Partial nephrectomy for T1 renal cancer can achieve an equivalent oncological outcome to radical nephrectomy with better renal preservation: the way to go

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ABSTRACT

Introduction: Patients who undergo partial nephrectomy have been shown to be at decreased risk of renal impairment compared with radical nephrectomy. We examined the oncological outcome of patients in our centre who underwent partial or radical nephrectomy for T1 renal cancer (7 cm or smaller), and compared the likelihood of developing chronic kidney disease.

Methods: This historical cohort study with internal comparison was conducted in a tertiary hospital in Hong Kong. A cohort of 86 patients with solitary T1 renal cancer and a normal contralateral kidney who underwent radical (38 patients) or partial (48 patients) nephrectomy between January 2005 and December 2010 was included. The overall and cancer-free survival, change in glomerular filtration rate, and new onset of chronic kidney disease were compared between the radical and partial nephrectomy groups.

Results: A total of 32 (84%) radical nephrectomy patients and 43 (90%) partial nephrectomy patients were alive by 31 December 2012. The mean follow-up was 43.5 (standard deviation, 22.4) months. There was no significant difference in overall survival (P=0.29) or cancer-free survival (P=0.29) between the two groups. Both groups enjoyed good oncological outcome with no recurrence in the partial nephrectomy group. Overall, 18 (21%) patients had pre-existing chronic kidney disease. The partial nephrectomy group had a significantly smaller median reduction in glomerular filtration rate (12.6% vs 35.4%; P<0.001), and radical nephrectomy carried a significantly higher risk of developing chronic kidney disease (hazard ratio=5.44; 95% confidence interval, 1.26-23.55; P=0.02).

Conclusions: Compared with radical nephrectomy, partial nephrectomy can prevent chronic kidney disease and still achieve an excellent oncological outcome for T1 renal tumours, in particular T1a tumours and tumours with a low R.E.N.A.L. score.

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New knowledge added by this study

- Partial nephrectomy for T1 renal tumour is associated with excellent overall and cancer-free survival, and better renal preservation than radical nephrectomy.

Implications for clinical practice or policy

- As a significant proportion of T1 renal cancers are still managed by radical nephrectomy in our locality, we recommend partial nephrectomy for T1a and selected T1b renal cancers, provided that relevant expertise is available.

Introduction

With the widespread use of advanced imaging such as computed tomography (CT), many renal tumours are now incidentally discovered before the patient becomes symptomatic. These tumours are often of small size. This has led to the emerging practice of partial nephrectomy (PN) rather than radical nephrectomy (RN) that has been the gold-standard treatment for localised renal tumours for over 40 years.[1] Studies have shown that cancer control can be achieved by PN in patients with T1a tumours,[2-5] and some studies also supported the extended use of PN for T1b tumours.[6-9] In addition, patients who undergo PN have been shown to be at decreased risk of renal impairment.[10]

Nonetheless, many surgeons in Hong Kong continue to perform RN for all renal tumours, regardless of their size. The major concerns are the

T1期腎癌患者進行腎部分切除術的療效可媲美根治性全腎切除術並能較好地保留腎功能：治療腎癌患者的一個可取方法

賴俊廷、馬偉傑、姚銘廣

引言：研究顯示腎部分切除術所帶來的腎功能損害風險比腎癌根治術低。本研究探討T1期腎癌患者（腫瘤大小為7 cm或以下）進行腎部分切除術或根治性全腎切除術的療效，並比較兩種手術發展成慢性腎病的可能性。

方法：這是在香港一所提供第三層醫療服務的醫院進行內部比較的歷史隊列研究。於2005年1月至2010年12月期間到上述中心應診的86名單發T1期腎癌的患者均被列入研究範圍。所有患者的對側腎均為正常；當中有38例進行根治性全腎切除術，另48例進行腎部分切除術。研究把兩組的總體生存率和無瘤生存率、腎小球濾過率的變化和慢性腎病的新發病例進行比較。

結果：直至2012年12月31日為止，32例（84%）根治性全腎切除術和43例（90%）腎部分切除術的患者仍然生存。平均隨訪時間為43.5（標準差22.4）個月。兩組間的總體生存率（P = 0.29）和無瘤生存率（P = 0.29）無顯著差異。所有患者均有良好的術後結果；腎部分切除術的患者亦沒有復發。18例（21%）原有慢性腎病。腎部分切除術患者的腎小球濾過率的下降率明顯較低（12.6%比35.4%，P<0.001）。根治性全腎切除術患者患上慢性腎病的風險顯著較高（風險比= 5.44；95%置信區間：1.26-23.55；P=0.02）。

結論：與根治性全腎切除術比較，腎部分切除術可預防慢性腎病，而且對於T1期腎癌患者來說能達至極佳的療效，對於T1a期腫瘤以及具有低R.E.N.A.L.分數的患者尤其有效。

technical difficulty of PN and the associated major postoperative complications.

