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Oncological and functional efficacy of nephron-sparing surgery versus radical nephrectomy in renal cell carcinoma stages ≥cT1b: a single institution, matched analysis

Ralf Veys[1], Firas Abdollah[2], Alberto Briganti[3], Maarten Albersen[1], Hein Van Poppel[1], Steven Joniau[1]

[1]*Department of Urology, University Hospitals Leuven, Leuven, Belgium*
[2]*Vattikuti Urology Institute, Center for Outcomes Research Analytics and Evaluation, Henry Ford Health System, Detroit, MI, USA*
[3]*Division of Oncology, Unit of Urology, URI, IRCCS Ospedale San Raffaele, Milan, Italy*

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Corresponding author
Ralf Veys
University Hospitals Leuven
Department of Urology
Herestraat 49
3000 Leuven, Belgium
ralf.veys@student.kuleuven.be

Introduction The purpose of this paper is to compare oncological outcomes of partial nephrectomy (PN) versus radical nephrectomy (RN) in renal cell carcinoma (RCC) clinical stages ≥T1b, in a retrospective propensity-score matched cohort of a high-volume, tertiary referral center. This paper also aims to compare renal function and complication rates between groups.

Material and methods Our single-institution RCC database was queried to select patients with clinical stages defined by tumor size (T), lymph nodes(N), and metastasis (M) scores of T1b-4 N0 M0, that underwent PN or RN between 2000 and 2014. All images of patients that underwent RN were reviewed, and only patients deemed eligible for PN were included. Medical records were reviewed to obtain data on tumor characteristics, comorbidities, renal function, and complications. After propensity score matching, 152 patients (76 per group) were included in the final analysis. Primary outcomes were cancer specific survival (CSS), overall survival (OS), and clinical progression-free survival (CPFS). Secondary outcomes were renal function preservation and post-operative complication rates.

Results Groups were propensity-score matched. The only parameters that were significantly different between groups were the median follow-up time (RN: 79 months, range 24.1–100.5 vs. PN: 38.5 months, range 20.5–72.1) and a better performance status in the RN group ($p = 0.002$). The five-year CPFS, CSS, and OS rates were 77.2%, 90.5%, and 86.4%, respectively, in the RN group, and 83.6%, 91.1%, and 82.0%, respectively, in the PN group ($p = 0.33$, $p = 0.55$, and $p = 0.33$, respectively). In the multivariate Cox model, the surgical method was not an independent predictor of CPFS, CSS, or OS. The RN group showed a significantly greater reduction in estimated glomerular filtration rate (RN: 14.1 vs. PN: 5.4 ml/min per 1.73 m^2; $p < 0.03$). There was no significant difference in complication rates between the two groups ($p = 0.3$). The main limitations of this study were its retrospective design and the medium-term follow-up.

Conclusions Our results demonstrated the efficacy and safety of PN in patients with RCC in clinical stages ≥T1b. We observed no significant difference in oncological outcomes between the PN and RN groups at medium-term follow ups. The surgical method did not influence these outcomes. Renal function was preserved significantly more frequently in the PN than in the RN group, but the groups had similar complication rates.

These findings suggested that PN could be considered an oncologically safe procedure for treating large RCC tumors; thus, PN should always be considered, when technically feasible, regardless of tumor stage.

Key Words: partial nephrectomy ‹› renal cell carcinoma ‹› nephron sparing surgery ‹› radical nephrectomy ‹› oncologic outcome ‹› chronic kidney disease

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 90% of all kidney cancer cases, and RCC is one of the 10 most frequent cancers in men. The incidence of RCC is highest in Western countries, and it has increased over the past few decades [1, 2]. This rise can be explained by increased detection of incidental tumors, due to the widespread use of noninvasive abdominal imaging techniques, including ultrasound (US), CT, and MRI [3].

To date, the only curative treatment for localized RCC is surgical resection [4]. For years, radical nephrectomy (RN), first described by Robson, has been the standard treatment of care for patients with a healthy contralateral kidney [5]. However, partial nephrectomy (PN), also known as nephron sparing surgery (NSS), has gained popularity during the past few decades. PN is popular due to its oncologic equivalence to RN for treating small renal masses (SRMs, <7 cm), and due to concerns associated with RN, regarding contralateral recurrence, the high percentage of benign lesions on final histopathological examinations (12.8–28% of all solid tumors) [6, 7], and the increased risk of developing chronic kidney disease (CKD), and consequently, cardiovascular morbidity and mortality [8, 9, 10]. In addition, some quality of life (QoL) data have shown that patients that underwent elective PN had better overall health-related quality of life (HRQoL) scores than patients that underwent RN [11]. Hence, the indications for PN have expanded, and PN is currently considered the gold standard, when technically feasible, for all patients with low-stages of RCC (e.g., clinical tumor size stage T1; cT1), including patients with a healthy contralateral kidney, according to the most recent European Association of Urology (EAU) and American Urological Association (AUA) guidelines [12, 13]. The latest update of the EAU guidelines also suggested that PN should be favored over RN in patients with cT1b tumors, whenever feasible. However, despite this recommendation, PN in cT1b and higher stage lesions remains underutilized to date, even in academic centers. This underutilization represents an important concern, in terms of the quality of care [14, 15].

