

# Robot-assisted partial nephrectomy: A single-center matched-pair analysis of the retroperitoneal versus the transperitoneal approach

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## ABSTRACT

**Objective:** Comparison of the retroperitoneal (RRPN) perioperative variables and the transperitoneal (TRPN) robot-assisted partial nephrectomy (RPN) using a matched-pair analysis.

**Material and methods:** A retrospective review was carried out for 224 patients who underwent RPN between 2014 and 2019. A matched-pair analysis was performed on 51 pairs of patients. The matching criteria were age, Charlson comorbidity index, body mass index, the grade of renal insufficiency, tumor diameter, and Pre-operative Aspects and Dimensions Used for an Anatomical Classification of Renal Tumors score.

**Results:** The time to reach the renal hilum ( $P < .001$ ), the overall complication rate ( $P = .008$ ), and the major complication rate ( $P = .01$ ) were lower in the RRPN group. The operative time was 143 vs 150 minutes ( $P = .63$ ) in RRPN vs TRPN, respectively. Warm ischemia time was 10 minutes in RRPN vs 12 minutes in TRPN ( $P = .07$ ). Early unclamping was used in 71% in RRPN vs 48% in TRPN ( $P = .02$ ). The length of hospital stay was 6 days in both groups ( $P = .11$ ). The cases' complexity, the rate of positive surgical margins, and postoperative kidney function were comparable in both groups ( $P > .05$ ).

**Conclusion:** The advantages of RRPN lie in the shorter time to reach the renal hilum and the lower complication rates; the comparability with the other parameters proves the safety and feasibility of the RRPN access for localized kidney tumors.

**Keywords:** Nephron-sparing surgery; renal neoplasms; retroperitoneal space; robot-assisted surgery.

## Introduction

The incidence rates of kidney cancer rapidly increased until the mid-1990s, when they reached a plateau or dropped for many countries.<sup>1</sup> Primarily due to increased detection of incidental tumors during radiological investigations of the upper abdomen,<sup>2</sup> ie, at a lower tumor stage and size,<sup>1</sup> this has changed renal cell carcinoma (RCC) into a surgically curable renal tumor.<sup>3</sup>

Partial nephrectomy is the treatment of choice for localized RCC (pT1).<sup>4</sup> Studies show better preservation of kidney function and, therefore, a decreased risk of developing cardiovascular diseases.<sup>5</sup> In 2004, Gettman et al.<sup>6</sup> presented the first series of robot-assisted partial

nephrectomy (RPN); since then, RPN's popularity has significantly expanded.<sup>7</sup> RPN is associated with lower complication rates, less blood loss, and shorter hospital stay while showing comparable oncological outcomes than open partial nephrectomy (OPN).<sup>8</sup> The RPN has widely replaced laparoscopic surgery as the preferred minimally invasive technique for localized renal tumors in centers with available robotic surgery.<sup>9</sup>

RPN approaches are the transperitoneal approach (TRPN) and the retroperitoneal (RRPN) approach. The RRPN approach tends to be more appropriate than the TRPN approach to access tumors on the dorsal renal surface, allowing more convenient access to

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the renal hilum and reducing the need to mobilize bowel or kidney.<sup>10</sup> Moreover, the TRPN approach has limitations in the presence of adhesions due to prior abdominal surgery.<sup>10</sup>

Our study compares the RRPN perioperative variables and the TRPN RPN using a matched-pair analysis.

## Material and Methods

From our prospective data register at our institution, we reviewed 224 consecutive RPN for treatment of renal masses over 5 years between 2014 and 2019; in 163 patients via a TRPN approach and 61 patients via a RRPN approach by three surgeons using a Da Vinci Si surgical system.

The choice of robot approach (RRPN vs TRPN) was based on tumor location: RRPN was primarily selected for posterior tumors, and TRPN was selected for, though not limited to, anterior tumors. Moreover, patient characteristics like body mass index (BMI) and prior abdominal surgery were considered when choosing the preferred approach.