The aim of this study was to compare the oncological outcome, survival, and changes in renal function in patients who underwent RN or PN for T1 renal cancer in our centre. Patients were predominantly of Chinese ethnicity.

Methods

We retrospectively reviewed the data of patients who underwent RN or PN at our centre between January 2005 and December 2010. Patients with a solitary tumour of 7 cm or less in diameter and a normal contralateral kidney were included. The decision to perform PN was based on tumour characteristics (size, proximity to collecting system and major vessels) and the surgeon's preference. Exclusion criteria were: end-stage renal failure (glomerular filtration rate [GFR] <15 mL/min/1.73 m^2), history of renal transplantation, known hereditary renal cancer, known poor or non-functioning contralateral kidney, history of nephrectomy, and preoperative evidence of tumour metastases.

Preoperative parameters including age, gender, serum creatinine, and estimated GFR were studied. We used the modified Charlson-Romano index to compare patient co-morbidity.[11] We also compared postoperative outcome for the RN and PN groups, including length of hospital stay, complications, and 90-day mortality. Severity of complications was graded using the Clavien-Dindo classification system.[12]

Our study outcome included 5-year overall survival, cancer-free survival, change in renal function in terms of estimated GFR (eGFR), and new onset of chronic kidney disease (CKD)—GFR was calculated with the four-variable Modification of Diet in Renal Disease formula: eGFR = 32 788 x serum creatinine $(\mu mol/L)^{-1.154}$ x $age^{-0.203}$ x [1.212 if black] x [0.742 if female][13]; CKD was defined as GFR of <60 mL/min/1.73 m^2. Patients were followed up according to international guidelines, with slight variation in timing of imaging due to examination waiting time issues. In general, follow-up was scheduled every 3 months within the first year of operation with measurement of serum creatinine and GFR, and CT scan was performed approximately 12 months following surgery. Patients were subsequently followed up every 6 months, with renal function checked at each visit, and imaging studies (ultrasonography or CT) performed annually for the first 5 years and thereafter once every 2 years.

For preoperative characteristics and postoperative outcome, P value was determined by the Chi squared test and Mann-Whitney *U* test for categorical and continuous variables, respectively. Kaplan-Meier model was used for 5-year overall and cancer-free survival, and the postulated 5-year probability of freedom from CKD. Risk of new onset of CKD was calculated with Cox proportional hazards regression, adjusted for age, Charlson Comorbidity Index (CCI), preoperative GFR, gender, and tumour size; with time to CKD development as dependent variable; death, loss to follow-up, or last follow-up date before 31 December 2012 were censored in the analysis. Overall survival was analysed by Cox proportional hazards regression adjusted with Fuhrman grade of tumour, in addition to the above factors. We did not include diabetes mellitus as it was included in the CCI. We considered a 2-sided P value of <0.05 as statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences (Windows version 20.0; SPSS Inc, Chicago [IL], US).

Results

A total of 86 patients were reviewed, with a mean (± standard deviation) follow-up time of 43.5 ± 22.4 months. Four (5%) patients were lost to follow-up with their status unknown by the end of our study.

Overall, RN was performed in 38 patients and PN in 48. Age, gender, and preoperative serum creatinine level and GFR were similar between the two groups. The mean age of RN and PN groups was 61 years and 63 years, respectively (P=0.48), with a respective mean preoperative GFR of 80.8 mL/min/1.73 m^2 and 75.0 mL/min/1.73 m^2 (P=0.38). Six (16%) patients in the RN group and 11 (23%) in the PN group had a preoperative GFR of <60 mL/min/1.73 m^2; one patient in the PN group had a preoperative GFR of <30 mL/min/1.73m^2. Most patients in the RN and PN groups had a CCI of <2 (84% vs 85%; P=0.87). The respective mean follow-up time was 42.1 ± 24.0 and 44.5 ± 21.3 months (P=0.62) [Table 1].

