Ipsilateral renal function preservation following minimally invasive partial nephrectomy: The effect of tumour characteristics and warm ischemic time

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Abstract

Introduction: The relative impact of preoperative and perioperative variables on renal function following partial nephrectomy (PN) is controversial. To further investigate, we assess the effects of tumour complexity, warm ischemic time (WIT), and volume of resected renal parenchyma on ipsilateral renal function (IRF) outcomes following minimally invasive PN.

Methods: Of patients who underwent laparoscopic or robotic-assisted PN between 2002 and 2011 at our institution, 99 met our inclusion criteria. The effects of preoperative tumour complexity (using RENAL nephrometry score), perioperative WIT, and pathological tumour volumes on ipsilateral renal function preservation (%IRF) were analyzed. %IRF was defined as the proportion of postoperative to preoperative ipsilateral renal function calculated using MAG3 nuclear renography.

Results: Increasing RENAL nephrometry score (RNS) and WIT were independently predictive of inferior %IRF at 6–12-week postoperative followup in univariate and multivariate analyses. Of RNS properties, masses that were endophytic, near the collecting system, or central in location were associated with inferior %IRF, with nearness to collecting system as the strongest predictor; however, RNS was no longer predictive of %IRF in cases requiring more than 30 minutes of WIT.

Conclusions: In renal masses amenable to resection by minimally invasive PN, longer WIT was the most important predictor of inferior %IRF. Although increasing RNS score influenced %IRF, the overall clinical significance of RNS is limited and should not influence operative decision-making in efforts to preserve renal function. Furthermore, small volumes of renal parenchyma can be safely resected without impairment of long-term IRF.

Introduction

Minimally invasive partial nephrectomy (PN) is commonly performed for the resection of small renal masses. Through preservation of renal function, PN confers favourable cardiovascular outcomes vs. radical nephrectomy[1] with equivalent oncological outcomes.[2,3] Nonetheless, reduced nephron mass secondary to PN continues to be a risk factor for subsequent de novo chronic kidney disease,[4] and in turn, cardiovascular events, hospitalization, and death.[5]

We have previously assessed non-modifiable preoperative (i.e., glomerular filtration rate and diabetes mellitus)[6] and modifiable perioperative factors (i.e., early clamp release)[7] that affect renal function following surgery. Although others have assessed the effect of tumour size, RENAL nephrometry score (RNS), and warm ischemic time (WIT) on ipsilateral renal function following PN, the relative impact of these factors has been inconsistent.[8-11] This is partly due to the use of estimated glomerular filtration rate (eGFR) in evaluation of postoperative renal function; eGFR underestimates ipsilateral renal impairment because compensatory hypertrophy and hyperfiltration occurs in the contralateral renal unit following PN.[12]

We investigated the effect of tumour size, piece size, volume of resected renal parenchyma, RNS, and WIT on ipsilateral renal function (IRF) following PN in our centre. To more accurately assess the impact of these factors on the affected renal unit, we measured differential renal function using nuclear renography during the preoperative period and once again 6–12 weeks postoperatively.

Methods

Study population

Following approval from our research ethics board, a retrospective review was performed on patients who underwent laparoscopic or robotic-assisted PN at our institution between October 2002 and November 2015. Of this sample, 99 patients met our inclusion criteria, which included preoperative and postoperative (at 6–12 weeks) serum creatinine and MAG3 nuclear renogram. WIT, radiographic and pathological tumour size, pathological piece size, and RNS from imaging studies were also included in our data set. All surgeries were performed at London Health Sciences Centre sites by one surgeon.

RNS

RNS was calculated based on criteria outlined by Kutikov and Uzzo:[13] R, radius (maximum tumour radiographic diameter); E, exophytic/endophytic properties; N, nearness of the tumour to the collecting system; A, anterior/posterior descriptor; and L, location relative to the polar line. Of the five criteria, only four (R, E, N, L) are assigned points on a scale of 1–3; the sum of these four criteria were calculated as the RNS in this study, excluding only the anterior/posterior descriptor.