## Technique Description

The TRPN approach is achieved by placing the patient in a flank position. The optical Hasson trocar is placed via mini-laparotomy pararectal and supraumbilical. Another four trocars are inserted under sight, a 12 mm trocar in the median lower abdomen and three 8 mm trocars, laterally below the costal arch, the lateral lower abdomen, and above the iliac spine.

The RRPN approach is achieved by placing the patient in the lateral decubitus position. The optical Hasson trocar is placed 2 cm above the lumbar triangle. The lumbodorsal fascia is traversed with Metzenbaum scissors, followed by blunt dissection of the perforation canal to achieve the stab incision. The created space is entered under vision with a laparoscopic 0° camera with a dilatation trocar (a 130-mm KiiR balloon trocar, Applied Medical), the trocar is inflated with 500 mL air. The dilatation balloon is removed, and a 12 mm optical Hasson trocar is placed.<sup>11</sup>

### Main Points

- RRPN is a safe and feasible approach for localized renal tumors.
- The time to reach renal hilum is significantly shorter in RRPN.
- RRPN should be part of robotic surgical training.
- An optimal RPN approach is not yet established, but the patient should be offered the best available option.

After creating the retroperitoneum, the first trocar is inserted 3 cm above and at least 7 cm away from the camera trocar along the posterior axillary line. The second trocar is placed along the anterior axillary line, and at least 7 cm away from the camera trocar, the working trocar is inserted 3 cm above the anterior superior iliac spine (Figure 1).

Patient demographics, operative, perioperative, and oncological and functional outcome data were analyzed retrospectively for all patients and arranged into an anonymized database.

Patient demographics were identified, including age, sex, BMI, Eastern Cooperative Oncology Group/World Health Organization Performance Status, Charlson Comorbidity Index, and solitary kidney.

Preoperative functional and oncological variables, including preoperative hemoglobin, estimated glomerular filtration rate (eGFR), Preoperative Aspects, and Dimensions Used for an Anatomical (PADUA) Classification of Renal Tumors PADUA score,<sup>12</sup> were obtained. Operative variables include the overall operative time, console time, warm ischemia time, time to reach the renal hilum, early unclamping, intraoperative complications, and conversion rates to OPN or radical nephrectomy. Post-operative variables were the length of hospital stay (LOS), renal function (eGFR), and any complications using the Clavien–Dindo classification system.<sup>13</sup> Tumor characteristics, including tumor diameter, pathologic staging, and positive surgical margin status, were also described.

Ethical committee approval was received from the Medical Faculty's Ethics Committee of Christian-Albrechts-University of Kiel (D 487/20). All procedures applied are part of standard routine care, in line with European Urology Association guidelines, with ethical principles following the latest version of Helsinki's declaration.

## Statistical Analysis

Matched-pair analysis between the RRPN and TRPN groups was performed using an algorithmic approach in Python programming language. The programming library sklearn (<https://scikit-learn.org>) was applied with logistic regression as a modeling method. The matching process simulates randomization—as a result, we get two groups of equal size, which are balanced for specific parameters.

A total of 51 pairs were matched with propensity score precision down to two digits. The matching criteria used were age,

Charlson comorbidity index, BMI, the grade of renal insufficiency, tumor diameter, and PADUA score.

A two-sample t-test and Mann–Whitney test for continuous parameters were employed to determine any significant differences for each matching characteristic between the two groups; the test showed that both groups are homogeneous. A  $P$ -value of  $<.05$  considered significant. The implementation was performed in Python with the library scipy (<https://docs.scipy.org/doc/scipy/reference/stats.html>).

Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis: A univariate analysis using two-sample t-test (mean and standard deviation for continuous variables), Mann–Whitney-test (median and range for continuous variables), and chi-square test (percentage for categorical variables) were employed to compare perioperative and postoperative data with statistical significance at  $P < .05$ .

## Results

After propensity score matching, 51 matched pairs were identified in both groups with a well-balanced distribution of preoperative demographic and tumor parameters (Table 1).

The median clinical tumor size was 26 mm vs 27 mm in TRPN and RRPN, respectively ( $P = .57$ ). The median PADUA score was 9 in the TRPN group and 8 in RRPN ( $P = .88$ ), with 33% highly complex tumors in both groups. TRPN was used for anterior 49% and RRPN, for posterior tumors 76% ( $P < .001$ ), in 14% tumor location was lateral (between anterior and posterior) (17.6% TRPN and 11.8% RRPN,  $P < .001$ ).