Tumours were more complex in the RN group in terms of the R.E.N.A.L. score[14] derived from preoperative CT (8.4 vs 6.7, P<0.001). The mean tumour size, based on final pathological examination, was also larger in the RN group (4.8 cm vs 2.5 cm, P<0.001). In the RN group, 24 (63%) patients had a T1b tumour compared with three (6%) in the PN group (P<0.001). Comparison of the first half of our study period (2005-2008) with the second half (2009-2010) revealed that tumour characteristics were similar in the PN group, in terms of both size (2.4 cm vs 2.5 cm; P=0.93) and R.E.N.A.L. score (6.2 vs 7.0; P=0.32). Most tumours in both groups were of the clear cell type. The RN group had more Fuhrman grade 3 tumours but the difference was not significant (Table 1). All resections enjoyed clear resection margins on final pathological examination.

All RNs were performed via a laparoscopic approach. An open procedure was performed for 29 (60%) of the PNs, eight (17%) were performed via a laparoscopic approach, and 11 (23%) with robotic assistance. Of the latter, conversion to an open procedure was required in two cases. Operating time was significantly longer in the PN group (250 mins vs 345 mins; P<0.001). None of the PNs were converted to RN.

All PNs were performed with vascular control achieved by hilar clamping. Overall, 28 (58%) PNs were performed with cold ischaemia using ice slush, with a mean cold ischaemia time of 70 minutes; among these, 23 (82%) were an open procedure and two were conversion of robotic-assisted laparoscopic PN to open procedure. Of the PNs, 20 (42%) were performed with warm ischaemia, and the mean warm ischaemia time was 32 minutes; all laparoscopic PNs were performed with warm ischaemia. The complexity of tumour in terms of R.E.N.A.L. score was significantly lower in the warm ischaemia group (5.7 vs 7.5; P=0.01).

Patients in the PN group had a longer postoperative hospital stay (6 vs 13 days; P<0.001); one of whom died within 90 days of surgery of cholecystitis and septic complications unrelated to the renal cancer.

TABLE 1. Patient demographics and tumour characteristics

Demographic/characteristic	No. (%) of patients or mean ± SD		P value
	RN (n=38)	PN (n=48)	
Gender			0.82
Male	27 (71)	32 (67)	
Female	11 (29)	16 (33)	
Age at diagnosis (years)	61 ± 14	63 ± 14	0.48
Preop serum creatinine (μmol/L)	87.7 ± 21.6	95.3 ± 32.4	0.52
Preop GFR (mL/min/1.73 m^2)	80.8 ± 22.6	75.0 ± 23.5	0.38
Preop CKD stage			0.83
1	12 (32)	12 (25)	
2	20 (53)	24 (50)	
3	6 (16)	11 (23)	
4	0	1 (2)	
Charlson Comorbidity Index			0.87
<2	32 (84)	41 (85)	
≥2	6 (16)	7 (15)	
Length of follow-up (months)	42.1 ± 24.0	44.5 ± 21.3	0.62
R.E.N.A.L. score*	8.4 ± 1.7	6.7 ± 1.8	<0.001
Tumour size (cm)	4.8 ± 1.2	2.5 ± 1.1	<0.001
Tumour stage			<0.001
T1a	14 (37)	45 (94)	
T1b	24 (63)	3 (6)	
Pathology			0.31
Clear cell	36 (95)	41 (85)	
Papillary	0	4 (8)	
Chromophobe	2 (5)	2 (4)	
Multilocular cystic RCC	0	1 (2)	
Fuhrman grade			0.08
1	3 (8)	10 (21)	
2	21 (55)	29 (60)	
3	14 (37)	9 (19)	

Abbreviations: CKD = chronic kidney disease; GFR = glomerular filtration rate; PN = partial nephrectomy; Preop = preoperative; RCC = renal cell carcinoma; RN = radical nephrectomy; SD = standard deviation

* R.E.N.A.L. score = Radius (maximal diameter in cm), Exophytic/endophytic properties, Nearness of tumour to the collecting system or sinus (mm), Anterior/posterior, Location relative to polar lines; R.E.N.A.L. score was missing in 33 patients

Postoperative complication rates were similar between the two groups (P=0.19), although the PN group had more Clavien grade III or above complications (0% vs 10%; Table 2). Four patients had persistent urine leakage that was successfully treated with retrograde injection of surgical adhesive glue; one patient developed pseudoaneurysm of the segmental branch of the renal artery, which was treated by angiographic embolisation. No long-term morbidity or mortality occurred. Complication rate was not associated with patient age, CCI, R.E.N.A.L.