The role of NSS in RCC stages ≥cT1b remains controversial, but recent studies have suggested that NSS can be performed safely in cT2 tumors [16, 17, 18, 26]. In cT2 tumors, PN has shown acceptable complication rates and oncologic outcomes comparable to RN outcomes. However, most of those studies were single- arm studies that did not match the PN group with a RN control group [16, 17]. Other studies used the final histopathological tumor stage (pT), rather than the clinical tumor (cT) stage, for analyses, which greatly limited the applicability and utility of the results for daily clinical practice [18, 19, 20].

The present retrospective study focused on a cohort from a high-volume tertiary referral center to investigate the role of PN in stages ≥cT1b RCC. We implemented propensity-score matching between PN and RN cohorts. The primary outcome was the oncological outcome. The secondary outcomes were renal function and complication rates. We aimed to provide additional evidence to the emerging notion that patient eligibility for NSS should be based on tumor location and technical feasibility, rather than on tumor size alone.

MATERIAL AND METHODS

Patient selection

Our single-institution RCC database was queried to select patients with clinical stages defined by tumor size (T), lymph nodes (N), and metastasis (M) scores of T1b-4 N0 M0. The database included patients that had received a surgical intervention, radiofrequency ablation, and/or targeted therapy between 2000 and 2014. All patients were staged with a triphasic CT scan or a magnetic-contrast-enhanced MRI of the abdomen and a plain X-ray or CT of the chest to evaluate local resectability, lymph node status, and distant metastasis.

All images of patients that had undergone RNs were reviewed by two independent investigators

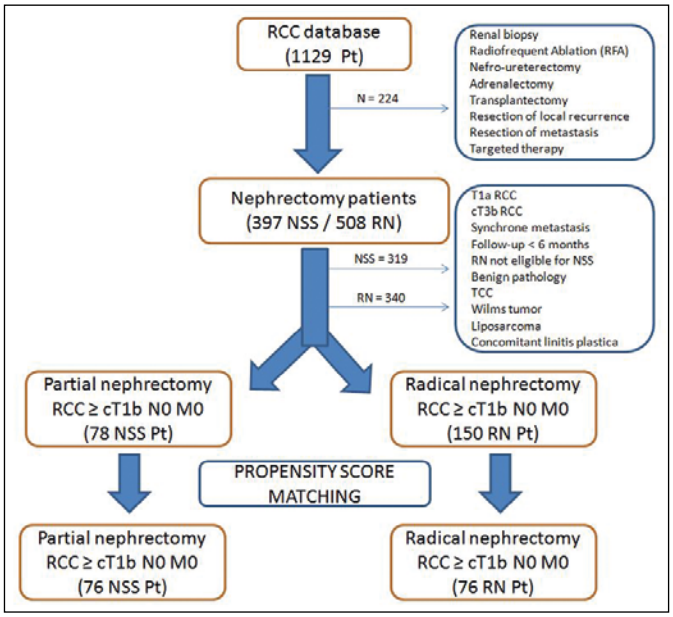

Figure 1. *Flowchart of patient selection.*

RCC – renal cell cancer; NSS – nehpron sparing surgery; RN – radical nephrectomy; TCC – transitional cell carcinoma; Pt – patients

(SJ & RV), and only patients deemed eligible for PN were included in the final analysis. Moreover, when a PN was not technically feasible, patients were excluded from the final analysis. Clinical stages were reassigned to match the March 2013 TNM staging classification system. Solitary kidneys, bilateral presentation, hereditary disease, and previous history of RCC were not considered exclusion criteria. Patients with T3b and T3c RCC were not eligible for PN; therefore, these clinical T-stages were excluded. Follow-up of >6 months was required; a follow-up was defined as the number of months from the date of surgery to either the date of an event outcome or the last follow-up consultation (Figure 1).

The study was approved by the Institutional Review Board and the local Ethics Committee (mp12064). Body mass index (BMI), American Society of Anesthesiologists (ASA) score, Charlson Comorbidity Index (CCI), and Eastern Cooperative Oncology Group (ECOG) performance status were collected by reviewing patient pre-operative medical records. Peri-operative data and postoperative complications were collected by reviewing patient medical records.

To ensure similar baseline characteristics, patients in the PN and RN groups were matched based on propensity scoring, which accounted for all available clinical variables (Table 1). We employed the nearest neighbor method, with a caliber-width of 0.2 of the standard deviation of the logit. This method provided a modest residual bias and the highest possible precision [21].

Surgical procedure

PNs were performed by multiple surgeons at our institution via a standard flank incision technique, as described previously [7]. Eligibility for PN was based on the surgeon's experience and the technical feasibility. In this cohort, no laparoscopic procedures were performed in the PN group.

RNs were also performed by multiple surgeons at our institution. In open surgery, the approach was retro- or transperitoneal, and in laparoscopy, the approach was transperitoneal [3, 22]. In both groups, hilar lymph nodes and nodes surrounding the great vessels were only sampled when malignancy was suspected pre- or peri-operatively.