Renal function assessment

IRF was calculated by multiplying the percentage contribution for the operated kidney from MAG3 renography by the total eGFR as calculated using the Cockroft-Gault formula (IRF= eGFR*% contribution). IRF has been used previously to avoid overestimation of renal function preservation secondary to compensatory contralateral hypertrophy.[14] Ipsilateral renal function preservation (%IRF) was defined as the proportion of postoperative-to-preoperative ipsilateral renal function (%IRF=postoperative IRF/preoperative IRF) and was calculated at intermediate (6–12 weeks) postoperative followup.

Volumetric assessment

Tumour size was calculated using the ellipsoid formula ($V=4/3\varpi xyz$) where x, y, and z were the three measured dimensions of the tumour by pathological assessment. The ellipsoid calculation has been used in previous studies to assess renal tumour size.[14,15] Piece size was calculated using a cone formula ($V=\varpi r^2h/3$) where r and h were the two largest measurements determined on pathological assessment. Volume of resected renal parenchyma (RP) was calculated by subtracting the tumour size from the corresponding piece size.

Statistical analysis

Patient demographics (age, gender, weight, preoperative serum creatinine), tumour characteristics (tumour size, piece size, resected RP, RNS), and intraoperative variables (WIT) were assessed. Univariate linear regression was performed to identify factors predicting decreased %IRF in the operated kidney after minimally invasive PN at 6–12 weeks postoperatively. The effect of RENAL nephrometry characteristics (radius, exophytic, nearness to collecting system, and location) on %IRF was analyzed using univariate linear regression. Similar analyses were performed on WIT subgroups (WIT less than vs. greater than 30 minutes). Statistical significance was set at $p<0.05$. Multivariate regression was performed on variables demonstrating linear relationship with %IRF with $p<0.15$. Analysis was performed using SPSS v20 software.

Surgical technique

Minimally invasive PN was performed by one surgeon either laparoscopically or robotic-assisted using a transperitoneal approach. All surgical specimens were removed with a margin and no enucleation techniques were performed. All patients received mannitol intravenously before renal artery clamping. Both renal artery and renal vein were clamped without use of cooling techniques. No off-clamp PN was performed in this group of patients.

Results

Patient demographics

Patient and tumour characteristics are detailed in Tables 1 and 2. These demographics are similar to those evaluated in other studies. Of 99 patients analyzed, 64 underwent laparoscopic and 35 underwent robotic-assisted PN. There were no significant differences in demographic variables between these groups.

Predictors of %IRF

Univariate linear regression was performed to explore the relationship between tumour size, piece size, volume of resected RP, WIT, and RNS on %IRF. This analysis demonstrated that RNS ($R^2=0.07$; $p=0.007$) (Fig. 1) and WIT ($R^2=0.134$; $p<0.0005$) (Fig. 2) were predictors of %IRF at intermediate (6–12 weeks) followup. There was no statistically significant association between tumour size, piece size, or RP on %IRF at intermediate followup (Fig. 3).

Table 1. Patient and tumour characteristics

Characteristics	All (N=99)
Age, years (mean, range)	60.24 (21–89)
Male gender, %	60.4
Patient weight, kg (mean, range)	82.34 (50–133)
Preoperative serum creatinine, mmol/L (mean, range)	84.47 (41–189)
RENAL score (median, IQR)	7 (5–9)
Warm ischemic time (mean, range)	30.30 (10–90)
Tumour size, cm^3 (mean, SD)	16.73 (22.86)
Piece size, cm^3 (mean, SD)	34.09 (35.44)
Resected renal parenchyma, cm^3 (mean, SD)	17.35 (28.02)

IQR: interquartile range; SD: standard deviation.