TABLE 2. Postoperative outcomes

Outcome	No. (%) of patients or mean ± SD		P value
	RN (n=38)	PN (n=48)	
Length of hospital stay (days)	6 ± 6	13 ± 12	<0.001
Complications			0.19
Urine leakage	0	4 (8)	
Ileus	1 (3)	1 (2)	
Urinary tract infection	1 (3)	1 (2)	
Urinary retention	1 (3)	2 (4)	
Renal artery pseudoaneurysm	0	1 (2)	
Acute tubular necrosis	0	1 (2)	
Lymph leakage	0	1 (2)	
Clavien classification			0.06
I	3 (8)	3 (6)	
II	0	1 (2)	
IIIa	0	5 (10)	
IIIb	0	0	
IV	0	0	
V	0	0	
90-Day mortality	0	1 (2)	<0.001

Abbreviations: PN = partial nephrectomy; RN = radical nephrectomy; SD = standard deviation

TABLE 3. Factors associated with overall survival

Factor	Hazard ratio (95% CI)	P value
Type of nephrectomy (RN vs PN)	0.84 (0.17-4.02)	0.82
Age	1.11 (1.02-1.22)	0.02
Charlson Comorbidity Index	1.55 (0.82-2.93)	0.18
Preoperative GFR	1.03 (0.98-1.07)	0.21
Gender (female vs male)	1.74 (0.33-9.05)	0.51
Tumour size	1.54 (0.90-2.62)	0.11
Fuhrman grade	0.96 (0.29-3.24)	0.95

Abbreviations: CI = confidence interval; GFR = glomerular filtration rate; PN = partial nephrectomy; RN = radical nephrectomy

TABLE 4. Factors associated with new-onset chronic kidney disease after operation

Factor	Hazard ratio (95% CI)	P value
Type of nephrectomy (RN vs PN)	5.44 (1.26-23.55)	0.02
Age	1.02 (0.90-1.06)	0.52
Charlson Comorbidity Index	1.45 (0.80-2.61)	0.22
Preoperative GFR	0.96 (0.91-1.01)	0.09
Gender (female vs male)	0.78 (0.31-1.99)	0.60
Tumour size	0.87 (0.57-1.34)	0.53

Abbreviations: CI = confidence interval; GFR = glomerular filtration rate; PN = partial nephrectomy; RN = radical nephrectomy

score of tumour, or operative parameters (operative approach, operating time, and ischaemia time).

An overall excellent oncological outcome was achieved by both groups. Extensive metastases were evident 3 months after operation in one patient in the RN group but these were not apparent before operation. By 31 December 2012, 32 (84%) RN and 43 (90%) PN patients were alive. The overall 5-year survival for the RN and PN groups was 84.2% and 89.6% (P=0.29) respectively, and the cancer-free survival was 97% and 100% (P=0.29) respectively. Both RN and PN did not affect overall survival (hazard ratio=0.84; 95% confidence interval [CI], 0.17-4.02; P=0.82), after adjustment for age, CCI, preoperative GFR, gender, tumour size, and Fuhrman grade (Table 3).

Patients who underwent RN had a greater median reduction in GFR than PN patients (35.4% vs 12.6%; P<0.001), and the degree of reduction was most distinctive in the first year after operation (Fig 1). In the PN group, one patient with a preoperative GFR of 30 mL/min/1.73 m^2 developed stage 5 CKD 4 years after surgery and required renal replacement therapy. Preoperative GFR was >60 mL/min/1.73 m^2 in 32 patients in the RN group and in 36 patients in the PN group. At their last follow-up, CKD was developed in 18 (56%) patients who underwent RN but new-onset CKD was evident in only five (14%) of the PN group (P<0.001). The majority of the CKD cases were stage 3 (94% in RN group and 80% in PN group); none was in stage 5. Cox proportional hazards regression model showed that RN was the most significant factor contributing to the development of CKD (RN vs PN, hazard ratio=5.44; 95% CI, 1.26-23.55; P=0.02; Table 4). The postulated probability of freedom from new-onset CKD in 5 years, by Kaplan-Meier model, was 33% and 81% in the RN and PN groups, respectively (P<0.001; Fig 2).

Discussion

Many surgeons have underestimated the impact of renal impairment after RN for renal cancer, on the basis that organ donors who undergo nephrectomy are not at increased risk of renal failure or death.[15-17] Nonetheless, donors represent a different population as they are often young and fit. Patients with renal cancer are often older and have co-morbidities such as hypertension and diabetes mellitus. In our study, 21% of our patients had a GFR of <60 mL/min/1.73 m^2 prior to surgery and 15% had a CCI of ≥2. Therefore it is logical that this cohort of patients may benefit from a surgical technique that preserves more of their renal function.

