BMJ Open Functional, oncological outcomes and safety of nephron-sparing surgery versus radical nephrectomy in patients with localised renal cell carcinoma with high anatomical complexity: a retrospective cohort study with propensity score matching method

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ABSTRACT

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Correspondence to Dr Song Bai; baisongcmu81@163.com **Background** Nephron-sparing surgery (NSS) is widely applied for small renal masses. However, the indication of NSS in patients with localised renal cell carcinoma (RCC) with high anatomical complexity is controversial. Thus, we compare functional and oncological outcomes, and safety of NSS versus radical nephrectomy (RN) in patients with localised RCC with high anatomical complexity Radius, Exophytic/endophytic, Nearness, Anterior/posterior, Location. (R.E.N.A.L.) score ≥ 10 .

Methods We evaluated 575 patients with localised RCC that underwent NSS or RN at our centre between January 2013 and December 2018. Demographic characteristics, comorbidities, tumour data, surgery procedure, perioperative data and survival data were recorded. After propensity score matching, the variables were compared by binary paired logistic regression. The change in estimated glomerular filtration rate (eGFR) was compared with covariance analysis adjusted for baseline value. Recurrence and survival were calculated using Kaplan-Meier curves with log-rank tests. P<0.05 was considered to be statistically significant. **Results** In the matched group, NSS showed lower eGFR loss compared with the RN group (17.81 mL/ min/1.73 m² vs 28.28 mL/min/1.73 m², p<0.001). Moreover, the recurrence-free survival (p=0.002), cardiocerebrovascular disease-specific survival (p=0.015) and overall survival (p=0.017) of patients with NSS were better than those that underwent RN. Cancer-specific survival in both groups showed no difference (p=0.323). The incidence of minor and major complications in the two groups showed no difference (p=0.144, p=0.108).

Conclusion NSS resulted in better preservation of renal function and oncological outcomes compared with RN, with acceptable complications. These findings could help improve clinical decision making for patients with localised RCC with high anatomical complexity.

Strengths and limitations of this study

- The study had a large sample size and a high followup rate.
- Propensity score matching was applied to balance baseline variables to decrease the bias.
- The R.E.N.A.L. Nephrometry Score was applied to describe anatomical complexity of renal masses.
- ► R.E.N.A.L. score ≥10 was included in this study and such high anatomical complexity was rare in previous studies.
- ► This study was a retrospective study.

Trial registration number ChiCTR2000040652.

INTRODUCTION

Renal cell carcinoma (RCC) is common, accounting for almost 3% of all carcinoma with a 2% annual increase in incidence worldwide.¹ It occurs at a rate of 4.4 to 11.1/100 000 persons per year. The 5-year overall survival (OS) for RCC is 49%.^{2 3} Patients with localised RCC have a 5-year disease-specific survival of >80%.⁴ However, up to 30% of patients with localised RCC develop tumour recurrence after treatment,^{5 6} which increases societal and financial burden.

Surgical management has been the benchmark for the treatment of localised RCC. There is now a significant improvement in the survival of patients with RCC, mainly due to the earlier detection methods and more advanced surgical management.⁷ Nephronsparing surgery (NSS) is widely applied for small renal masses and has better preservation of renal function, which may decrease the risk of cardiovascular-related and metabolic-related consequences and improve the overall prognosis compared with radical nephrectomy (RN).^{8 9} However, there is an ongoing debate over whether NSS can be applied to large renal masses with high anatomic complexity. Several multicentre studies have shown the survival benefit of NSS compared with RN in patients with RCC with tumour stage \geq T2.^{10 11} In contrast, several studies have shown equivalent survival outcomes between NSS and RN in patients with tumour size >7 cm.^{12 13} In addition, studies have shown that NSS might have a higher rate of complications compared with RN perioperatively.¹⁴ Therefore, only NSS is recommended for T1 renal tumours by the European Association of Urology guidelines.^{15 16}

Although a more complex surgical procedure is required, with potentially a higher rate of complications, patients with highly anatomically complex RCC that undergo NSS show better preservation of renal function compared with RN. Several studies have demonstrated that patients with chronic kidney disease (CKD) have increased risk of developing cardiovascular events,917 and that CKD was common in patients with RCC.¹⁸ Thus, the investigation of postoperative renal function change is warranted. According to previous research, studies that compared NSS and RN in highly anatomically complex RCC were sparing and often biased. Notably, most current studies have investigated patients with RCC that were only classified by tumour size, which cannot comprehensively describe the anatomical complexity. Besides, few studies have paid attention to postoperative renal function changes and cardiovascular sequelae that may play an important role in the OS.

