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Comparison of robot-assisted partial nephrectomy for complex renal tumors with RENAL scores ≥10 and non-complex tumors: A single-center experience

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ABSTRACT

Objectives

To compare functional and surgical outcomes of robot-assisted partial nephrectomy for complex tumors with RENAL scores ≥10 and non-complex tumors at a single academic institution.

Methods

We retrospectively analyzed the date of all patients who performed robot-assisted partial nephrectomy at our institution from 2011 to 2020. Functional and surgical outcomes for complex tumors (RENAL score ≥10) were compared with those of patients with non-complex tumors (RENAL <10). Outcomes analyzed included blood loss, warm ischemia time, console time, perioperative complications, and preoperative and postoperative renal function.

Results

A total 348 patients were included in our present study with a median follow-up time of 35.1 months. Of these, 299 patients (85.9%) had non-complex

tumors and 49 patients (14.1%) had complex tumors. Warm ischemia time and console time were significantly longer in the complex tumors group. Major perioperative complications (Clavien–Dindo classification system ≥3) were significantly more frequent in the complex tumors group than the non-complex tumor group (16.3% vs. 5.7%, p=0.018). Postoperative preservation of estimated glomerular filtration rate and percentage of chronic kidney disease upstage by 1 year were significantly inferior in the complex tumors group. The positive surgical margin rate was 0% and 0.3% in the complex and non-complex tumor groups, respectively. There were no significant differences in recurrence-free survival between the two groups (p=0.11).

Conclusions

Robot-assisted partial nephrectomy for complex renal tumors is safe with no difference in oncological outcomes, although more postoperative complications and decreased renal function were observed than non-complex tumors at a single academic institution.

Key words: Carcinoma, Renal Cell / surgery; Kidney neoplasms / surgery; Nephrectomy / methods; Retrospective Studies; Robotic Surgical Procedures / adverse effects

Abbreviations

3D	three-dimensional
ASA	American Society of Anesthesiologists
BMI	Body mass index
CKD	Chronic kidney disease
CT	Computed tomography
EBL	Estimated blood loss
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
eGFR	Estimated glomerular filtration rate
IQR	Interquartile range
LOS	Length of stay
PN	Partial nephrectomy
PSM	Positive surgical margin
RAPN	Robot-assisted partial nephrectomy
SD	Standard deviation
WIT	Warm ischemia time

Introduction

Partial nephrectomy (PN) has been established as the standard treatment for localized renal cancer due to its equivalent cancer control, superior long-term survival outcomes, and functional outcomes compared with those of radical nephrectomy [1,2]. In addition, minimally invasive PN is considered superior to open PN with less pain, less blood loss, shorter length of hospital stay, and lower rates of perioperative complications while maintaining comparable oncological outcomes [2,3]. Compared to laparoscopic PN, robot-assisted PN (RAPN) appears to provide shorter warm ischemia time (WIT), shorter length of hospital stay, and better preservation of renal function[4].

The RENAL nephrometry scoring system quantifies anatomical aspects of individual renal tumor characteristics, which are summed to determine the total score and to categorize a renal mass according to its complexity. Scores of 4–6 are considered low, 7–9 are considered intermediate, and ≥10 are considered high complexity. These complexity levels are associated with complication risks, ischemia time, histological aggressiveness, and postoperative renal function [5–7]. Some reports have shown that patients with high RENAL score masses are more likely to perform radical nephrectomy

or open partial nephrectomy [6,8]. However, the influence of high RENAL score ≥10 on patients' outcomes with RAPN has not yet been reported. Hence, the objective in our present study was to compare functional and surgical outcomes of RAPN between complex tumors with RENAL scores ≥10 and non-complex tumors at a single academic institution.

Methods

Data was extracted from the institutional medical record database for 348 consecutive RAPN cases underwent at a single tertiary academic institution between 2011 and 2020. **In our institution, the treatment algorithm for a cT1 renal mass does not include radical nephrectomy. In addition, radical nephrectomy, regardless of traditional open or laparoscopic surgery, is considered for patients with a renal mass ≥cT2. In the present study, four surgeons performed RAPNs. Each surgeon has performed partial nephrectomies in more than 100 patients and robot-assisted surgeries for more than 200 patients. In this study, one case required conversion from RAPN to radical nephrectomy due to lymph node metastasis diagnosed**

intraoperatively by frozen section. Therefore, this patient was excluded from the present study.