Table 1. *Clinical variables used in propensity-matching between the radical nephrectomy (RN) and partial nephrectomy (PN) groups. Statistical significance was based on non-parametric tests: Mann-Whitney test for continuous data, and Chi² test for categorical data*

	Total group (n = 152)		RN group (n = 76)		PN group (n = 76)		p-value
	Median/n	[IQ range]	Median/n	[IQ range]	Median/n	[IQ range]	
Age	63.1	[54.5–71.1]	62.1	[52.1–71.7]	63.8	[55.8–70.6]	0.64
ASA	1 2 3 4	23 (15.1%) 93 (61.2%) 35 (23.0%) 1 (0.7%)	16 44 16 0	(21.1%) (57.9%) (21.1%) (0%)	7 49 19 1	(9.2%) (64.5%) (25.0%) (1.3%)	0.17
ECOG	0 1 2	108 (71.1%) 39 (25.7%) 5 (3.3%)	63 13 0	(82.9%) (17.1%) (0%)	45 26 5	(59.2%) (34.2%) (6.6%)	0.002
CCI	0 1 2 3	69 (45.4%) 17 (11.2%) 34 (22.4%) 32 (21.1%)	43 7 14 12	(56.6%) (9.2%) (18.4%) (15.8%)	26 10 20 20	(34.2%) (13.2%) (26.3%) (26.3%)	0.051
Gender	Female Male	46 (30.3%) 106 (69.7%)	25 51	(32.9%) (67.1%)	21 55	(27.6%) (72.4%)	0.60
BMI	26.2	[24.1–29.3]	26.2	[24.1–28.4]	26.3	[24.1–29.75]	0.74
SCr pre-op	1.1	[0.9–1.3]	1.07	[0.95–1.30]	1.04	[0.91–1.31]	0.58
eGFR pre-op	66.1	[56.8–82.5]	64.58	[56.79–74.89]	69.43	[26.6–87.6]	0.21
cT	cT1b cT2 cT3a cT4	113 (74.3%) 27 (17.8%) 9 (5.9%) 3 (2.0%)	52 16 6 2	(68.4%) (21.1%) (7.9%) (2.6%)	61 11 3 1	(80.3%) (14.5%) (3.9%) (1.3%)	0.40
Previous RCC	No Yes	146 (96.1%) 6 (3.9%)	74 2	(97.4%) (2.6%)	72 4	(94.7%) (5.3%)	0.68
Follow-up			79	[24.1–100.5]	38.5	[20.5 –72.1]	<0.05

ASA – American Society of Anesthesiologists; ECOG – Eastern Cooperative Oncology Group; CCI – Charlson Comorbidity Index; BMI – body mass index; eGFR – estimated glomerular filtration rate; cT – clinical tumor; RCC – renal cell cancer

Primary outcomes

Clinical progression-free survival (CPFS), cancer specific survival (CSS), and overall survival (OS) rates were primary endpoints. CPFS was defined as the time to clinical failure (CF), including a local recurrence (LR) or metastasis (M+). CSS was defined as the time to mortality due to RCC-related causes. OS was defined as the time to mortality due to any cause.

Follow-ups included checkups every three months, during the first two years after surgery; every six months, during the third to fifth years; and every year thereafter. The checkups included a physical examination, serum creatinine (SCr) levels, and abdominal US combined with plain chest X ray, alternating with abdominal CT, or MRI combined with chest CT.

Follow-up data included the cause and date of death. These data were collected by reviewing patient medical records.

Secondary outcomes

Renal function

Renal function was evaluated pre- and post-operatively, based on the measured SCr concentration and the estimated glomerular filtration rate (eGFR). The eGFRs were based on the modified Modification of Diet in Renal Disease (MDRD) formula. Patients were consequently classified according to chronic kidney disease (CKD) stage [23]. The delta-GFR was defined as the difference between pre- and post-operative eGFRs. The post-operative SCr and eGFR were defined as the measurements at the latest follow-up.

Post-operative complications

Complications were stratified according to the Clavien-Dindo Classification of Surgical Complications [24]. Post-operative complications within the first thirty days after surgery were recorded.

Statistical analysis

CSS, OS, and CPFS were estimated with Kaplan-Meier analyses, and differences between groups were assessed with the log-rank test. Cox proportional hazard regression models were constructed. Only clinical variables with univariate p-values <0.1 were considered for the multivariate analysis.