The R.E.N.A.L. Nephrometry Score is a common scoring system to describe anatomical complexity of renal masses, in which the complexity of renal tumour scoring includes: the radius (tumour size), exophytic/ endophytic character, nearness of the tumour to the deepest portion of the collecting system or sinus, anterior/posterior descriptor and location relative to the polar line. It is stratified into three categories: low (4–6), moderate (7–9) and high.^{10–12 19} We aim to compare functional, oncological outcomes and safety of NSS versus RN in patients with localised RCC with high anatomical complexity (R.E.N.A.L score \geq 10) using propensity score matching (PSM).

METHODS Patients

A total of 1128 patients underwent nephrectomy in our centre between 1 January 2013 and 31 December 2018. Five hundred fifty-three patients were excluded due to the low R.E.N.A.L. score, loss of follow-up, data loss, solitary kidney, multiple tumours or bilateral tumour. In total, 575 patients were included in the final cohort (see details in figure 1).

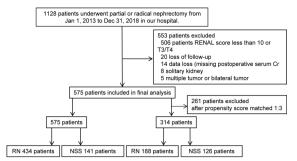


Figure 1 Flow chart of this study. Cr, creatinine; NSS, nephron-sparing surgery; RN, radical nephrectomy.

Patient and public involvement

This study was done without involving patients or members of the public in the design, conduct, reporting and disseminating plans of the research.

Inclusion and exclusion criteria

The inclusion criteria were as follows: patients diagnosed with localised RCC by pathology (tumour stage was T1–T2N0M0)²⁰; pathological type diagnosed by pathology, which includes clear-cell RCC, papillary RCC and chromophobe RCC; R.E.N.A.L. score of patients >9 and patients were surgically treated by NSS or RN. Patients with multiple tumours or bilateral tumours were excluded.

Surgery procedure

NSS and RN were performed using standard open or laparoscopic surgical techniques as previously reported.^{19 20} Open NSS was via the extraperitoneal approach with cold ischaemia, and laparoscopic NSS was via the transperitoneal approach with warm ischaemia. Finally, RN was via laparoscopy with the transperitoneal approach. All the interventions have been done by the experienced surgeon.

Characteristics, outcome and follow-up

Patient demographics were mean age, gender and body mass index (BMI). Comorbidities were hypertension, diabetes mellitus, coronary heart disease and the American Society of Anesthesiologists (ASA) scores. Tumour data were tumour side, tumour stage and pathological type. Patients with RCC were diagnosed by pathology after surgery. Intraoperative data were duration of operative time, estimated blood loss, blood transfusion rate, whether conversion to open and whether conversion to RN. Clavien-Dindo score was used to estimate the complications after surgery.²¹ Postoperative data were minor complications (Clavien 1-2), major complications (Clavien 3-4), urine fistula, haemorrhage need selective renal artery embolisation (SAE), perioperative mortality (Clavien 5), duration of postoperative hospital stay, bowel recovery (days) and time to drain removal. Prognostic data were recurrence-free survival (RFS) rate, OS rate, cardiocerebrovascular diseases-specific survival (CVDSS) rate and cancer-specific survival (CSS) at 5 years preoperative and postoperative estimated glomerular filtration rate (eGFR). eGFR (preoperative and postoperative) were used to estimate the patients' renal function. The eGFR was based on four-variable dietary modifications in the renal disease equation.²²

Follow-up protocol was every 3 months in the first 2 years, 6 months in the third year and then once a year. Follow-up examinations included physical examination, chest and abdominal CT, biochemical analysis and bone emission CT scan as necessary.

Statistical analysis

The data were collected and analysed by SPSS V.25.0 for Windows (SPSS, Chicago, Illinois, USA). Continuous variables were expressed as median (IQR); categorical variables were reported as number (percentage). Before PSM, independent samples Student's t-test was used to compare mean of two continuous normally distributed variables and the Mann-Whitney U test was used to compare the mean of two continuous non-normally distributed variables, The χ^2 test or Fisher's exact test was used for categorical variables.