The mean operative time was statistically comparable in both groups, with 143 in RRPN vs 150 minutes in TRPN ( $P = .63$ ). Off-clamp resection of the tumor was performed in two TRPN and two RRPN cases. Access to the renal hilum was significantly earlier in RRPN, with 21 minutes than 41 minutes in the TRPN group ( $P < .001$ ). The warm ischemia time was comparable in both groups, with 10 in RRPN vs 12 minutes in TRPN ( $P = .07$ ). Early unclamping was done in 71% of RRPN cases than 48% of TRPN cases ( $P = .02$ ). The conversion was necessary for four patients (two TRPN, two RRPN,  $P = 1.00$ ) with three robot-assisted nephrectomies and one open nephrectomy. Both groups show no difference in the negative surgical margins, 94.1% in TRPN and 98% in RRPN,  $P = .30$ .

In the post-operative course, complications were documented in 28 patients with 39.2% in the TRPN group and 15% in the RRPN group ( $P = .008$ ), including major complications

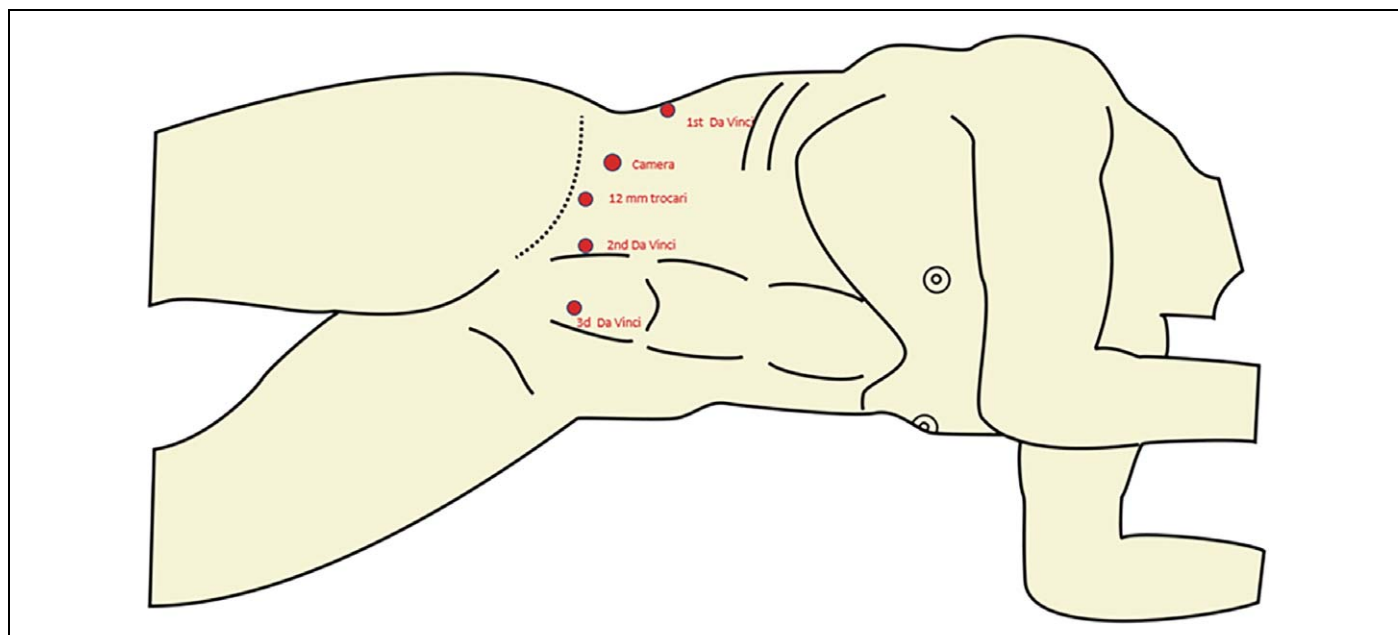


Figure 1. Schematic imaging for trocar positioning for the retroperitoneal approach. The patient is placed in the lateral decubitus position. The camera trocar is placed 2 cm above the lumbar triangle; the first trocar is inserted 3 cm above and at least 7 cm away from the camera trocar along the posterior axillary line. The second trocar is placed along the anterior axillary line and at least 7 cm away from the camera trocar; the working trocar 3 cm is inserted above the anterior superior iliac spine (image courtesy of Daniar Osmonov, MD).