Proportions were compared with Fisher exact tests, and Wilcoxon rank sum tests were used to compare continuous variables. Evaluations of continuous data were expressed as the median and interquartile

Table 2. *Cox forward univariate and multivariate analysis results for* **(A)** *cancer specific survival,* **(B)** *overall survival, and* **(C)** *clinical progression-free survival*

(A)

	CPFS					
	Univariate			Multivariate		
	HR	CI	P	HR	CI	P
Age	0.98	[0.95–1.01]	0.27			
ASA	1.16	[0.64–2.09)	0.64			
ECOG	1.04	[0.51–2.13]	0.92			
CCI	1.18	[0.88–1.59)	0.27			
Gender	1.07	[0.47–2.43]	0.87			
BMI	0.99	[0.93–1.07]	0.87			
Creat pre-op	1.46	[0.90–2.36]	0.13			
eGFR pre-op	0.99	[0.97–1.00)	0.12			
cT	4.37	[2.72–7.04]	<0.001	4.36	[2.71–7.03]	<0.001
Previous RCC	3.50	[1.21–10.09]	0.02	3.10	(1.05–9.13)	0.04
Surgical method	0.83	[0.38–1.78]	0.63			

(B)

	CSS					
	Univariate			Multivariate		
	HR	CI	P	HR	CI	P
Age	0.99	[0.95–1.04]	0.97			
ASA	1.65	[0.68–4.04]	0.27	2.95	[0.99–8.82]	0.05
ECOG	1.50	[0.62–3.66]	0.37			
CCI	1.28	[0.82–1.97]	0.28			
Gender	2.23	[0.50–10.01]	0.30			
BMI	1.00	[0.90–1.12]	0.93			
Creat pre-op	0.99	[0.65–1.50]	0.96			
eGFR pre-op	0.99	[0.97–1.01]	0.39			
cT	4.00	[2.34–6.83]	<0.0001	5.39	[2.80–10.39]	<0.001
Previous RCC	6.21	[1.71–22.55]	0.006	11.38	[2.71–47.87]	0.001
Surgical method	1.41	[0.46–4.31]	0.55			

(C)

	OS					
	Univariate			Multivariate		
	HR	CI	P	HR	CI	P
Age	1.04	[1.01–1.08]	0.02	1.04	[1.00–1.09]	0.08
ASA	2.01	[1.06–3.80]	0.03	1.97	[1.02–3.87]	<0.05
ECOG	1.71	[0.93–3.13]	0.09			
CCI	1.21	[0.89–1.66]	0.23			
Gender	1.62	[0.61–4.13]	0.33			
BMI	1.01	[0.94–1.09]	0.80			
Creat pre-op	1.12	[0.93–1.35]	0.23			
eGFR pre-op	0.98	[0.96–0.99]	<0.01	0.99	[0.96–1.01]	0.19
cT	2.32	[1.51–3.55]	<0.001	2.45	[1.55–3.87]	<0.001
Previous RCC	4.11	[1.41–11.93]	0.01	6.1	[1.87–19.95]	<0.01
Surgical method	1.5	[0.67–3.37]	0.33			

CPFS – clinical progression-free survival; HR – hazard ratio; CI – confidence incontinence; ASA – American Society of Anesthesiologists; ECOG – Eastern Cooperative Oncology Group; CCI – Charlson Comorbidity Index; BMI – body mass index; eGFR – estimated glomerular filtration rate; cT – clinical tumor; RCC – renal cell cancer; CSS – cancer specific survival; OS – overall survival

range and evaluations of categorical data were expressed as the proportion or percentage.
Propensity-score matching was performed with the R statistical package (R Foundation, Vienna, Austria). Other statistical analyses were performed with MedCalc software. Statistical significance was set as $p < 0.05$ for each analysis.

RESULTS

Patient selection and surgical procedure

After patient selection (Figure 1) and propensity-score matching, our case and control cohorts comprised of 76 patients per group (RN vs. PN; Table 1). At diagnosis, a bilateral RCC presentation was present in nine patients in the RN group (11.8%) and 12 patients in the PN group (15.8%) ($p = 0.64$). In the PN group, 20 patients (26%) had an absolute indication, based on the presence of bilateral RCC (n = 11), nonfunctioning contralateral kidney (n = 4), a prior contralateral RN for RCC (n = 1), horseshoe kidney (n = 2), or congenital renal agenesis (n = 2). Another 26 patients (34%) had relative indications. The remaining 30 patients (40%) had elective PNs.
RN and PN groups showed no significant difference in mean operation time (RN: 117 vs. PN: 103 min; $p = 0.1$) or mean blood loss (RN: 353 vs. PN: 506 mL; $p = 0.3$). Additional hemostatic sealants were required for five patients (7%) in the RN group and 36 patients (48%) in the PN group. Renal pedicle clamping was performed in 47 of 72 patients (65.3%) in the PN group, including surface hypothermia in three patients (4%). The mean warm ischemia time was 18 min, and the mean cold ischemia time was 33.7 min.