Our study showed that PN resulted in less renal deterioration in terms of GFR, with RN having a hazard ratio of 5.44 for development of CKD, after taking into consideration the patient co-morbidities, gender, age, and tumour size. The postulated

probability of freedom from new onset of CKD in 5 years in our series was 33% following RN and 81% following PN. This echoes the finding of Huang et al[10] who reported the 3-year probability of freedom from new onset of CKD as 35% after RN and 80% after PN; RN remained an independent risk factor for development of new-onset CKD with a hazard ratio of 3.82.

A community-based study showed that CKD was an independent risk factor for the development of cardiovascular events, hospitalisation, and death.[18] In a population-based cohort of 7769 patients, RN was associated with a 1.23-fold increase in overall mortality compared with PN (P=0.001), and a higher rate of non–cancer-related mortality.[19] Huang et al[10] also demonstrated that RN was associated with a 1.46-fold increased risk of overall mortality, although the risk of a cardiovascular event was not increased in the RN group. Evidence that PN decreases overall mortality remains contradictory. A randomised controlled trial showed that RN had comparable overall survival with PN after a median follow-up of 9.3 years.[20] In our study we did not show a significant difference in overall survival between PN and RN groups.

Another concern of PN is its cancer control, since the prevention of local recurrence is of paramount importance. The extent of resection is affected by tumour size, proximity to the collecting system, and location and degree of exophytic growth. It is generally accepted that PN can achieve excellent oncological outcome for tumours smaller than 4 cm, with a long-term 5-year and 10-year cancer-free survival rates of 92% to 100%.[2,21-23] Studies have demonstrated the feasibility of PN for tumours larger than 4 cm without compromising the oncological outcome, although there was a higher risk of peri-operative bleeding and other complications.[23,24] In our cohort, we achieved a 100% clear surgical resection margin with PN, and no local recurrence was found after 5 years.

Increased peri-operative morbidity is traditionally a concern in PN. There were more Clavien grade III complications and a longer hospital stay for patients who underwent PN in our cohort. The most common complication in an open PN series was urine leakage, with a mean incidence of 6.5% (range, 2.1%-17%).[25,26] In a multicentre review of 51 laparoscopic PNs, postoperative urine leakage was observed in three (6%) patients.[27] The results of a previous series by Gill et al,[28] supported by our results, suggested that both tumour location and diameter were not related to the occurrence of urine leakage. In contrast to the logical thinking that calyceal entry was not observed during renorrhaphy, it has been suggested that central coagulation necrosis with electrocautery is responsible for fistula formation.[27] The use of a ureteral catheter and

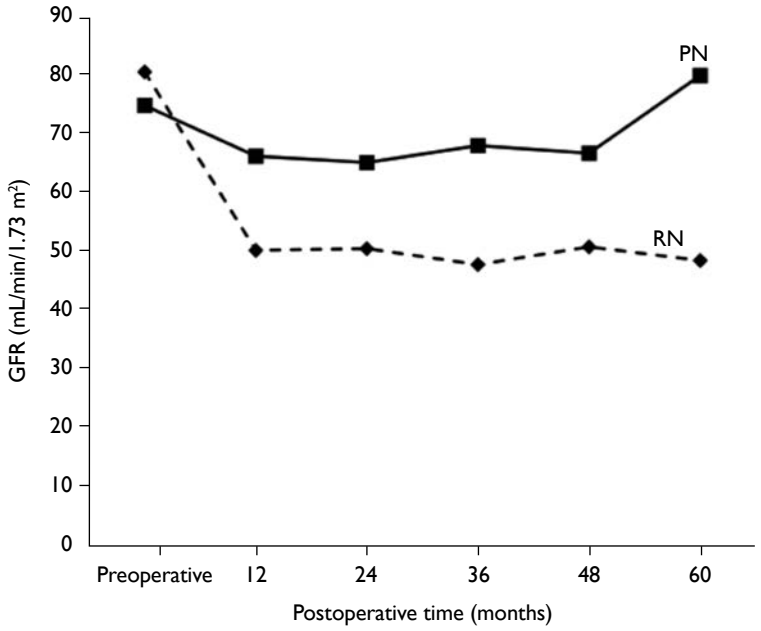

FIG 1. Change of glomerular filtration rate (GFR) after surgery of patients undergoing partial nephrectomy (PN) and radical nephrectomy (RN)
RN patients had a higher median reduction in GFR than PN patients (35.4% vs 12.6%; P<0.001), and the difference was most distinctive in the first year after operation, and sustained throughout the years