Table 2. RENAL nephrometry score characteristics

	1	2	3
Radius (R)	67 (67.7%)	30 (30.3%)	2 (2%)
Exophytic (E)	55 (59.8%)	25 (27.2%)	12 (13.0%)
Nearness (N)	36 (39.6%)	14 (15.4%)	41 (45.1%)
Location (L)	32 (35.6%)	23 (25.6%)	35 (38.9%)

To explore the predictive value of the different components of the RNS, we performed a univariate linear regression using R, E, N, and L on %IRF. Of the RENAL nephrometry variables (Table 2), E (R^2=0.04; p=0.034), N (R^2=0.043; p=0.05), and L (R^2=0.061; p=0.019) were predictive of inferior %IRF at intermediate followup.

Predictors of WIT

Analysis by univariate linear regression demonstrated that WIT was not predicted by tumour size (p=0.830), piece size (p=0.553), or RP (p=0.566). Furthermore, WIT was not predicted by RNS (p=0.579), or its components: R (p=0.290), E (p=0.675), N (p=0.361), or L (p=0.375) in univariate or multivariate (p=0.601) analysis.

WIT subgroup analyses

WIT subgroups (greater vs. less than 30 minutes) were not significantly different in tumour size (p=0.479), piece size (p=0.558), RP (p=0.874), or RNS (p=0.934). Furthermore, tumour size, piece size, and RP were not predictive of %IRF in WIT subgroups. Masses requiring less than 30 minutes of WIT for resection had significantly better postoperative %IRF at intermediate followup compared to masses requiring greater than 30 minutes of WIT (Fig. 4).

RNS was predictive of inferior %IRF only in tumours requiring less than 30 minutes of clamp time for resection (R^2=0.129; p=0.006) (Fig 3). Of RNS variables analyzed, R (R^2=0.113; p=0.009) and L (R^2=0.075; p=0.039) were predictive of inferior %IRF at intermediate followup, but only in tumours requiring less than 30 minutes of WIT for resection. None of the RNS variables were statistically significant predictors of %IRF in cases requiring WIT greater than 30 minutes.

Multivariate analysis

A multivariate regression was performed to predict %IRF from WIT and RNS. These variables statistically significantly predicted %IRF (F(2, 87)=9.883; R^2=0.185; p<0.0005). Both variables added significantly to the prediction (p<0.05). RNS variables with demonstrated linear relationships with %IRF in our sample (E, N, and L relative to polar lines) were not included in the multivariate analysis, as they are included in the RNS.

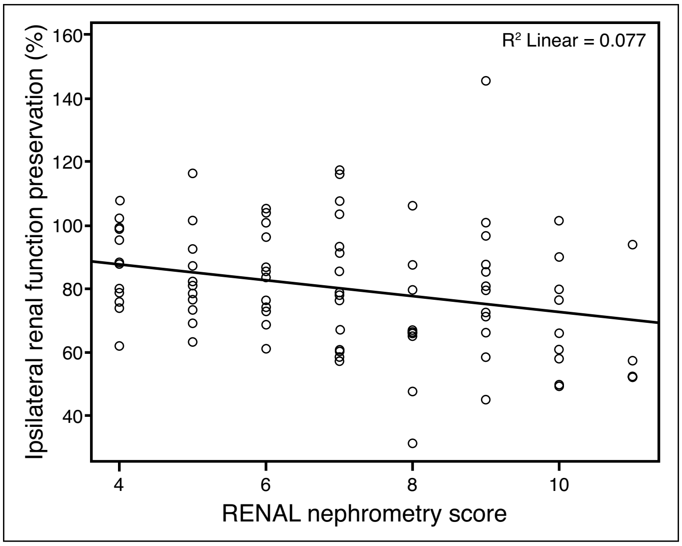

Fig. 1. RENAL nephrometry score correlates with % ipsilateral renal function preservation (%IRF) at intermediate postoperative followup (R^2=0.077; p=0.007).

WIT over time

Mean WIT decreased over time (Fig. 5). Furthermore, WIT between quartiles of cases over time were significantly different, as described in Fig. 5. The spread of WIT permitted analysis of effects between an era in which WIT was >40 minutes to one in which WIT was <20 minutes.