Primary outcomes

During the follow-up period of this study, 26 patients (17.1%) had died before the last follow-up, 14 patients in the RN group and 12 in the PN group. In the RN group, six patients died from RCC-related causes, and eight patients experienced non-cancer-related deaths (NCRDs). In the PN group, six patients died from RCC, and six experienced NCRDs.
CF was reported in 29 patients (19.1%); 17 patients in the RN group and 12 patients in the PN group ($p = 0.4$). Six patients with CF (three patients in each group) exhibited LR and synchronous M+. LR only was present in 12 patients (7.9%), including five patients in the RN group and seven in the PN group. M+ only was present in 23 patients (15.1%), including 15 patients in the RN group and eight in the PN group ($p = 0.1$). Two patients (2.6%) in the RN group had positive surgical margins on the final histopathological exami-

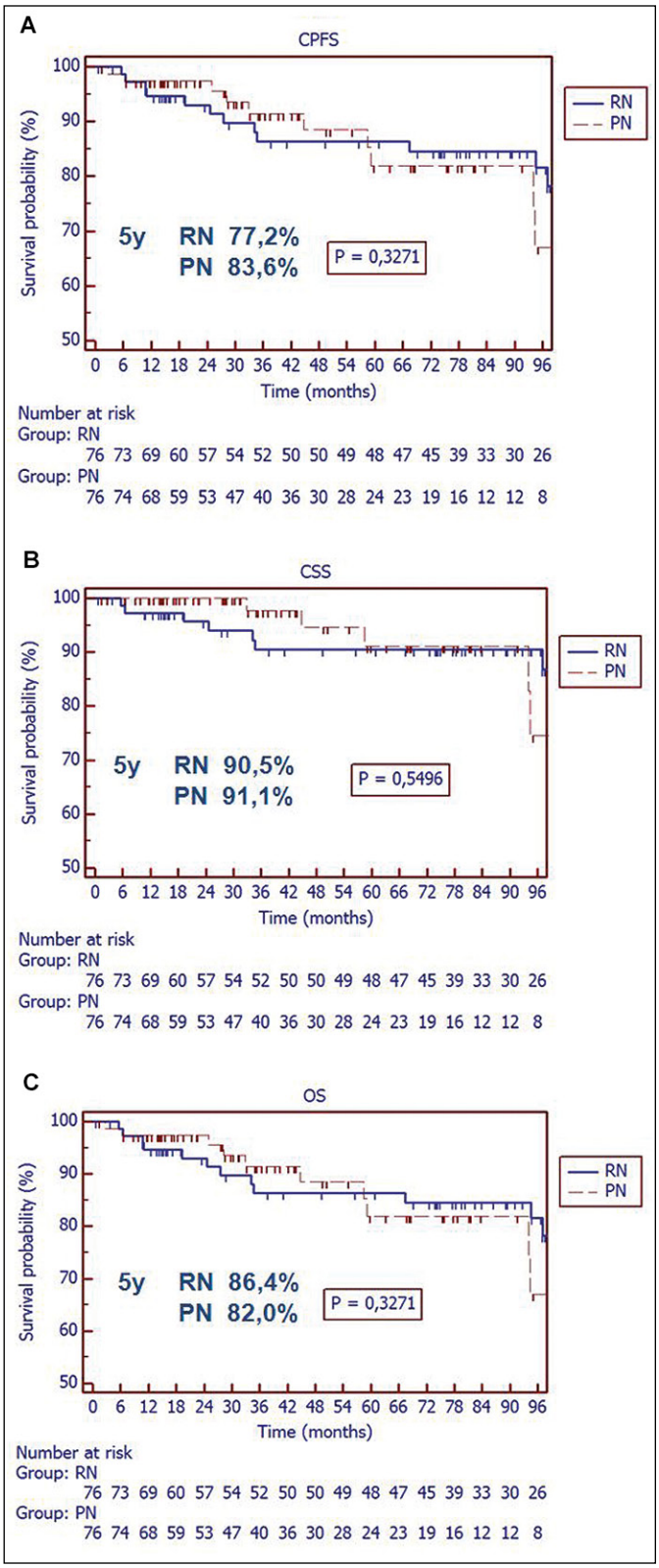

Figure 2. *Survival rates of patients with renal cell carcinoma treated with radical nephrectomy (RN) or partial nephrectomy (PN).* **(A)** *Kaplan-Meier curve of cancer specific survival (CSS)* **(B)** *Kaplan-Meier curve of overall survival (OS).* **(C)** *Kaplan-Meier curve of clinical progression-free survival (CPFS).*

nation; of these, one developed LR after 2.8 months. Eight patients (10.5%) in the PN group had positive surgical margins; of these, none developed LR or M+.
The 5-year CPFS, CSS, and OS rates were explored with Kaplan-Meier curves, stratified according to the surgical procedure (Figure 2C). No significant differences were found between the RN and PN groups in these analyses.
Cox univariate and multivariate proportional regression analyses were performed to identify predictors of CPFS, CSS, and OS (Table 2A-C). The surgical approach did not influence any outcome, after adjusting for all other covariates. The clinical T-stage and a previous history of RCC were the only negative prognostic factors for all three outcomes. The pre-operative ASA score was an additional predictor of OS.
Subgroup analyses of patients with cT1b RCC and patients with RCC >cT1b demonstrated that the two subgroups were well matched (p = 0.4, Table 1). The five year CPFS, CSS, and OS rates in the subgroup of RCC >cT1b were 45.5%, 69.9%, and 66.4% for the RN group and 74.3%, 83.3%, and 77.8% for the PN group, respectively (p = 0.1, 0.7, and 0.9, respectively).