Tumor complexity was evaluated using the RENAL nephrometry scoring system based on preoperative magnetic resonance imaging and computed tomography (CT) characteristics [6]. Complex renal tumors were defined as renal tumors with RENAL nephrometry score ≥10. Date for each patient were retrospectively collected from the prospectively structured institutional database.

The present study received approval from the relevant Institutional Review Board (approval number B210044) before its commencement.

Study variables

Patient characteristics were recorded including gender, age, body mass index (BMI), Eastern Cooperative Oncology Group – Performance Status (ECOG-PS) score, American Society of Anesthesiologists (ASA) score, preoperative serum creatinine levels, preoperative estimated glomerular filtration rate (eGFR), chronic kidney disease (CKD), and solitary kidney status. Data was also collected on tumor characteristics, including tumor side, tumor size, tumor complexity, and histology (benign or malignant). For tumor

complexity, we categorized tumors based on exophytic properties, size, depth, and location into non-complex (RENAL nephrometry score: 4–9) group and complex (RENAL recorded included hospital length of stay (LOS) and postoperative complications. **Surgeon's experience was defined as the total number of RAPNs performed by each surgeon before each patient's operation [9].** Postoperative complications within ≤30 days of RAPN were reported and categorized according to the Clavien–Dindo classification [10]. Serum creatinine and eGFR were assessed up to 5 years after RAPN. eGFR was calculated by the modification of diet in renal disease formula nephrometry score: 10–12) group. Operative variables collected included WIT, console time, estimated blood loss (EBL), extraction weight, surgical margin, surgeon's experience, and intraoperative complications. Postoperative variables [11]. eGFR preservation was defined as postoperative eGFR during follow-up divided by preoperative eGFR x100. CKD was defined as GFR <60 mL/min/1.73m^2. CKD stages were based on eGFR: eGFR 90 mL/min/1.73m^2 or greater was considered CKD stage 1, eGFR 89 to 60 mL/min/1.73m^2 considered stage 2, eGFR 59 to 30 mL/min/1.73m^2 considered stage 3, eGFR 29 to 15

mL/min/1.73m^2 considered stage 4, and eGFR less than 15 mL/min/1.73m^2 considered stage 5 [11].

The most recent chest and abdominal imaging were assessed for evaluation of renal cell carcinoma local recurrence or metastases.

Trifecta achievement was defined as no postoperative complications (Clavien–Dindo ≥3), a WIT of <25 min, and a negative surgical margin [12].

Surgical technique

The standard RAPN technique used in patients in our institution has been described in detail previously [13]. The surgical approach, transperitoneal or retroperitoneal, was chosen based on surgeon preference and tumor location. We used the three-dimensional (3D) reconstruction model of dynamic CT for identifying renal vessels and tumors. The console surgeon used a robotic ultrasound probe to plan the surgical margin and evaluate tumor depth in all cases.

Outcomes

Cases were classified based on RENAL nephrometry scores ≥10 vs <10. The groups were compared with regard to operative (console time, WIT, intraoperative complications, EBL, extraction weight, surgical margin, and

surgeon's experience), postoperative (complications, LOS), functional (serum creatinine, eGFR, and CKD upstage), and oncological (recurrence-free survival) outcomes.

Statistical analysis

Continuous variables were reported as the mean and standard deviation (SD) if distribution met normality criteria or as the median and interquartile range (IQR) if distribution did not meet normality criteria. The Mann–Whitney U-test was used to analyze continuous variables. The chi-squared test was used to analyze categorical variables. **The Pearson correlation coefficient was used to analyze association between two continuous variables. Multiple linear regression was used to analyze multivariate analysis of continuous variables.** Recurrence-free survival was determined using the Kaplan–Meier analysis and evaluated using log-rank test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using EZR [14], a graphical user interface for R commander designed to add statistical functions frequently used in biostatistics.

