 59.5)	n.s.
ASA	2 (1; 4)	2 (1; 4)	n.s.
Prior abdominal surgeries	1 (0; 13)	1 (0; 5)	<0.001
Tumour characteristics			
Side left	172 (55%)	247 (49.4%)	n.s.
Size (cm)	4.2 (1; 20.4)	3 (0.4; 10)	<0.001
Exophytic tumour	24 (9.49%)	35 (7.94%)	n.s.
PADUA score	10 (6; 13)	8 (6; 14)	<0.001
Low-risk (6, 7)	34 (13.4%)	139 (31.7%)	
Mid-risk (8, 9)	65 (25.7%)	152 (34.6%)	
High-risk (≥10)	154 (60.9%)	148 (33.7%)	
Primary outcome			
Complications			<0.001
Any	110 (35.2%)	122 (24.4%)	
Minor	72 (23%)	100 (20%)	
Major	38 (12.2%)	22 (4.4%)	
Trifecta	182 (58.1%)	294 (58.8%)	n.s.
MIC	221 (70.6%)	315 (63.0%)	<0.05
Secondary outcome			
Operating time (min)	118 (44; 280)	157 (52; 376)	<0.001
Blood loss (ml)	300 (10; 2600)	200 (0; 2600)	<0.001
WIT (min)	13 (0; 38)	15 (0; 43)	<0.01
Off-clamp excisions	60 (19.2%)	76 (15.6%)	n.s.
PSM	22 (7.2%)	32 (6.4%)	n.s.
Transfusion rate	40 (12.78%)	44 (8.8%)	n.s.
Length of stay (day)	10 (4; 56)	6 (3; 49)	<0.001

Note: Values in bold are statistically significant and have a p -value < 0.05 .

Abbreviations: ASA, American Society of Anaesthesiologists; BMI, body mass index; MIC, margin ischaemia complications; OPN, open partial nephrectomy; PN, partial nephrectomy; PSM, positive surgical margin; RAPN, robot-assisted partial nephrectomy; WIT, warm ischemia time.

department and, from then on, all consecutive OPN and RAPN over more than 10 years. The annual caseload of PNs considerably increased from 42 in 2008 to 118 in 2017 (see Figure 1). This can be mainly attributed to an increase of RAPN, reflecting higher acceptance of robotic kidney surgery, not only in our department but also in urology in general, within the last years.¹⁹ On the other hand, the OPN caseload remained constant, highlighting its continued importance for selected indications, such as to avoid otherwise unnecessary, minimally invasive nephrectomies.¹¹

As a primary outcome, we compared the complication rates of OPN with RAPN (see Table 1). In accordance with Ficarra et al. and

TABLE 1 Overall comparison of patient demographics, tumor characteristics and surgical outcomes of 313 OPN and 500 RAPN

Porpiglia et al., the postoperative complication rates were significantly higher after OPN.^{13,20} Consequently, the surgical approach showed to have a significant impact on complication rates in the multivariate regression analysis: the risk was lowered by 34% for minor and up to 64% for major complications for the robotic approach (see Table 2). Likewise, Peyronnet et al. found the risk of postoperative complications to be 2.2 times higher in OPN.¹⁵ In addition, patient-specific factors (higher patient age or ASA score) were predictive for complications. In contrast to other publications, prior abdominal surgery proved to have a significant impact (OR 1.2, $p < 0.01$).²¹ Nonetheless, prior abdominal surgery is not

TABLE 2 Multivariate logistic regression model of complications and Trifecta/MIC fulfilment, only significant associations are shown

Variable	OR (95% CI)	p-value
Any complication		
OPN versus RAPN	0.66 (0.48; 0.92)	<0.05
ASA	1.48 (1.31; 1.93)	<0.01
Prior abdominal surgery	1.21 (1.06; 1.38)	<0.01
Minor complications		
ASA	1.35 (1.00; 1.80)	<0.05
Prior abdominal surgery	1.25 (1.09; 1.43)	<0.001
Major complications		
OPN versus RAPN	0.34 (0.2; 0.59)	<0.001
Age	1.03 (1.01; 1.06)	<0.05
Trifecta		
ASA	0.74 (0.56; 0.94)	<0.05
Prior abdominal surgery	0.76 (0.66; 0.86)	<0.001
MIC		
OPN versus RAPN	0.61 (0.43; 0.87)	<0.01
PADUA score	0.92 (0.75; 0.91)	<0.001
BMI	0.97 (0.93; 0.99)	<0.05

Abbreviations: ASA, American Society of Anaesthesiologists; BMI, body mass index; MIC, margin ischemia complications; OPN, open partial nephrectomy; RAPN, robot-assisted partial nephrectomy.

contraindicative for minimally invasive kidney surgery at our department. We did not conduct retroperitoneoscopic PN, which potentially could reduce the risk of complications caused by prior abdominal surgery.²² In contrast, the PADUA score, and therefore tumor complexity, did not impact complication rates in the regression analysis (see Table 2).