Secondary outcomes

Renal function

The median pre-operative SCr and eGFR values (Table 1) were not statistically different between the RN and PN groups. None of the patients received permanent dialysis pre-operatively.
Pre- and post-operative SCr and eGFR levels are shown in Table 3A for each group, including patients that received permanent dialysis. Both groups experienced reduced renal function due to the surgical intervention. When explored in detail, the absolute reduction in renal function (delta GFR) was more pronounced in the RN group that in the PN group (p = 0.03; Table 3B). This finding was reflected in pre- and post-operative CKD stages of both groups (Table 3C). Patients in the RN group shifted towards higher CKD stages post-operatively (p = 0.01), but this shift was not observed among patients in the PN-group (p = 0.4).

Table 3. *Comparison of pre-operative and post-operative status in radical nephrectomy (RN) and partial nephrectomy (PN) groups.* **(A)** *Serum creatinine (SCr) and estimated glomerular filtration rate (eGFR) values,* **(B)** *Delta-GFRs,* **(C)** *CKD stages*

(A)

	RN (n = 76)			PN (n = 76)		
Permanent dialysis	6 Pt (7.9%)			7 Pt (9.2%)		p = 0.78
Remaining group	70 Pt (92.1%)			69 Pt (90.8%)		
	pre-operative median [IQ-range]	post-operative median [IQ-range]	p	pre-operative median [IQ-range]	post-operative median [IQ-range]	p
SCr	1.06 [0.95–1.25]	1.27 [1.03–1.49]	<0.001	1.00 [0.88–1.18]	1.06 [0.93–1.16]	0.04
eGFR	65.11 [57.63–75.18]	57.65 [41.57–69.41]	<0.001	74.84 [62.44–90.19]	69.80 [53.21–89.47]	0.03

(B)

	RN (n = 76)	PN (n = 76)	
Permanent dialysis	6 Pt (7.9%)	7 Pt (9.2%)	p = 0.78
Remaining group	70 Pt (92.1%)	69 Pt (90.8%)	
	median [IQ-range]	median [IQ-range]	
Delta-GFR	14.14 [2.44–30.73]	5.4 [-9.50–22.65]	p = 0.03

(C)

		RN (n = 76)			PN (n = 76)		
Total group		76 Pt (100%)			76 Pt (100%)		
		pre-operative n (%)	post-operative n (%)	p	pre-operative n (%)	post-operative n (%)	p
CKD stage	1	7 (9.2%)	3 (4.0%)	0.01	17 (22.4%)	16 (21.1%)	0.4
	2	41 (54.0%)	28 (36.8%)		38 (50.0%)	34 (44.7%)	
	3	27 (35.5%)	34 (44.7%)		17 (22.4%)	18 (23.7%)	
	4	1 (1.3%)	5 (6.6%)		3 (4.0%)	2 (2.6%)	
	5	0 (0%)	6 (7.9%)		1 (1.3%)	6 (7.9%)	

CKD – kidney disease

Table 4. *Post-operative complications in radical nephrectomy (RN) and partial nephrectomy (PN) groups, according to the Clavien-Dindo Classification of Surgical complications (p = 0.33)*

Clavien Dindo Score	RN (n = 76)	PN (n = 76)	
0	64 (84.2%)	60 (78.9%)	
I	2 (2.6%)	5 (6.6%)	fever, oesophagitis, hematoma, ventricular fibrillation
II	6 (7.9%)	5 (6.6%)	pulmonary embolism, pneumonia, arterial hypertension...
III a	0 (0%)	2 (2.6%)	postoperative bleeding (embolisation)
III b	0 (0%)	1 (1.3%)	acute abdomen (explorative laparotomy)
IV a	3 (3.9%)	3 (3.9%)	cardiac failure, renal failure
IV b	1 (1.3%)	0 (0%)	hypovolemic shock
V	0 (0%)	0 (0%)	
	12 (15.8%)	16 (21.1%)	

Post-operative complications

The post-operative complications are shown in Table 4. In the RN group, 12 patients developed 13 complications. In the PN group, 15 patients developed 16 complications. There was no difference in complication rates between the groups (p = 0.3). None of the complications were lethal, and nearly all complications resolved completely after adequate treatment. We performed subgroup analyses for patients with complications that were resolved with bedside treatment (grades 1+2) and patients with complications that required re-intervention or organ replacement therapy (grades 3+4). We found no significant differences between the RN and PN subgroups (p = 0.6).

DISCUSSION

The incidence of RCC has increased during the last few decades, due to more frequent diagnoses with the widespread use of non-invasive imaging techniques (US, CT, and MRI). Many times, the incidental detection of an RCC leads to diagnosis in an early stage, and thus, they are defined as SRMs. The standard of care treatment for SRMs has become a PN, when technically feasible, due to emerging evidence that the PN can provide oncologic treatment equivalent to the RN. Moreover, it has become increasingly clear that long term preservation of renal function is important, even for elective indications. However, a substantial number of RCCs is detected at clinical stages higher than an SRM. Currently, discussions are ongoing about the standard treatment for higher stages of RCC. Recently, the role of PN has expanded to become the standard of care therapy for all cT1 tumors, whenever technically feasible [12, 13]. For clinical T2 and larger RCCs, the standard of care remains RN, although the role of the PN is gaining ground.