(Calvien–Dindo classification > II) in 25.5% vs 4% ( $P = .01$ ) in TRPN vs RRPN, respectively. The most frequent major complication was hemorrhage requiring intervention (TRPN 15.6% vs RRPN 0%,  $P = .39$ ) followed by urinoma (TRPN 2% vs RRPN 0%,  $P = .15$ ). Moreover, post-operative blood transfusion rates were higher after TRPN (17.6% vs 7.8%,  $P = .13$ ). The median LOS was 6 days in both groups ( $P = .11$ ). Renal functional results were comparable between both groups; median eGFR before discharge was 62 vs 104 mL min<sup>-1</sup> in TRPN and RRPN, respectively ( $P = .01$ ) with no delta eGFR loss in both groups and with an increase in 1 mL min<sup>-1</sup> in the TRPN group vs 3 mL min<sup>-1</sup> in the RRPN group ( $P = .33$ ) (Table 2).

Histopathology revealed malignancy in 74.5% of the cases, with a clear cell renal carcinoma as the most common pathology (58.8 vs 31%,  $P = .07$ ). A positive surgical margin was detected in 5.9% of the TRPN and 2% of the RRPN cases ( $P = .30$ ).

## Discussion

The RRPN tends to be more appropriate than the TRPN to excise tumors on the dorsal renal surface,<sup>14</sup> allowing more

accessible access to the renal hilum, as the renal artery lies anterior to the renal vein on the dorsal aspect of the kidney<sup>15</sup>; RRPN also reduces the necessity to mobilize the bowel or the kidney. The TRPN approach has its limitations in the presence of adhesions following prior abdominal surgery.<sup>16</sup> In a multi-center cohort study, the RRPN approach was preferred in patients with previous abdominal surgery (11.2% vs 5.4%); the presence of dorsal tumors in those patients was similarly prevalent in patients without prior abdominal surgery (38.8% vs 43.3%,  $P = .286$ ).<sup>17</sup> Another recent cohort study of the RRPN approach in 110 obese patients with BMI > 30 kg m<sup>-2</sup> showed shorter operation time and warm ischemia time and less blood loss than TRPN.<sup>18</sup>

Our matched-pair analysis on 51 pairs of patients shows that RRPN shows a comparable operative time, warm ischemia time, and LOS with a shorter time to reach the renal hilum ( $P < .001$ ) and fewer complication rates ( $P = .008$ ).

Localized renal tumors (cT1) can be either accessed via a RRPN approach (mainly posterior tumors) or TRPN approach (mainly anterior tumors) depending on the preference of the

**Table 1. Patients' Demographics and Radiological Characteristics of Renal Tumors**

Parameter	TRPN	RRPN	P-Value
<b>Patient demographics</b>			
Median age, years	68 (41-83)	68 (33-86)	.79
Median BMI, kg m <sup>-2</sup>	27.4 (19.9-43.5)	27.8 (16-44)	.75
Female patients, n (%)	18 (35.3)	20 (39.2)	.68
Median Charlson comorbidity index	2	2	.96
Solitary kidney, n (%)	2 (3.9)	2 (3.9)	1.00
Mean preop hemoglobin, g dL <sup>-1</sup>	13.5 (9.7-16.4)	13.3 (8.4-16.3)	.49
Renal insufficiency grade	2 (1-4)	2 (1-5)	1.00
<b>Tumor characteristics</b>			
Median tumor size, mm	26 (8.2-72)	27 (6.6-65)	.57
Right-sided tumor, n (%)	30 (58.8)	27 (52.9)	.83
Median PADUA score	9 (6-12)	8 (6-12)	.44
PADUA			.88
• Low complexity, n (%)	16 (31.4)	27 (52.6)	
• Intermediate complexity, n (%)	18 (35.3)	20 (39.2)	
• High complexity, n (%)	17 (33.3)	17 (33.3)	
Face	25 (49)		<.001
• Anterior, n (%)	17 (33.3)	6 (11.8)	
• Posterior, n (%)	9 (17.6)	39 (76.4)	
• Lateral, n (%)		6 (11.8)	