PSM was applied to balance baseline variables to decrease the deviation. Multivariate logistic regression analysis was used to determine propensity scores for each patient based on all baseline variables: demographic characteristics (mean age, gender and BMI), comorbidities (hypertension, diabetes mellitus, coronary heart disease and ASA), tumour data (tumour side, tumour stage and pathological type) and surgical procedure (laparoscopy vs open). The NSS and RN groups were matched 1:3 using a calliper width of 0.1 for the propensity score through the nearest neighbour matching (see details in figure 2). After PSM, the categorical variables were compared by binary conditional logistic regression. Paired samples Student's t-test was used to compare mean of two continuous normally distributed variables and the Wilcoxon test was used to compare the mean of two continuous non-normally distributed variables. Recurrence and survival were calculated using Kaplan-Meier curves with log-rank tests. The eGFR was compared with

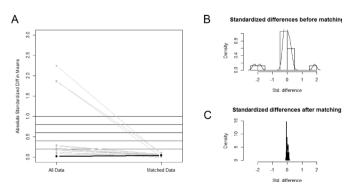


Figure 2 Plot of propensity score matching (PSM). (A) Dot plot of standardised mean differences. (B) Histogram of standardised mean differences before PSM. (C) Histogram of standardised mean differences after PSM.

covariance analysis adjusted for baseline value. Twotailed p values <0.05 were considered statistically significant.

Results

In total, 575 patients included in the cohort were divided into two groups: 434 patients in the RN and 141 patients in the NSS. The median follow-up period of RN and NSS was 37.0 and 26.0 months, respectively. A balance of baseline variables between the two groups after PSM was achieved. In the matched groups, 434 patients that underwent RN and 141 patients that underwent NSS were matched with 188 patients that underwent RN and 126 patients that underwent NSS, respectively. Demographics, comorbidity, tumour characteristics and perioperative data are detailed in table 1.

In matched cohorts, the mean follow-up time was 38.0 months and 27.0 months in the RN and NSS groups, respectively. There were four variables with statistical differences. Patients that underwent NSS had a longer duration of postoperative hospital stay (p<0.001), bowel recovery (p<0.001) and time to drainage removal (p<0.001). Patients in the NSS group had lower eGFR loss (eGFR change, p<0.001) compared with those in the RN group (see details in table 2).

Patients that underwent NSS had better RFS, CVDSS and OS at 5 years than patients that underwent RN. The RFS was 95.90% vs 77.50% (p=0.002), the CVDSS was 92.30% vs 75.10% (p=0.015) and the OS was 95.60% vs 80.40% (p=0.017) in the NSS versus RN groups at 5 years, respectively. The CSS of patients was 97.30% vs 92.40%, which was not statistically different (p=0.323) (see details in figure 3).

Besides, we also compared two paired groups using multilevel regression model for baseline variables. The results of sensitivity analysis (multilevel regression model) are consistent with those of binary conditional logistic regression (see details in online supplemental table 1). We analysed these data using inverse probability treatment weighting (IPTW) for outcome variables. The results of IPTW are consistent with those of binary conditional logistic regression (see details in online supplemental table 2).

DISCUSSION

Many retrospective studies have shown that NSS has an advantage over RN in small renal masses due to better preservation of renal function and similar oncological control. However, NSS requires a higher level of technical skills, and has a higher rate of complications with the increasing anatomical complexity of the renal tumour. Furthermore, the studies addressing this issue are scarce and the conclusion is inconsistent. Thus, this study aimed to compare functional, oncological outcomes and safety of NSS and RN in patients with localised RCC with high anatomic complexity (R.E.N.A.L. score ≥ 10).