Discussion

Through use of nuclear renography, we have demonstrated that higher RNS and longer WIT were predictive of inferior %IRF following minimally invasive PN at 6–12-week

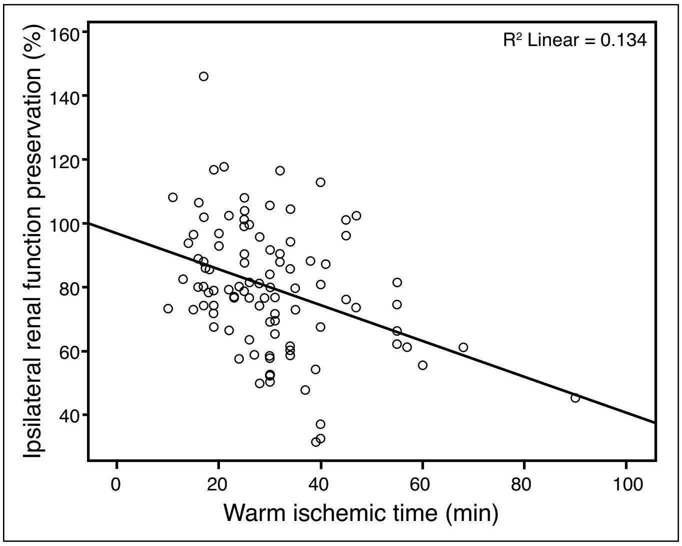

Fig. 2. Warm ischemic time (minutes) predicts reduction in % ipsilateral renal function preservation (%IRF) at intermediate postoperative followup (R^2=0.134; p<0.0005).

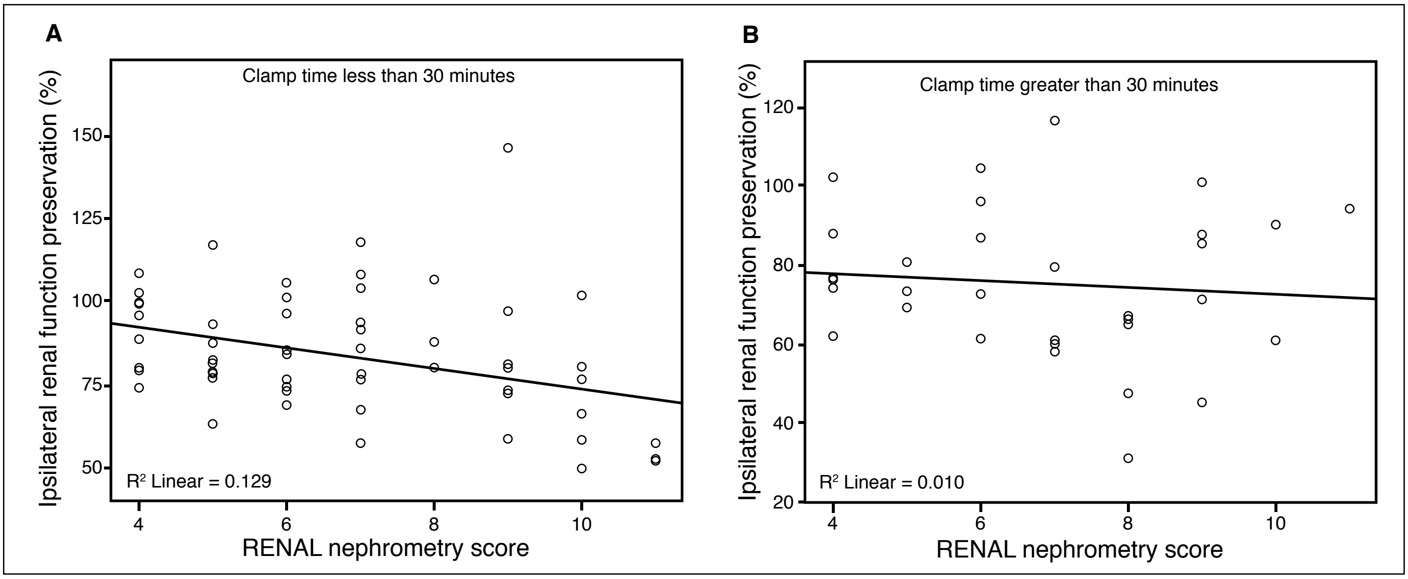

Fig. 3. RENAL nephrometry score predicts % preservation of ipsilateral renal function preservation (%IRF) with ***(A)*** warm ischemic time less than 30 minutes (R^2=0.129; p=0.006), but not ***(B)*** warm ischemic time greater than 30 minutes (p=0.479).