TRPN, transperitoneal robotic-assisted partial nephrectomy; RRPN, retroperitoneal robotic-assisted partial nephrectomy after propensity score matching.

surgeon, based primarily on the experience of the surgeon and the surgical characteristics of the patient.<sup>11</sup> In our cohort, only 11.8% of anterior tumors were in the RRPN group; on the opposite, 33.3% of posterior tumors in the TRPN group ( $P < .001$ ) 76% of the RRPN group were posterior tumors.

The RRPN group showed a comparable operative time with 143 vs 150 minutes in the TRPN group ( $P = .63$ ). In earlier studies, the operative time showed a greater variation with 120 vs 153 minutes<sup>19</sup> and 217.2 vs 231.7 minutes<sup>11</sup> in RRPN vs TRPN, respectively. In most similar comparative studies, operative time was significantly shorter in RRPN<sup>19–22</sup> (Table 3). However, the time needed to access the renal hilum has not previously been described; in our cohort, it was significantly shorter in the RRPN group with a mean of 21 minutes compared to 41 minutes in the TRPN group ( $P < .001$ ). Our study reveals the RRPN approach's advantage to reach the renal hilum, as it is anatomically more accessible, with reduced time for mobilizing the bowel or the kidney, in contrast to the TRPN approach.

In our patients, the warm ischemia time was shorter in the RRPN group with 10 vs 12 minutes ( $P = .07$ ). In previous studies, the warm ischemia time also varied between 10.8 minutes for the RRPN approach vs 11.1 minutes ( $P = .98$ ) by Abaza et al.<sup>23</sup> and 27 vs 30 minutes ( $P < .01$ ) reported by Sharma et al.<sup>24</sup> Our results, however, dispute those by Tanaka et al.,<sup>25</sup> Hughes-Hallett et al.,<sup>26</sup> and Maurice et al.<sup>27</sup> have shown longer warm ischemia time in the RRPN groups.

The rates of early unclamping procedures were significantly higher for 71% of the cases in RRPN compared to 48% of the cases in TRPN ( $P = .02$ ), showing that the RRPN approach may offer better exposure and easier control of the renal artery as well as ease of tumor resection and bleeding control.

Although our results show approximately 23% more early unclamping in RRPN than TRPN, warm ischemia time in the RRPN group was 2 minutes shorter, however without clinical significance. Compared to other studies, however, our average warm ischemia time was very short in general (10 vs 12

**Table 2. Operative and Post-operative Parameters**

Parameter	TRPN	RRPN	P-Value
Intraoperative parameters			
Warm ischemia, n (%)	30 (61)	47 (94)	<.001
Median warm ischemia/selective/no clamping time, minute	12 (0-32)	10 (0-26)	.07
Early unclamping, n (%)	23 (47.9)	34 (70.8)	.02
Mean time to reach hilum, minute	41 (25-50)	21 (15-42)	<.001
Intraoperative transfusion, n (%)	0 (0)	2 (3.9)	.31
Conversion, n (%)	2 (3.9)	2 (3.9)	1.00
• To robotic nephrectomy, n	2	1	
• To open nephrectomy, n	0	1	
Postoperative course			
Overall complications, n (%)	20 (39.2)	8 (15.1)	.008
Postoperative transfusion, n (%)	9 (17.6)	4 (7.8)	.13
Major surgical complication (Clavien > 2), n (%)	13 (25.5)	2 (4)	.01
Urinoma, n (%)	2 (3.9)	0 (0)	.15
Median length of hospital stay, days	6 (4-20)	6 (4-21)	.11
Laboratory and pathology results			
Mean hemoglobin D1, g dL <sup>-1</sup>	10.9 (6.5-13.8)	10.9 (7.4-14.4)	.97
Mean eGFR before discharge, mL min <sup>-1</sup>	62.8 (15-102)	104 (101-107)	.01
Median loss of eGFR, mL min <sup>-1</sup>	4 (-36 - 40)	1 (-28 to -33)	.33
Median pathological tumor size, mm	25.5 (2-178)	30 (7-70)	.19
Negative surgical margin, n (%)	48 (94.1)	50 (98)	.30