Propensity before 575 patients	Propensity before 575 patients	patients		Propensity after 314 patients	atients	
Variables	RN	NSS	P value	RN	SSN	P value
Number of patients (%)	434.00 (100.00)	141.00 (100.00)		188.00 (100.00)	126.00 (100.00)	
Demographic characteristics						
Mean age (years)	59.00 (51.00, 65.00)	57.00 (51.00, 64.00)	0.256^{\dagger}	59.00 (51.00, 65.00)	57.00 (51.00, 64.25)	0.667
Gender (male)	275.00 (63.40)	95.00 (67.40)	0.388	122.00 (64.90)	82.00 (65.10)	0.979
BMI (kg/m ²)	24.22 (22.86, 26.92)	24.97 (23.44, 28.08)	0.001 [†]	24.48 (22.86, 27.05)	24.92 (23.44, 27.65)	0.266
Comorbidities						
Hypertension (yes)	110.00 (25.30)	48.00 (34.00)	0.045	41.00 (21.80)	22.00 (17.50)	0.466
Diabetes mellitus (yes)	44.00 (10.20)	26.00 (18.40)	0.045	58.00 (30.90)	40.00 (31.70)	0.879
Coronary heart disease (yes)	21.00 (4.90)	4.00 (2.80)	0.010	22.00 (11.70)	16.00 (12.70)	0.947
ASA scores	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	0.157†	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	0.992
Tumour data						
Tumour side (left)	202.00 (46.50)	85.00 (60.30)	0.005	89.00 (47.30)	72.00 (57.10)	0.189
T stage (pathology)			<0.001*			0.155
T1b (4 cm < and ≤ 7 cm)	183.00 (42.20)	135.00 (95.70)		168.00 (89.70)	120.00 (95.20)	
T2a (7 cm ≤ and < 10 cm)	166.00 (38.20)	5.00 (3.50)		15.00 (8.00)	5.00 (4.00)	
T2b (>10 cm)	85.00 (19.60)	1.00 (0.70)		5.00 (2.70)	1.00 (0.80)	
Pathological type			0.271*			0.782
Clear-cell RCC	415.00 (95.60)	130.00 (92.20)		178.00 (94.70)	120.00 (95.20)	
Papillary RCC	4.00 (0.90)	5.00 (3.50)		2.00 (1.10)	2.00 (1.60)	
Chromophobe RCC	15.00 (3.50)	6.00 (4.30)		8.00 (4.30)	4.00 (3.20)	
Surgery procedure (laparoscopy)	434.00 (100.00)	97.00 (68.80)	N/A	188.00 (100.00)	86.00 (68.30)	N/A
Preoperative eGFR (mL/min/1.73 m^2)	94.38 (73.88, 113.20)	100.72 (82.00, 119.24)	0.028 [†]	97.55 (79.96, 118.06)	98.75 (81.97, 117.91)	0.810
Continuous variables were expressed as median (IQR); categorical variables were reported as number (percentage). Independent samples Student's t-test was used to compare mean of two continuous normally distributed variables and the Mann-Whitney U test was run to determine mean of two continuous non-normally distributed variables. The χ^2 test or Fisher's exact test was used for categorical variables. The χ^2 test or Fisher's exact test was used for categorical variables. The χ^2 test or Fisher's exact test was used for categorical variables.	dian (IQR); categorical variable d the Mann-Whitney U test wa ared by binary paired logistic	is were reported as number (s run to determine mean of th regression.	oercentage). Ind wo continuous n	spendent samples Student's t on-normally distributed variak	-test was used to compare r bles. The χ^2 test or Fisher's e	rean of two kact test was

*Fisher's exact test.
†Mann-Whitney U test.
American Society of Anesthesiologists; BMI, body mass index; eGFR, estimated glomerular filtration rate; N/A, not applicable; NSS, nephron-sparing surgery; PSM, propensity score matching; RN, radical nephrectomy.