followup. The predictive effect of RNS, however, was lost in cases requiring WIT greater than 30 minutes. RNS characteristics that are associated with poorer %IRF include endophytic property, nearness to collecting system, and location relative to polar lines. WIT was not significantly different between laparoscopic and robotic-assisted PN groups, and was not predicted by tumour size, piece size, resected RP, or RNS.

RNS was initially described to standardize the classification of renal tumour size, location, and depth to improve description and comparison of renal masses in clinical practice and the urological literature.[13] Since its introduction, the utility of RNS in predicting functional outcomes has been of considerable interest, with some studies demonstrating that lower RNS confers better postoperative renal function preservation following PN.[9,11,16] Many of these studies used estimates of GFR using serum creatinine. Such calculations, however, do not account for compensatory contralateral hypertrophy. Nuclear renography, alternatively, measures individual renal perfusion and function through quantification of intravenous radioisotope (MAG3 or DTPA) clearance,[17] and can be used to evaluate individual kidney function while avoiding the overestimation associated with global estimates of GFR.[14]

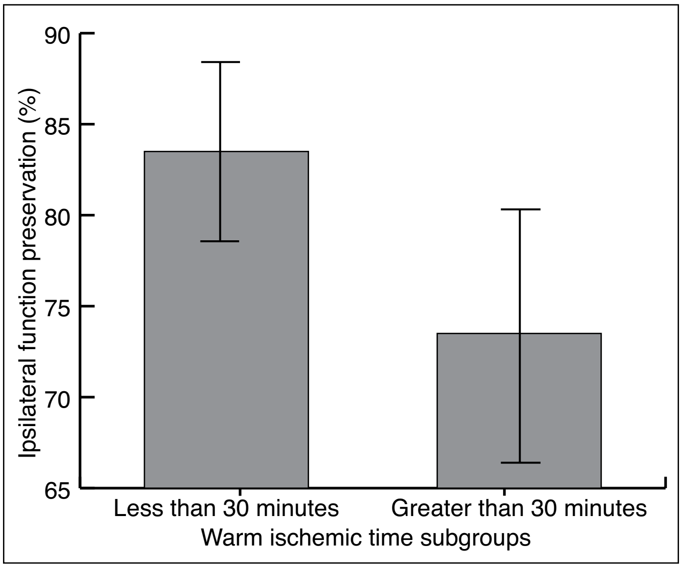

Fig. 4. Masses requiring less than 30 minutes of warm ischemic time for resection (0.83±0.19) had significantly better postoperative ipsilateral renal function preservation (%IRF) at intermediate followup compared to cases requiring more than 30 minutes of warm ischemic time (0.73±0.21; t(95)=2.472; p=0.015).