It has also been a major objective to improve 'success rates' in PN in recent years, and Trifecta and MIC rate are two ways of measuring this.^{6,18} When comparing RAPN and OPN cohorts overall, the Trifecta rates did not differ (see Table 1). However, the MIC rates were higher for OPN than RAPN (70.6% vs. 63.0% $p < 0.05$). As the PSM rates did not differ, and complication rates were much higher for OPN, the difference in MIC fulfilment resulted mainly from a longer WIT for RAPN (15 vs. 13 min, $p < 0.01$). A longer WIT in RAPN has also been described elsewhere.^{13,23} Most likely, a difference of 2 min in WIT will not have any effect on postoperative renal function, as long as the WIT is no longer than 20–25 min.²⁴ Recently, it has clearly been shown that preoperative renal function and the amount of preserved renal parenchyma are more important predictors of postoperative renal function.²⁵ Correspondingly, Takagi et al. compared OPN versus RAPN only in patients with chronic kidney disease and found no difference in outcomes.²⁶ However, other groups also described higher Trifecta and MIC rates and shorter WIT in RAPN.^{15,20}

When comparing both groups overall, patient demographics and tumor characteristics differed in three aspects: tumour size ($\Delta 1.2$ cm), PADUA score (8 vs. 10), and the number of prior abdominal surgeries (for all $p < 0.001$). For this reason, we performed a 1:1 propensity score matching and matched a total of 432 patients as case controls (see Table S1). It is important to highlight that more than 50% of patients had high-risk tumors, with a PADUA score ≥ 10 , within this matched cohort. Regardless, neither primary nor secondary outcomes changed in comparison with the overall comparison. Only blood loss was no longer statistically significant between OPN and RAPN after propensity score matching, and it remained slightly lower for RAPN (250 vs. 300 ml, see Table S1).²⁷ Operating time and WIT were longer for RAPN, which is in line with other studies.^{23,28} RAPN still had fewer postoperative complications than OPN ($p < 0.001$), which has been published for (highly) complex lesions.^{29,30} Similarly, Harke et al. compared completely endophytic, and therefore complex, tumors and found higher Trifecta rates for RAPN than OPN (75% vs. 68%, n.s.).³¹ The length of hospital stay was shorter for RAPN as well (6 vs. 10 days, $p < 0.001$, see Table S1). However, others report even shorter length of stays for RAPN ranging from 3 to 5 days.^{15,30} This can be attributed to differences in national health care systems, as German reimbursement covers a longer hospital stay.^{32–34} In fact, patients could have been discharged earlier from a surgical point of view, but it has not been a crucial parameter for us, either for RAPN or OPN.

We suspected that an inherent learning curve in the RAPN cohort might affect the surgical results. Learning curves of robotic surgeons have shown to be steeper than in laparoscopy and do not level out until 300 RAPN cases.^{35,36} For this reason, we conducted a time-dependent subgroup analysis by comparing cases from 2007 to 2012 with 2013 to 2018 only within RAPN and OPN groups (see Table S2). In both cohorts, solely the tumor characteristics changed minimally over time. In contrast to OPN, where the surgical results remained stable, RAPN clearly showed an inherent learning curve: MIC rates increased (54.5%–66.4%) while operating time (172–152 min), WIT (18–13 min), and length of stay (7–6 days) further decreased (for all $p < 0.05$). At the same time, tumors became more complex, and mid- and high-risk tumors were operated on to a greater extent (see Table S2).³⁷

To assess the impact of the inherent learning curve in RAPN compared with OPN, we compared cases from 2007 to 2012 and from 2013 to 2018 between the groups (see Table 3). It was not surprising that RAPN did not reach lower postoperative complication rates than OPN from 2007 to 2012. Larcher et al. recently illustrated a learning curve for a complication-free course as a function of the robotic surgeon's experience.³⁶ They showed that increasing experience lowered the risk of complications in RAPN. In line with these results, the annual complication rate of RAPN fell below that of OPN in 2010 in our cohort (see Figure 2). Although the tumors in the RAPN group were significantly more complex (see Table S2), increasing experience made lower overall complication rates possible four years after the initiation of a robotic program at our institute. Accordingly, the MIC rates were no longer superior for OPN, and the

TABLE 3 Time-dependent subgroup analysis of OPN versus RAPN only in 2007–2012 and 2013–2018