		c/c patients		Propensity after 314 patients	tients	
	RN	NSS	P value	RN	SSN	P value
Number of patients (%)	434.00 (100.00)	141.00 (100.00)		188.00 (100.00)	126.00 (100.00)	
Follow-up period (months)	37.00 (27.00, 49.00)	26.00 (18.00, 40.00)		38.00 (23.00, 58.00)	27.00 (19.00, 41.00)	
Intraoperative data						
Duration of operative time (minutes)	120.00 (90.00, 180.00)	126.00 (98.00, 162.00)	0.875	120.00 (90.00, 171.75)	125.50 (96.00, 158.50)	0.535
Estimated blood loss (mL)	150.00 (150.00, 300.00)	150.00 (100.00, 200.00)	0.168	100.00 (100.00, 200.00)	150.00 (100.00, 200.00)	0.312
Blood transfusion rate	20.00 (4.60)	5.00 (3.50)	0.592	5.00 (2.70)	4.00 (3.20)	0.836
Conversion to open (yes)	0.00 (0.00)	0.00 (0.00)	N/A	0.00 (0.00)	0.00 (0.00)	N/A
Conversion to RN (yes)	N/A	0.00 (0.00)	N/A	N/A	0.00 (0.00)	N/A
Postoperative data						
Minor complications (Clavien 1–2)	10.00 (2.30)	9.00 (6.40)	0.024*	4.00 (2.10)	8.00 (6.30)	0.144
Major complications (Clavien 3-4)	0.00 (0.00)	3.00 (2.10)	0.999*	0.00 (0.00)	3.00 (2.40)	0.108
Urine fitula (yes)	0.00 (0.00)	2.00 (1.50)	1.000*	0.00 (0.00)	2.00 (2.10)	0.707
Haemorrhage need SAE	0.00 (0.00)	1.00 (0.70)	1.000*	0.00 (0.00)	1.00 (1.03)	0.464
Perioperative mortality (Clavien 5)	1.00 (0.20)	0.00 (0.00)	0.999*	0.00 (0.00)	0.00 (0.00)	1.000*
Duration of postoperative hospital stay	5.00 (3.00, 6.25)	10.00 (8.00, 14.00)	<0.001	4.00 (3.00, 6.00)	10.50 (8.00, 14.00)	<0.001
Bowel recovery (days)	3.00 (2.00, 4.00)	4.00 (3.00, 5.00)	<0.001	3.00 (2.00, 3.00)	4.00 (3.00, 5.00)	<0.001
Time to drainage removal	3.00 (1.00, 5.00)	7.00 (5.00, 9.00)	0.004	2.50 (1.00, 4.00)	7.00 (5.00, 9.00)	<0.001
Postoperative eGFR (mL/min/1.73 m ²)	67.95 (54.70, 85.94)	79.00 (64.49, 98.74)	<0.001†	67.25 (54.88, 83.26)	78.62 (62.39, 95.95)	<0.001†
eGFR changes (before-after operation)	23.04 (11.68, 36.02)	17.71 (5.71, 30.77)	<0.001	28.28 (17.03, 39.92)	17.81 (5.76, 30.73)	<0.001
Prognostic data						
RFS rate at 5 years	73.90%±5.49%	96.30%±3.72%	<0.001‡	77.50%±7.25%	95.90%±3.92%	0.002‡
OS rate at 5 years	76.60%±5.68%	95.90%±4.70%	<0.001‡	80.40%±7.64%	95.60%±5.10%	0.017‡
CVDSS rate at 5 years	72.40%±6.08%	92.80%±6.86%	0.001	75.10%±8.43%	92.30%±7.25%	0.015‡
CSS at 5 years	92.20%±3.33%	97.50%±3.72%	0.139‡	92.40%±5.10%	97.30%±4.12%	0.323‡
Continuous variables were expressed as median (IQR); categorical variables were reported as number (percentage). Independent samples Student's t-test was used to compare mean of two continuous normally distributed variables. The X ² test or Fisher's exact test was used for categorical variables. Recurrence and survive were calculated using Kaplan-Meier curves with log-rank tests. The eGFR was compared with covariance analysis adjusted for baseline variables were compared by binary paired logistic regression. *Fisher's exact test. †Covariance analysis adjusted for baseline value. #Log-rank test. §Mann-Whitney U test.	QR); categorical variables w Mann-Whitney U test was ru d survive were calculated us vere compared by binary pai vere	ere reported as number (perc n to determine the mean of t ing Kaplan-Meier curves with red logistic regression.	entage). Inde wo continuou i log-rank tes	ependent samples Student's t- us non-normally distributed va its. The eGFR was compared v its.	test was used to compare metables. The χ^2 test or Fisher's with covariance analysis adjus	an of two exact test ited for

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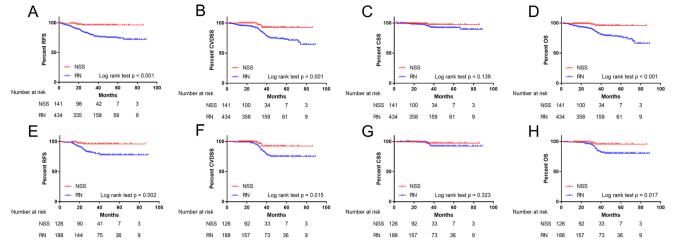


Figure 3 Survival curve stratified by surgery method before and after PSM. (A) RFS curve before PSM. (B) CVDSS curve before PSM. (C) CSS curve before PSM. (D) OS curve before PSM. (E) RFS curve after PSM. (F) CVDSS curve after PSM. (G) CSS curve after PSM. (H) OS curve after PSM. CSS, cancer-specific survival; CVDSS, cardiocerebrovascular disease-specific survival; NSS, nephron-sparing surgery; OS, overall survival; PSM, propensity score matching; RFS, recurrence-free survival; RN, radical nephrectomy.