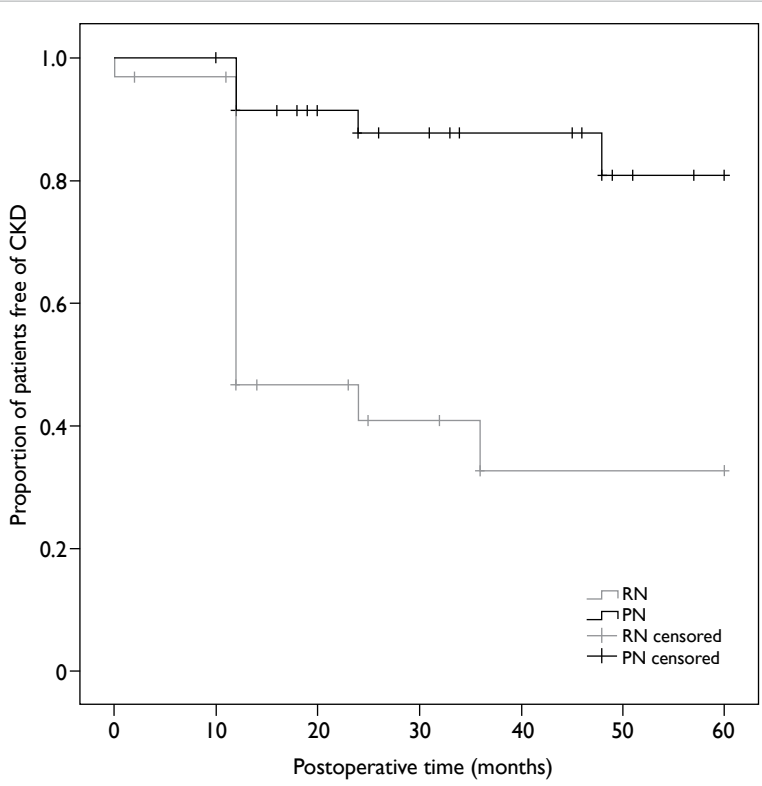

FIG 2. The postulated probability of freedom from new-onset chronic kidney disease (CKD) in 5 years was 33% and 81% in radical nephrectomy (RN) and partial nephrectomy (PN) groups, respectively (P<0.001)

retrograde dye injection after haemostasis has been advocated to help identify any calyceal opening, but this was not supported in a retrospective series by Bove et al[29] that involved 54 patients with and 49 patients without ureteral catheter placement. We believe that the adoption of cold cutting and elevation of the tumour from the tumour bed by the suction cannula, which also simultaneously aspirates the blood, can avoid coagulation necrosis and a clear operative field can be maintained so that any breaching of calyceal integrity can be identified. The use of a ureteral catheter can be an adjunct measure in equivocal cases when the tumour is abutting the calyceal lining on preoperative imaging.

Our study have some limitations. Since it was a retrospective study, patients were not randomised and there was a selection of smaller and less complex tumours in the PN group. There were also other confounding factors such as patient's smoking status that were not included, hence the two groups were not totally comparable, although other patient demographics were similar. As a proportion of preoperative imaging could not be retrieved, the R.E.N.A.L. score could not be calculated for every patient included, and this contributed another confounding factor. Only three patients had T1b renal cancer in the PN group, thus the oncological outcome may be more certain in T1a renal cancer. Our stratified analysis in T1a renal cancer had a similar result with PN having an equivalent oncological outcome and superior renal function preservation, although the result is not shown here. In addition, the risk of tumour recurrence, negative effect of CKD and their effect on survival might not be truly reflected in our relatively short follow-up time. Nonetheless with experience, renal tumours of 4 cm or more in diameter may be amenable to safe PN with equivalent oncological outcome and a lower chance of progression to CKD. This may translate into improved overall survival.[30]

Conclusions

Partial nephrectomy can preserve more renal function and reduce the risk of development of CKD compared with RN. Excellent cancer control and a low local recurrence rate can still be achieved with PN for T1 tumours, in particular T1a tumours and tumours with a low R.E.N.A.L. score. Although RN continues to constitute a significant proportion of surgical procedures for T1 renal cancer in our locality, we recommend that, if technically feasible, PN should be performed for all T1a and selected T1b renal cancers.

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