TRPN, transperitoneal robot-assisted partial nephrectomy; RRPN, retroperitoneal robot-assisted partial nephrectomy after propensity score matching.



minutes in the respective groups), which may explain why early unclamping has not shown a significant reduction in warm ischemia time. This raises the need for a prospective randomized study to assess the approach's role and other possible factors affecting early unclamping and warm ischemia time.

Complication rates reported for RRPN and TRPN vary in the literature; Mittakanti et al.<sup>22</sup> report overall complication rates of 53.1% for RRPN vs 46.9% for TRPN ( $P = .88$ ); and major complications rates (Clavien–Dindo classification  $> II$ ) in RRPN were 28.6% vs 12.2% in TRPN. In contrast, Kim et al.<sup>28</sup>

have found overall complication rates as low as 7% in RRPN vs 10% in TRPN ( $P = .37$ ). Similar to Mittakanti, Tanaka et al.<sup>22,25</sup> and Choo et al.<sup>19</sup> also report higher complication rates in RRPN than in TRPN: 10% vs 6.25%,  $P = .72$  and 14% vs 4%,  $P = .28$ , respectively. In contrast to most of the studies mentioned above, our study shows a higher rate of complications in the TRPN group (39.2%) than the RRPN group (15.1%) ( $P = .08$ ), as the rate of major complications was 25.5% in the TRPN group and only 4% in the RRPN group ( $P = .012$ ). The TRPN also showed higher hemorrhage requiring intervention rates (15.6% vs 0%,  $P = .39$ ), which could be explained by adopting the RRPN approach after the initial

**Table 3. Review of the Literature Comparing Data of Matched-Paired Analysis between RRPN and TRPN**

Author	Our study		Laviana et al. <sup>20</sup>		Maurice et al. <sup>27</sup>	Choo et al. <sup>19</sup>		Paulucci et al. <sup>21</sup>	Mittakanti et al. <sup>22</sup>
Study design	Retrospective, matched-paired		Retrospective, matched-paired, bi-center		Retrospective, matched-paired, multicenter	Retrospective, matched-paired		Retrospective, matched-paired	Retrospective, matched-paired
Sample size (n)	224		355		610	107		519	544
RRPN (n) vs TRPN (n)	51 vs 51		78 vs 78		74 vs 296	43 vs 43		157 vs 157	166 vs 166
Conversion rate (%)	2 vs 2 ( $P = 1$ )		NR		NR	0 vs 1 (to RN)		NR	2.1 vs 3.8 (to RN), 1 RP patient to open
Operative time, minute	143 vs. 150 ( $P = .63$ )		167 vs 191.1 ( $P = .001$ )		176 vs 176 ( $P = .93$ )	120 vs 153 ( $P = .028$ )		157 vs 185 ( $P < .001$ )	162 vs 191 ( $P < .001$ )
Warm ischemia time, minute	10 vs 12 ( $P = .07$ )		20.8 vs 21.9		21 vs 19 ( $P = .01$ )	23 vs 25.5 ( $P = .28$ )		17 vs 17 ( $P = .61$ )	18 vs 18 ( $P = .66$ )
Complications (%)	15.1 vs 39.2 ( $P = .008$ )		24.4 vs 35.9 ( $P = .106$ )		12.2 vs 14.2 ( $P = .65$ )	NR		11.5 vs 12.1 ( $P = .86$ )	53.1 vs 46.9% ( $P = .88$ )
Major complications (%)	4 vs 25.5		5.1 vs 6.4		5.4 vs 3	0		5.1 vs 3.2	28.6 vs 12.2
(Clavien–Dindo grade $> II$ )	$(P = .012)$		$(P = .739)$		$(P = .30)$			$(P = .29)$	$(P = .88)$
Tumor location	RP posterior 76%, anterior 11.8%	TP posterior 33.3%, anterior 49%	RP posterior 92.3%	TP posterior 85.9%	NR	RP posterior 44%, anterior 14%	TP posterior 19%, anterior 42%	Posterior 100%	NR
	$P < .001$					$(P < .0001)$			
Tumor size, cm	3 vs 2.5 ( $P = .199$ )		NR		2.4 vs 2.5 ( $P = .59$ )	2.8 vs 2.7 ( $P = .77$ )		2.9 vs 3 ( $P = .741$ )	3.1 vs 3.3 ( $P = .3$ )
Hospital stay, days	6 vs 6 ( $P = .11$ )		1.8 vs 2.7 ( $P < .001$ )		2.2 vs 2.6 ( $P = .01$ )	NR		1 vs 2 ( $P = .017$ )	1.7 vs 1.9 ( $P = .006$ )
Positive margins, %	2 vs 5.9 ( $P = .30$ )		3.9 vs 2.6 ( $P = .65$ )		1.4 vs 1.7 ( $P = 1.0$ )	0 vs 2		3.9 vs 2.4 ( $P = .501$ )	2.8 vs 1.9 ( $P = .48$ )