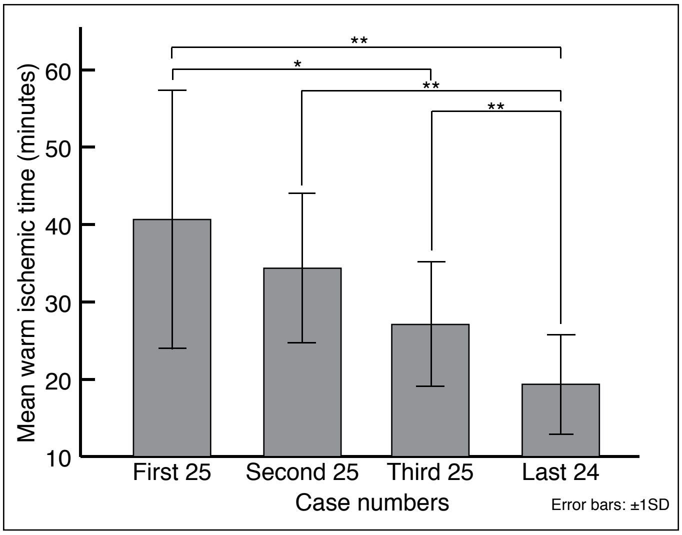

Fig. 5. Mean warm ischemic time (WIT) decreases as skills and techniques evolved over time. *if p<0.05; **if p<0.0005. SD: standard deviation.

In this study, we show that RNS is predictive of inferior %IRF at intermediate followup (6–12 weeks) in univariate and multivariate analysis. This is consistent with previous studies that have found a significant association between higher RNS and loss of functional renal parenchyma, blood loss, WIT, and perioperative complications in minimally invasive PN.[11,18] A similar study investigating IRF by Zargar,[14] however, found that RNS was not predictive of %IRF. This discrepancy in findings may be attributed to differences in WIT, as their study included zero ischemia techniques and had a median WIT of 20 minutes, compared with 29 minutes in our study. Our sample also contains a larger range of WIT, as our data was collected between 2002 and 2015 (compared with 2007 to 2013). As skills and techniques evolved during that period, WIT diminished (Fig. 5).

The RNS variables that predicted inferior %IRF in this series included: endophytic property, nearness to closest portion of the collecting system, and location relative to polar line. The relative clinical significance of these three characteristics, however, is complex, as they are not mutually exclusive. For example, a tumour that is near the collecting system is also likely to be endophytic in character. Preservation of ipsilateral renal function was better predicted by these variables in combination, rather than in isolation.

WIT was independently predictive of %IRF in our sample; this finding is consistent with other studies evaluating %IRF following PN.[14,19,20] Furthermore, WIT was independent of preoperative variables (tumour size, RNS, and RNS variables), as well as perioperative variables (piece size and RP). Efforts to reduce WIT during PN, therefore, should be pursued. Techniques to minimize WIT, such as early clamp release or off-clamp procedures, have been found to be associated with better postoperative renal function, shorter operative times, and fewer complications;[7,21] however, off-clamp procedures are currently reserved for small and peripheral renal masses due to technical demand[22] and have uncertain benefits when compared with on-clamp procedures with WIT less than 30 minutes.[8] In our sample, RNS, tumour radius, and tumour location were significantly associated with inferior %IRF in cases requiring WIT less than 30 minutes. This suggest that in tumours requiring WIT greater than 30 minutes, damage secondary to prolonged ischemia or intraoperative events requiring extended WIT are more predictive of %IRF than tumour complexity. Furthermore, our study fails to demonstrate that tumour complexity is correlated with prolonged WIT, which has previously been hypothesized.

The present study has a number of limitations and is part of a high-volume series performed over an extended period by a single surgeon in order to limit the effects of surgical approaches of multiple surgeons. Of this series, only 99 patients had the complete nuclear renogram data required for the analysis performed in this study. Furthermore, estimations of piece size and tumour size may be slightly inaccurate secondary to overestimation using cone and ellipsoid volume calculations or underestimated due to shrinkage effects from formalin fixation and tissue processing.[23] Lastly, there were few heminephrectomies or large central tumours in our sample, which may have limited the impact of the RNS on functional renal loss following PN.

Conclusion

For renal masses amenable to resection by minimally invasive PN, WIT is the most important variable to consider in efforts to optimize postoperative renal function preservation. Anatomical complexity (as measured by RNS), furthermore, should not guide decision-making with regards to surgical approach, but may be predictive of poorer %IRF when WIT are less than 30 minutes. Small volumes of renal parenchyma can be safely resected during PN without deterioration of renal function preservation in the affected renal unit.

Competing interests: The authors report no competing personal or financial interests.

This paper has been peer-reviewed.

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