Antonelli et al. were one of the first groups to suggest that a PN might be oncologically equivalent to a RN in RCCs of 4–7 cm. They compared pathology reports, but the patient groups were not matched [25]. More recently, Becker et al. suggested that NSS could be performed in tumors ≥7 cm, with acceptable complication rates and oncologic outcomes equivalent to those observed in RN series [16]. However, that study was a retrospective, single arm study, without a control group, and patients with bilateral lesions or pre-operative renal dysfunction had been excluded. Breau et al. stated that a PN could be safely and efficiently performed in relatively advanced, localized RCCs (pT2–pT3a) [18]. They examined pathological data between RN and PN groups (the RN/PN ratio was 3/1), which were exactly matched for tumor stage and pre-operative SCr levels. The two groups were also matched as closely as possible for gender, age, surgery year, and tumor diameter.

The present retrospective cohort study investigated oncological outcomes based on clinical T-stages in a well-matched reference cohort of 152 patients, with a RN:PN ratio of 1:1, and short-term follow ups. The median follow-up differed significantly between our two groups; the RN group had a longer median follow up than the PN group (Table 1). This discrepancy could be explained by the trend of the past decade favoring NSS. Because PN is a newer technique, the PN group had a shorter median follow-up. This trend has also been described by other authors [14, 15].

It is difficult to compare oncological PN to RN outcomes in a retrospective series, due to the inherent selection bias, which introduces confounding by indication. Indeed, the propensity to perform a PN is typically based on various tumor factors that portend a favorable outcome [18]. Nonetheless, in this study we attempted to reduce confounding by matching the RN and PN groups for propensity scores on pre-operative clinical variables (Table 1). We limited the effects of a selection bias for PN, because pre-operative images of the RN group were reviewed by two independent investigators, and only patients deemed eligible for NSS were included in the final analysis. Although a perfect match was not possible, these groups were quite well matched in pre-operative clinical variables.

The primary endpoints in the present study were the five year CPFS, CSS, and OS rates. These rates did not differ significantly between the RN and PN

groups (Figure 2 A-C). In the PN group, the primary endpoints were comparable to those reported for other contemporary series [16]. The CPFS, CSS, and OS rates were 83.6%, 91.1%, and 82.0%, respectively. More importantly, the surgical method (RN vs. PN) did not influence survival rates, after adjusting for all other pre-operative clinical covariates in univariate and multivariate analyses.

In this study, we conducted subgroup analyses of patients with cT1b RCC and those with RCC >cT1b. First, we demonstrated that the RN and PN subgroups remained well matched. In the RCC >cT1b subgroups, the five-year CSS, OS, and CPFS rates did not differ between PN and RN groups ($p = 0.7$; 0.9, and 0.1, respectively). This finding suggested that PN could be expanded to the subgroup of patients with RCC >cT1b, with acceptable oncological results. Recently, Alanee et al. reviewed data on T2 tumors treated with PN in the surveillance, epidemiology, and end results (SEER) database, and they reported good CSS rates [26]. Kopp et al. reported similar findings [27].

The PN is not optimal for lymph node dissections, and it has a higher risk of positive section margins (PSMs). Some authors believe that these drawbacks might result in increased LRs. However, in this study, we found no difference in CPFS between the PN and RN groups. LR was observed in 12 patients (7.9%), including five in the RN group and seven in the PN group. These findings were comparable to findings reported in other series (0–10%) [28]. It has been shown that PSMs occurred more frequently in absolute indications and in intrarenal tumors; hence, one might expect that more PSMs should occur in more locally advanced tumors. We could not address this hypothesis in the present study, because no PSM was detected in patients in the PN group that developed LR. In fact, so called LRs are unlikely to arise from incomplete tumor removal; instead, they should be considered de novo tumors [28]. Furthermore, Bensalah et al. provided evidence that the presence of PSM is not always associated with a higher rate of LR or M+; moreover, PSMs appeared to have a negligible impact on OS and CSS in patients treated with PN for a localized tumor [29, 30]. The importance of preserving renal function should be kept in mind, because LRs are generally not rare, and because patients with CF often require adjuvant therapy, which may be poorly tolerated when renal function is severely compromised [18].

In the present study, we examined renal function preservation as a secondary endpoint. In general, surgery impaired renal function in both groups (Table 3A). However, renal function was significantly more impaired in the RN group than in the PN group (Table 3B). The negative impact of RN on renal function was also reflected in the significant changes between pre- and post-operative CKD stages observed in the RN group, but not in the PN group (Table 3C). However, renal function preservation in the PN group did not reflect an increased OS. This result might have been expected, according to some studies [8, 31]. However, the only large prospective EORTC study to date could not demonstrate an OS benefit with PN after a follow-up of nine years [32]. In this study, the short-term follow-up and the limited numbers of events in a relatively small cohort might explain our failure to detect an OS benefit with PN.