NR, not reported; RP, retroperitoneal approach; TP, transperitoneal approach; RN, radical nephrectomy.

In all fields, RRPN vs TRPN, respectively. The gray box shows significant differences.

experience with the TRPN approach; however, a learning curve focused study would be needed to confirm our thesis.

In our study, the conversion was necessary for only four patients (two TRPN and two RRPN,  $P = 1$ ) with three radical robot nephrectomies and one open radical nephrectomy representing only 1% in each arm; conversion to radical nephrectomy was because of surgical difficulty or intraoperative complication that interferes with carrying out a partial nephrectomy. Hughes-Hallett et al.<sup>26</sup> reported conversion to an open approach in 2.3% of RRPN vs 8.4% of TRPN,  $P = .23$ , and Mittakanti et al.<sup>22</sup> reported a conversion rate of (2.1% RRPN vs 3.8% TRPN) most to radical nephrectomy but one to OPN.

The median LOS was 6 days in both groups ( $P = .119$ ). The LOS is significantly shorter for RRPN in early studies like in Hughes-Hallett et al.,<sup>26</sup> ie, 2.5 vs 4.6 days ( $P < .01$ ) and Gin et al.,<sup>29</sup> 1.5 vs 2 days ( $P = .001$ ), adding more favorability to the RRPN approach.

The German health system requires a minimum LOS to ensure full compensation of the medical intervention costs; early discharge would harm the intervention's profitability. The comparison will not equate with health systems that encourage early patient discharge; in other words, the parameter "LOS" is not comparable in different health care systems.

The limitations of our study lie in its retrospective nature, particularly inherent selection bias. Moreover, we could only assess the results of a limited number of surgeons; although they come from different surgical backgrounds, they all started their learning curve in the TRPN approach. It was not before they had developed advanced robotic surgery skills, then they started the RRPN approach, which might affect the rate of complications, conversion rates, and operative time. More studies are required, particularly a prospective multicenter randomized controlled trial comparing the two approaches regarding operative, perioperative variables, survival, and oncological outcomes.

The advantages of RRPN lie in the shorter time to reach the renal hilum and the lower complication rates; the comparability with the other parameters proves the safety and feasibility of the RRPN access for localized kidney tumors.

The RRPN approach should be part of the robot surgical training to enable surgeons to master both approaches to treat localized renal tumors. Further studies are needed to identify objective selection criteria for the optimal choice of surgical access.

**Ethics Committee Approval:** Ethical committee approval was received from the Medical Faculty's Ethics Committee of Christian-Albrechts-University of Kiel (D 487/20).

**Informed Consent:** Verbal informed consent was obtained from all participants who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - D.O.; Design - D.O.; Supervision - K.P.J., D.O.; Data Collection and/or Processing - A.E., C.H.; Analysis and/or Interpretation - A.E., M.T.F.; Literature Search - A.E.; Writing Manuscript - A.E.; Critical Review - K.P.J., D.O., N.N.H.

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