Results

A total of 348 patients performed RAPN at our institution during the study period, with 299 (85.9%) non-complex tumors and 49 (14.1%) complex tumors. The median follow-up for our study was 35.1 months, with 108.6 months as the longest follow-up. Patients and disease characteristics are detailed in Table 1. There were no significant differences between the groups for sex, age, BMI, ECOG-PS, or ASA score. The percentage of a solitary kidney was 1.7% in the non-complex group and 4.1% in the complex group. The median radiographic tumor size was 2.9 cm (2.2–3.6) and 4.1 cm (2.8–4.5) for the non-complex group and complex group, respectively, and was significantly larger in the complex group ($p<0.01$). There were no significant differences in serum creatinine between groups. However, preoperative eGFR was significantly higher in the non-complex group (69.3 vs. 63.3 ml/min per 1.73 m^2, $p=0.033$).

The operative and postoperative outcomes are described in Table 2. There were no significant differences in the rate of retroperitoneal approaches between the two groups ($p=0.52$). The console time ($p<0.001$) and median WIT (26 vs. 21 min, $p<0.001$) were significantly longer in the complex group. The median EBL was significantly lower for the complex group, although no patients

in either group required an intraoperative blood transfusion. **There were 7 patients (2.0%) with pT3a renal cell carcinoma. Among them, 3 patients had perirenal fat invasion, 3 patients had renal vein invasion, and 2 patients had renal sinus invasion.** One patient in the non-complex group had a microscopic positive surgical margin (PSM), whereas no patients in the complex group had a PSM. **The median surgeon's experience was 57 cases (32–96) in the complex group and 49 cases (21–89) in the non-complex group. Statistical analysis revealed no difference in surgeon experience between the complex and non-complex groups (p=0.13).** The overall incidence of complications was larger for the complex group (11.0% vs. 20.4%, p=0.06) but did not reach statistical significance. However, major (≥grade 3) complications (5.7% vs. 16.3%, p=0.018) occurred more often in the complex group. No surgery-related death occurred during the observation period. Trifecta achievement rates were 70.2% and 40.8% in the non-complex and complex groups, respectively (p<0.01). There were no significant differences in LOS between the two groups.

The preservation of eGFR and percentage of CKD upstage at follow-up are summarized in Table 3. During the first postoperative year, the

percentage of eGFR preservation was significantly lower in the complex group ($p<0.01$). However, by 3 and 5 years postoperatively, no significant differences were observed between the two groups.

The rates of postoperative CKD upstage at 1 month, 3 months, and 1 year were significantly higher in the complex group ($p<0.01$). However, similar to eGFR preservation rate, no significant differences were observed between the two groups at 3 and 5 years.

Local recurrences and metastases occurred for 5 patients in the non-complex group and 2 patients in the complex group. The Kaplan–Meier survival analysis showed no significant differences in recurrence-free survival between the two groups (log-rank test, $p=0.11$). The 5-year recurrence-free survival rate was 98.1% and 92.2% in the non-complex group and complex group, respectively. (Figure 1)

No disease-specific mortality was reported in our series to date.

Discussion

The present single-center study shows that RAPN can be performed safely without positive surgical margins in patients with complex renal tumors

(RENAL nephrectomy score ≥10). A postoperative eGFR preservation rate of approximately 75% or higher was also achieved in the complex tumor group.

One of the most important oncological outcomes is the PSM, which is associated with an increased risk of recurrence in patients undergoing PN for clinically localized renal cell carcinoma [15]. In our study, a PSM rate of 0% was achieved in the complex group. Similarly, Kim et al. [16] reported a PSM rate of 0% in the RAPN group when comparing the outcomes of RAPN with those of open PN in patients for complex tumors (RENAL score >10). In contrast, Hennessey et al. [17] found a PSM rate of 3.2% in patients with a RENAL nephrometry score ≥10 who underwent RAPN. Several aspects of surgical technique and guidance may explain the low rate of PSM in our institution. First, the technique used by the surgeons in this study involves tumor resection with an adequate safety margin without enucleation [13]. While which resection technique achieves a lower PSM rate remains controversial [18], the resection technique may be associated with the PSM rate. Secondly, a robotic ultrasound probe for tumor resection was used in all cases [13] to optimize tumor identification [19]. Last, 3D reconstruction of CT images was used to guide the

surgical approach in all cases [13], which improves preoperative evaluation of the renal tumors for resection [20].