	2007–2012			2013–2018		
	OPN (n = 155)	RAPN (n = 143)	p-value	OPN (n = 158)	RAPN (n = 357)	p-value
Primary outcome						
Complications			n.s.			<0.001
Any	43 (32.3%)	43 (30.1%)		60 (37.9%)	79 (22.1%)	
Minor	31 (20%)	36 (15.1%)		41 (25.9%)	64 (17.8%)	
Major	19 (12.3%)	7 (15%)		19 (12%)	15 (4.2%)	
Trifecta	91 (58.7%)	77 (53.8%)	n.s.	91 (57.6%)	217 (60.8%)	n.s.
MIC	107 (69%)	78 (54.5%)	<0.05	114 (72.2%)	237 (66.4%)	n.s.
Secondary outcome						
Operating time	114.5 (48;246)	172 (68; 356)	<0.001	120 (44; 280)	152 (52; 376)	<0.001
Blood loss	300 (10; 2100)	220 (20; 2000)	n.s.	300 (20; 2600)	200 (0; 2600)	<0.001
WIT	12 (0; 37)	18 (0; 43)	<0.001	13 (0; 38)	13 (0; 40)	n.s.
Off-clamp	30 (19.4%)	12 (8.6%)	<0.01	30 (19%)	64 (18.4%)	n.s.
PSM	14 (9%)	9 (6.5%)	n.s.	8 (5%)	23 (7.3%)	n.s.
Transfusion rate	19 (12.3%)	18 (12.6%)	n.s.	21 (13.3%)	26 (7.3%)	<0.05
Length of stay	9 (5; 56)	7 (4; 29)	<0.001	10 (4; 42)	6 (3; 49)	<0.001

Note: Values in bold are statistically significant and have a p -value < 0.05.

Abbreviations: ASA, American Society of Anaesthesiologists; MIC, margin ischemia complications; OPN, open partial nephrectomy; PSM, positive surgical margin; RAPN, robot-assisted partial nephrectomy; WIT, warm ischaemia time.

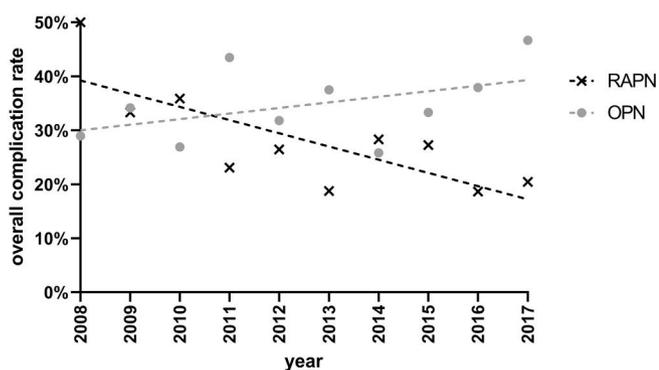


FIGURE 2 Annual overall complication rate of open (grey dots) and robot-assisted partial nephrectomies (black crosses). The trend of annual complication rates in linear regression analysis for OPN and RAPN is indicated by dashed lines. OPN, open partial nephrectomy; RAPN, robot-assisted partial nephrectomy

differences in WIT were no longer significant from 2013 to 2018. In addition, blood loss and transfusion rates became significantly different in favor of RAPN ($p < 0.05$).

Therefore, we conclude that RAPN is not better than OPN per se, because good results rely on experience that needs to be gained beforehand. Correspondingly, the current European guidelines on RCC state that the choice of surgical approach should be 'based on surgeon's expertise and skills'.¹¹ However, RAPN is not superior to OPN in all terms. Although the difference in operating times

decreased from 57.5 to 32 min, OPN was still the significantly shorter approach, even from 2013 to 2018 ($p < 0.001$).

This study is not devoid of limitations. Due to its retrospective nature, cohorts were not perfectly balanced in terms of caseload, patient, and tumor characteristics. Regression analysis and propensity score matching are appropriate methods to reduce imbalance, but they cannot replace randomized study designs. For this reason, the OpeRa study (Open vs. robotic assisted PN, NCT03849820) has started enrolling patients in a prospective, randomized fashion. Furthermore, we could not fully control for the impact of the inherent learning curve of RAPN in pairwise comparisons, as there were no obvious learning effects for OPN. In fact, the learning curve for OPN had been passed much earlier because the experience of the senior staff with OPN reached back more than 30 years.³⁸

In summary, we analyzed one of the largest monocentric cohorts so far comparing OPN with RAPN. We conclude that RAPN is clearly superior to OPN in terms of the perioperative results. Nonetheless, not all advantages of robotic surgery can be reached immediately when establishing a robotic partial nephrectomy program, as a learning curve must be passed.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Philip Zeuschner, Matthias Saar; methodology: Philip Zeuschner; data acquisition: Philip Zeuschner, Leonie Greguletz, Irmengard Meyer; analysis: Philip Zeuschner, Leonie Greguletz, Irmengard Meyer, Gudrun Wagenpfeil, Stefan Wagenpfeil; writing: Philip Zeuschner; review and editing: all authors; supervision: Matthias Saar.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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