Ultimately, in our study, patients in the NSS group had a better preservation of renal function, higher postoperative eGFR (p<0.001) and lower eGFR decrease (p<0.001). In line with this study, Deng *et al*²³ retrospectively studied 148 patients with RCC with a R.E.N.A.L. score \geq 7 and showed the same conclusion; that NSS had a better protection of renal function compared with RN. This finding may be due to there being more functioning nephrons preserved in NSS compared with RN. On the contrary, in a subgroup analysis, Kopp *et al*¹⁴ suggested NSS was lacking in renal functional benefit compared with RN in patients with a R.E.N.A.L. score >10. The possible reason for this is that the high anatomical complexity renal tumours had prolonged surgery duration and ischaemia time, which may have caused damage to the remaining renal parenchyma.

Studies have shown that if preservation of renal function is poor, it has a close association with higher occurrence of cardiovascular incidents, even with poor OS.²⁴ Weight *et al*²⁵ suggested the risk of cardiac death increased by 25%, due to the loss of renal function by RN. In this study, NSS had better CVDSS (p=0.015) and OS (p=0.017) compared with RN, which is mainly due to better preservation of renal function after NSS. Consistent with this study, Deng *et al*²⁴ also showed that patients that underwent NSS had a longer OS than those that underwent RN. Besides, Umberto *et al* found that RN was associated with a higher developing postoperative hypertention risk (HR 2.89; p=0.006) than NSS in patients without a medical history of cardiopathy based on a prospective cohort study.²⁶

In this cohort, NSS had better PFS (p=0.002), while there was no difference in CSS compared with RN. However, in a study comprising 123 patients with a tumour size >7 cm, Janssen *et al*²⁷ showed that NSS had longer OS and CSS compared with RN. On the contrary, Jeldres *et al*²⁸ studied 29 patients with RCC with a tumour size >7 cm in a matched analysis and showed NSS was associated with a higher rate of cancer-specific mortality. These discrepancies were mainly due to different inclusion criteria, and here, our study only focused on patients with high anatomical complexity (R.E.N.A.L. score ≥ 10).

There was no difference in either intraoperative characteristics or minor and major complications between RN and NSS in this study. However, NSS showed longer duration of postoperative hospital stay, slower bowel recovery and longer time to drainage removal. In the study by Kopp *et al*,²⁹ NSS had higher risk of high-grade complications compared with RN. However, in a more recent study conducted by Deng *et al*,²³ NSS had a higher risk of low-grade complications compared with RN, whereas there was no difference in high-grade complications between the two groups. This discrepancy may be due to the improvement in surgical technique and equipment.

The duration of postoperative hospital stay in NSS group was significantly shorter than RN group in this study. The main reason for this might be that there was higher rate of postoperative complication in NSS group than in RN group, such as urine fitula, haemorrhage need SAE and so on, which need more duration of hospital stay.

There were several limitations in this study. First, it was a single-centre retrospective study, which carries selection bias and historical bias. In addition, it fails to adjust for unknown confounders, even though PSM method was used. These limitations can lead to incorrect results and spurious associations. Second, robotassisted nephrectomy was excluded in this study. Although previous studies have suggested that robotassisted nephrectomy has an advantage in dealing with highly anatomically complex renal masses,³⁰ robot-assisted nephrectomy requires higher surgical skill and a longer period of study, and may not be costeffective. This may mean robot-assisted nephrectomy will not be rapidly popularised worldwide in the short term, especially in low-income and middle-income

countries. Third, there may have been some bias in changes of renal function between preoperative and postoperative data, which were evaluated using eGFR rather than renal scintigraphy. Fourth, the follow-up peroid of this study was short. A larger prospective randomised controlled trial in multicentre is required to verify the accuracy of the conclusion drawn from this study. Nevertheless, this study is the first to compare functional, oncological outcomes and safety of NSS and RN in patients with highly anatomically complex localised RCC.

CONCLUSION

NSS resulted in better preservation of renal function and oncological outcomes compared with RN, with acceptable complications. These findings could help improve clinical decision making for patients with localised RCC with high anatomical complexity.

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Contributors SB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: SB. Acquisition of data, analysis and interpretation of data: XZ, ZS, PL, ZL and SB. Drafting of the manuscript and critical revision of the manuscript for important intellectual content: XZ, ZS and SB. Statistical analysis: XZ, ZS and SB. Obtaining funding and other (figures): SB is responsible for the overall content as the guarantor for this study.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by ethical statement. Ethical approval (ethical committee no. 2020PS678K) was provided by the Institutional Research and Ethics Committee of the Shengjing Hospital Affiliated China Medical University in Shengyang, China. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. SB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data are available on reasonable request (baisongcmu81@163.com).

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