Nonetheless, the association between anatomical tumor complexity and the PSM rate is not clear. Several studies have reported the lack of relationship between tumor size, location, and growth pattern, and PSM rates with RAPN [21–23]. White et al. [24] found no difference in PSM rates with RAPN between low complex tumors (RENAL score <7) and highly complex tumors (RENAL score ≥7). Similarly, we found no significant difference in PSM rates between tumors classified using a RENAL score of ≥10 as highly complex. However, the lack of difference may be due to the very low incidence of PSM overall and may need larger studies to confirm the lack of relationship.

The RENAL nephrometry score is a unique scoring system that quantifies tumor complexity and is associated with various outcomes. Simhan et al. [25] compared the complication rate of 390 patients who performed PN for renal tumors categorized by the RENAL nephrometry score. This study found that high complexity (RENAL score ≥10) was a significant independent predictor of major complications. In line with their findings, major complications were significantly more frequent in the complex group of the present study.

Previous reports have shown the probability of major postoperative complications after RAPN for complex (RENAL score ≥10) tumors to be between 3.2% and 11.8% [16,17]. In the present study, the rate of major complications for complex tumors was 16.3%, slightly higher than in the previous studies. The slightly higher rate may be related to the learning curve of surgeons in our institution. The learning curve in terms of postoperative complications after RAPN is reported to be endless [9]. In line with this consideration, the rate of major complications in the latter half cases (12.5%) was lower than the first half (20%).

Patients with large tumors, hilar tumors, and endophytic tumors tend to have a longer WIT [21–23], and the RENAL nephrectomy score may predict a long WIT with RAPN [24]. In our study, the median WIT in the complex group was 26 (23–30) minutes. Consistent with our findings, previous studies of RAPN for complex renal tumors (RENAL score >10) have reported median (IQR) WITs of 27 (21–33) [24], 23 (18.5–29) [17], and 24 (19–34) [16] minutes. Although WIT for anatomically complex renal tumors tends to be prolonged, shortening the WIT is critical, even for anatomically complex tumors, because prolonged WIT is associated with decreased renal function after PN [26].

We assessed the correlation between WIT and each factor of the RENAL nephrometry score. As a result, Radius (R score), nearness of the tumor to the collecting system or sinus (N score), and location relative to the polar lines (L score) showed significant correlation with WIT. In contrast, exophytic/endophytic properties (E score) and anterior/posterior (A) showed no significant correlation with WIT. With multiple linear regression analyses, the predicted values for WIT were "WIT = 14.295 + L score*0.378 + N score*1.666 + R score*3.100". Hence, in the present study, the factor in the RENAL nephrometry score most significantly associated with WIT was Radius (R score).

Improved preservation of the renal function is an essential surgical outcome to consider, with the RENAL score reliably predicting early and late postoperative renal function outcomes [7]. In our study, complex tumors had a more considerable decrease in postoperative eGFR than non-complex tumors by 1 year postoperatively. Decreased renal function may be unavoidable when resecting sufficient margins for large tumors. However, prior studies have reported an increased risk of CKD with RN [27], and renal function preservation

remains an important consideration for the safe operation of a PN, even for anatomically complex tumors.

The trifecta is an evaluation of short-term RAPN outcomes. In prior studies, the PADUA (preoperative aspects and dimensions used for an anatomical) score, tumor diameter, and hilar location were the factors that affected trifecta achievement [12,28]. The RENAL score has also been shown to be associated with achieving the trifecta, with a lower score increasing the odds of trifecta achievement (OR 3.38, $p<0.001$) [29]. In our study, the trifecta achievement rate for complex tumors was significantly lower than for non-complex tumors (40.8% vs 72.6%, $p<0.01$). The lower rate of trifecta achievement was influenced by the longer WITs in the complex group, with a WIT greater than 25 minutes in 51% of the complex group. Accordingly, to improve this outcome, shorter WITs need to be achieved.

Our study demonstrates the efficacy and safety of RAPN for anatomically complex tumors (RENAL score ≥10). However, in general, underutilization of nephron-sparing surgery for feasible renal masses remains a serious problem [30]. Further research and accumulation of evidence on the feasibility of RAPN for high-difficulty tumors, as in this study, are expected.