Despite the lack of a survival benefit with PN, the value of renal function preservation should not be underestimated, because contralateral lesions might occur after the initial treatment. Moreover, RN treatments for unanticipated benign lesions (12.8–28%) were associated with a worse OS than PNs [6, 7, 33]. Some authors reported significantly more cardiovascular events and increased risk of death by any cause in patients treated with RNs compared to those treated with PNs [9, 34]. Miller et al. highlighted more adverse renal outcomes with the RN than with the PN. Compared to PNs, RNs were associated with more frequent dialysis services, dialysis access surgeries, and renal transplantations. PNs appeared to reduce the frequency of subsequent CKD [10]; indeed, patients were 90% more likely to develop postoperative CKD with a RN compared to a PN [35]. In addition to the preservation of renal function and avoidance of dialysis, with its complications and metabolic consequences, patients that underwent PN had better overall quality of life (QoLs) and health related quality of life (HRQoLs) in the years after surgery, according to Lesage [11]. All these findings suggested that NSS should be implemented, whenever technically feasible, to preserve renal function.

Another secondary endpoint examined in this study was the rate of post-operative complications. Currently, PN is believed to be associated with a higher complication rate than RN, although the complication rates for PNs have substantially decreased over the past years. Post-operative hemorrhage and urinoma were two of the most frequent complications related to PN in treating advanced stage disease [18]. These complications typically resolve completely without significant morbidity when treated conservatively or with minimally invasive techniques (e.g., arterial embolization, ureteral stenting). In the present study, the RN and PN groups showed no difference in complication rates (Table 4, $p = 0.33$). We found that most complications were not related to the type of surgical procedure. Moreover, none of the complications were lethal, and complication

rates were comparable to those reported in other contemporary series [12, 16].

We analyzed subgroups of patients with complications that were resolved with bedside treatment (grades 1+2) and complications that required re-intervention or organ replacement (grades 3+4). We found no differences between the RN and PN subgroups ($p = 0.69$). However, of note, hemostatic agents were used more frequently in the PN group (48%) than in the RN group (7%); therefore, observations of postoperative hemorrhage may have been biased in favor of the PN group.

Currently, PN is the cornerstone treatment for cT1 RCC, due to its oncological equivalence to RN, its benefit of renal function preservation, and its acceptable complication rates. Nevertheless, PN remains underutilized, even for SRMs. Some authors believe its underuse is due to the increased operative time required compared to RN, and the risk of incomplete tumor removal. We found no difference between PN and RN groups in mean operative times ($p = 0.10$) or LR rates. The underutilization of PN (for cT1a RCC) over the last decades, and even currently, has given rise to a concern over quality of care. In 2000, RNs were performed for SRMs of 0–2 cm and 4–7 cm in 58 to 94% of all nephrectomies, respectively, in the United States [14]. A larger study in 2006 affirmed those results [36]. A more promising review in 2007 demonstrated an increasing trend (4.5-fold increase) of utilizing PN compared to its use in 1987. That author stated that the trend towards NSS may maximize the extent of renal function preservation, and thus, could be considered indicative of excellent quality of care [37]. Nevertheless, the use of PN remains suboptimal in the community setting (49% in 2008) relative to tertiary care centers (90% in 2007), even for treating SRMs <4 cm [34]. Hence, one may assume that the PN will also be underutilized for resecting larger renal masses (≥cT1b). Consequently, a quality of care concern might arise, because the optimal treatment has been neglected [14].

This study had some limitations. First, it had a retrospective design. Second, there was a potential inherent selection bias in the cohort. However, we minimized the selection bias with the propensity-score matching and our reassessments of images in the RN group to confirm that these patients had been eligible for PN. However, no perfect match based on clinical variables was possible. Moreover, there may have been other unknown confounders, which we did not correct for, that may have biased the analysis. Third, our cohort represented a relatively small sample size with a relatively short follow-up. Thus, the limited numbers of events may also have influenced the outcomes. Longer follow-up data might have improved the precision of our results, particularly in the PN group. Finally, all surgical interventions were performed by a urologist with extensive experience and training in advanced renal surgery. Therefore, the outcomes may not be generalizable to all surgeons or institutions. Prospective randomized trials are needed to confirm our results.

CONCLUSIONS

This retrospective study demonstrated, in propensity score-matched groups representative of patients in daily practice, that RN and PN showed similar efficacy and safety for treating RCC stages ≥cT1b. To the best of our knowledge, this was the only study in this subgroup of RCC to date that assessed a control arm (RN) of patients eligible for PN and matched the two groups based on propensity scores of clinical variables. We demonstrated that PN has excellent oncological results, comparable to other contemporary series. We found no significant difference in oncological outcomes between groups. Moreover, the surgical method was not found to be an independent predictor of survival outcomes. Therefore, PN should be considered an oncologically safe procedure in this subgroup of patients. Renal function was preserved significantly more frequently in the PN than in the RN group. Complication rates were similar between groups. These findings suggest that, in the absence of N+M+ disease, regardless of tumor stage or size, NSS should always be considered when technically feasible. However, adequate surgical experience is imperative, because PN might be technically demanding. Nonetheless, we believe that PN could be feasible for most surgeons, given adequate training, technical attention, and conscientious patient selection. RN should remain an appropriate treatment option for select renal tumors not amenable to NSS.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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