Our study is not devoid of limitations. It is retrospective in design and is not a prospective randomized study. Patient backgrounds between the two groups are not matched, and there may be differences between the groups. Despite these limitations, the present study provides further evidence and support for the efficacy and safety of RAPN for anatomically complex renal tumors.

In conclusion, RAPN is an effective and safe treatment for selected patients with complex renal tumors defined as RENAL nephrometry score ≥10, including large, endophytic, and hilar renal tumors. The robotic system features can successfully provide minimally invasive treatment to PN for these challenging cases.

Conflict of interest

The authors have no conflicts of interest to declare.

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Figure legend

Figure 1. Recurrence-free survival

Abbreviations: RFS, recurrence-free survival

Table 1 Patient characteristics

Variable	RNS <10 (n=299)	RNS ≥10 (n=49)	P value
Age (yr), median (IQR)	64 (54–71)	67 (58–72)	0.32
Sex, n (%)			0.73
Male	79 (26.4)	14 (28.6)	
BMI (kg/m^2), median (IQR)	23.9 (21.7–26.6)	24.9 (23.2–28.2)	0.06
ECOG-PS, median (IQR)	0 (0–0)	0 (0–0)	0.85
ASA score, median (IQR)	2 (1–2)	2 (1–2)	0.86
Tumor side, n (%)			0.36
Right	162 (54.2)	23 (46.9)	
Solitary kidney, n (%)	5 (1.7)	2 (4.1)	0.26
Radiographic tumor size (cm), median (IQR)	2.9 (2.2–3.6)	4.1 (2.8–4.5)	<0.01*
Preoperative eGFR, ml/min/1.73m^2 (median, IQR)	69.4 (58.1–78.7)	63.3 (48.0–74.7)	0.033*
Preoperative serum creatinine, mg/dl (median, IQR)	0.84 (0.72–0.97)	0.87 (0.75–1.16)	0.15

* indicates statistical significance with $P < 0.05$

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group – Performance Status; eGFR, estimated glomerular filtration rate; IQR, interquartile range; RNS, RENAL nephrectomy score

Table 2 Operative and postoperative outcomes

	RNS <10 (n=299)	**RNS ≥10 (n=49)**	**P value**
Surgical approach, n (%)			0.52
Transperitoneal	199 (66.6)	30 (61.2)	
Retroperitoneal	100 (33.4)	19 (38.8)	
Console time (min), median (IQR)	202 (168–250)	242 (196–282)	<0.01*
Estimated blood loss (ml), median (IQR)	10 (10–50)	10 (10–100)	<0.01*
Extraction weight (g), median (IQR)	24 (15–42.5)	51 (27–67)	<0.01*
WIT (min), median (IQR)	21 (18–25)	26 (23–30)	<0.01*
WIT ≥25 min, n (%)	70 (23.4)	25 (51.0)	<0.01*
Pathology results, n (%)			0.34
Malignant	278 (93.0)	48 (98.0)	
Benign	21 (7.0)	1 (2.0)	
pT3a	**5 (1.7)**	**2 (4.1)**	
Positive surgical margins, n (%)	1 (0.3)	0 (0)	1
Surgeon's experience (case), median (IQR)	**49 (21-89)**	**57 (32-96)**	**0.13**
Overall complications, n (%)	32 (10.7)	10 (20.4)	0.061
Major (Clavien–Dindo ≥3) complications, n (%)	17 (5.7)	8 (16.3)	0.018*
List of major complications, n (%)			
Pseudoaneurysm	8 (2.7)	3 (6.1)	
Pneumothorax	6 (2.0)	0 (0)	
Urine leakage	2 (0.7)	3 (6.1)	
Others	1 (0.3)	2 (4.1)	
Trifecta achievement, n(%)	217 (72.6)	20 (40.8)	<0.01*

Length of stay (days), median (IQR)	10 (8–12)	10 (9–13)	0.31

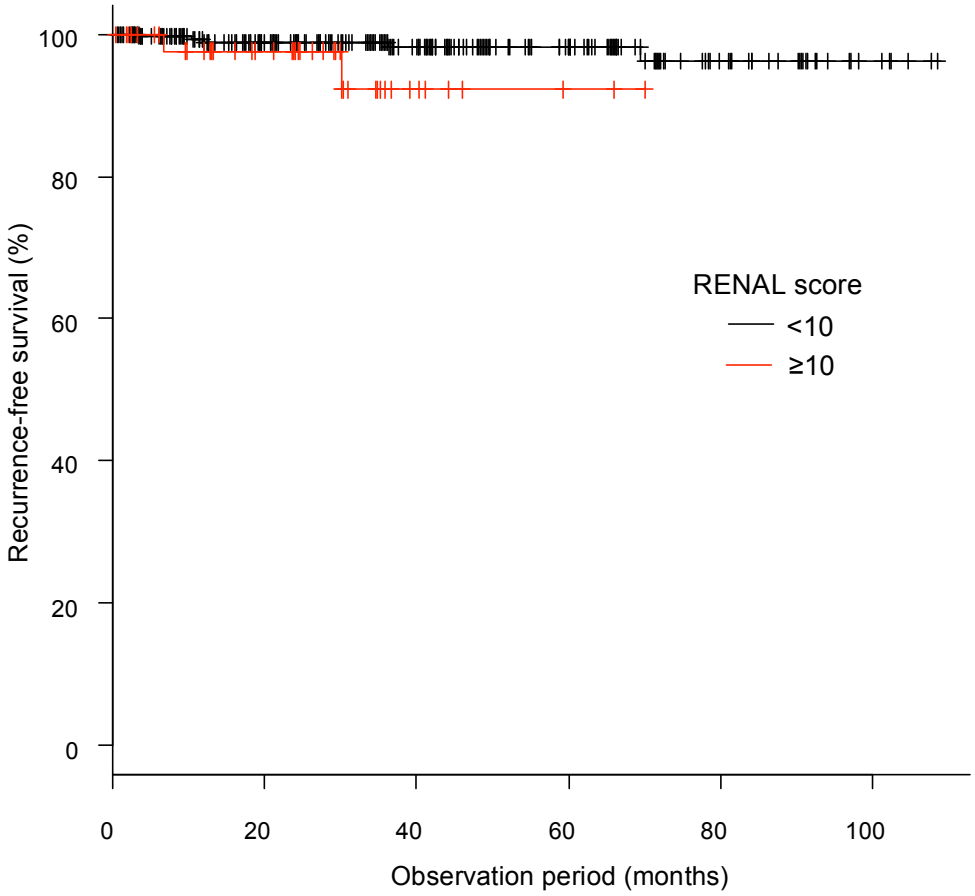
* indicates statistical significance with P < 0.05. Abbreviations: IQR, interquartile range; RNS, RENAL nephrectomy score; WIT, warm ischemia time

Table 3 Postoperative renal function and CKD upstage outcomes

Postoperative time	Outcome	RNS <10 (n=299)	RNS ≥10 (n=49)	P value
1 week	eGFR preservation (%), median (IQR)	83.6 (73.5–92.6)	69.8 (63.5–80.0)	<0.01*
	CKD upstage, n (%)	108 (36.1)	25 (51.0)	0.057
1 month	eGFR preservation (%), median (IQR)	86.0 (79.1–94.0)	75.8 (64.8–83.1)	<0.01*
	CKD upstage, n (%)	81 (27.1)	25 (52.1)	<0.01*
3 months	eGFR preservation (%), median (IQR)	86.2 (77.8–92.8)	76.1 (66.7–81.4)	<0.01*
	CKD upstage, n (%)	87 (29.8)	22 (46.8)	0.028*
1 year	eGFR preservation (%), median (IQR)	84.2 (77.6–91.5)	74.5 (69.1–82.0)	<0.01*
	CKD upstage, n (%)	71 (29.1)	23 (57.5)	<0.01*
3 years	eGFR preservation (%), median (IQR)	83.5 (76.4–92.7)	77.7 (73.2–85.3)	0.22
	CKD upstage, n (%)	51 (30.7)	6 (37.5)	0.58
5 years	eGFR preservation (%), median (IQR)	79.5 (75.1–89.0)	76.0 (74.1–79.0)	0.20
	CKD upstage, n (%)	26 (22.4)	1 (20)	1

* indicates statistical significance with $P < 0.05$

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; RNS, RENAL nephrectomy score


100
80
60
40
20
0
Recurrence-free survival (%)
RENAL score
<10
≥10
0
20
40
60
80
100
Observation period (months)