Saving Nephrons: Current Surgical Options in Partial Nephrectomy

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Abstract: Partial nephrectomy has become the 'gold standard" for treatment of suspicious renal masses when surgery is required. The advantages in terms of renal preservation without compromising cancer control are well accepted provided lesions are carefully selected. The challenge now is to improve upon patient selection for partial nephrectomy, optimising the surgical technique and also considering how to reduce ischaemic time to the kidney that will remain. This article explores such issues and summarises the current status of partial nephrectomy.

Keywords: Kidney, neoplasms, surgery, nephrectomy, partial nephrectomy.

INTRODUCTION

In the last two decades we have witnessed a steady increase in the incidence of renal cancer [1, 2]. Widespread use of cross-sectional imaging has resulted in an increase of incidentally detected low-stage renal tumours [1, 3]. Historically all operable renal masses were treated by radical nephrectomy (RN). Partial Nephrectomy (PN) is now the current gold standard treatment of small renal masses <4cm and when possible masses 4 – 7cm [4, 5]. Compared to RN it is widely recognised that PN is a more challenging operation to perform. Multiple studies comparing PN and RN have demonstrated that PN has equivocal short and long-term outcomes regarding tumour control and minimising post-operative morbidity and mortality [6-9]. PN is also associated with a significantly lower risk of chronic renal impairment (CRI), which in itself is associated with adverse cardiovascular events, prolonged hospitalisation and mortality [4, 10-12]. As a result RN is virtually obsolete in the treatment for small renal masses <4cm.

Over the past decade open partial nephrectomy (OPN) has become well established for removal of small renal tumours but increasingly minimally invasive techniques, such as laparoscopic partial nephrectomy (LPN) and robotic partial nephrectomy (RPN) are being utilised with equivocal oncological outcomes at 7 years [13]. Open partial nephrectomy (OPN) is recognised by the European Association of Urology (EAU) guidelines as the standard of care, where as LPN should only be considered in experienced centres [14]. Renal 'nephrometry' scoring has been developed to quantify anatomical characteristics of tumours, which influence the feasibility of PN. Three nephrometry scoring systems: RENAL, PADUA and C-Index allow standardised pre-operative assessment of renal masses (discussed below).

Warm ischaemia time (WIT) is a term, which describes the period of surgically induced ischaemia to the kidney by clamping of the renal artery and/or vein at the renal hilum. This is an acknowledged step in the process of PN. Longer WIT is associated with minimally invasive techniques such as LPN and RPN [13]. Since prolonged WIT has been suggested to correlate with worse post-operative renal function, several 'reduced-ischaemia' techniques have been developed [15-20]. Two recent papers have introduced methods for a new and exciting concept of 'zero-ischaemia' PN [21-23].

This review will summarise and discuss current tumour classification methodologies, surgical approaches and methods of ischaemia, and the concept of 'zero-ischaemia' PN.

NEPHROMETRY SCORING

Renal 'nephrometry' developed from radiological analysis of morphological features of renal masses. The decision to proceed with PN or RN surgical can be clarified by the application of these various 'nephrometry' scoring systems. This allows for standardised pre-operative assessment of the pertinent characteristics of a renal mass. The three main nephrometry scoring systems include: RENAL, PADUA and C-Index.

RENAL Nephrometry

The 'RENAL' nephrometry system, first described by Kutikov *et al*. [24], includes the following tumour

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parameters: radius (tumour size as maximal diameter), exophytic/endophytic properties, nearness of tumour to the renal collecting system, anterior/posterior descriptor and the location in relation to the polar line. The acronym 'RENAL' is devised from a letter allocated for each component: R = radius, E = exophytic/endophytic, N = nearness to collecting system A = anterior/posterior and L = location. The summation for each feature (Table **1**) yields an overall nephrometry score [25].

Final RENAL scores can be grouped into predicted complexity: low (nephrometry sum 4 to 6), moderate (nephrometry sum 7 to 9) and high (nephrometry sum 10 to 12) [24].

Surgeons often view the renal mass size as the most important variable in the determination of case complexity. The radius is defined as the maximal diameter of the tumour in any given plane therefore adequate cross-sectional images with multi-planer reconstruction is essential to assess a mass for PN. Exophytic masses have points assigned based on the predominant feature of any axis and are generally considered easier to excise than endophytic masses. Nearness to collecting system aims to quantify the deepest portion of the mass close to the renal collecting system, which is relevant when assessing ease of resection.

The anterior/posterior position of the mass and location relative to the polar line assist in determining the most appropriate approach (transperitoneal Vs. retroperitoneal) or surgical technique (open Vs. laparoscopic Vs. robotic). The suffix *a* denotes an anterior position, *p* denotes a posterior position and *x* when neither designation is possible [24].

PADUA Scoring System

PADUA is an alternative classification system described by Ficarra *et al*. [26]: 'Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification of renal tumours'. The PADUA system categorizes tumours based on 7 anatomical parameters: 1) anterior/posterior position; 2) longitudinal location; 3) rim location; 4) relationship to sinus; 5) relationship to collecting system; 6) percentage of tumour extending into kidney; and 7) maximal cm tumour diameter.[1]

The main difference between RENAL and PADUA is that the latter assigns points separately for the nearness of the tumour to the renal sinus and to the collecting system whilst RENAL nephrometry groups these two criteria together as a single measurement (N = nearness to collecting system) [25]. In addition, the PADUA assesses lateral versus medial rim location and also independently factors involvement of the urinary collecting system [26].

Centrality Index

The Centrality Index (C-Index) by Simmons *et al.* is the final major nephrometry system. It differs from RENAL and PADUA as it focuses on tumour size and central location as the two most important criteria for determining technical difficulty of PN. The CI method was designed to enable measurements using standard 2-dimensional CT cross-sectional images and is based on the ratio of the distance (c) between the tumour center and the kidney center and the tumour radius (r). [25]. The C-Index measurement is a calculation of the length of a line drawn between the center of the tumour and the center of the kidney. This distance is then divided by the maximum tumour radius and the lower

Table 1: Summary of RENAL Nephrometry Scoring [24]

Anatomical Feature	1point	2points	3points
Radius (cm)	≤4	>4 to <7	≥7cm
Exophytic/Endophytic	≥50%	<50%	Entirely endophytic
Nearness of tumour to collecting system (mm)	≥7	>4 but <7	≤4
Anterior/ Posterior	No points assigned. Mass descriptive only – A or P or X which is suffixed after the total score.		
Location relative to polar lines	Entirely above the upper or below the lower polar line	Mass crosses polar line	>50% of mass crosses polar line OR mass crosses axial renal midline OR mass entirely between polar lines

Table 2: Summary of the PADUA Scoring System [25]

Anatomical Feature	Score or suffix
Anterior / Posterior Face	
Anterior	A (suffix)
Posterior	P (suffix)
Equal	No Suffix
Longitudinal polar location (in relation to sinus lines)	
Whole tumour or < 50% above/below sinus line	1
Whole tumour or > 50% inside sinus lines	2
Exophytic rate	
≥ 50%	1
<50%	2
100 % Endophytic	3
Renal rim location	
Lateral	1
Medial	2
Renal Sinus	
Not involved	1
Involved	2
Urinary collecting system	
Not involved	1
Involved	2
Tumour size (cm)	
≤ 4	1
4.1 - 7	2
> 7	3

the C-Index, the higher the degree of difficulty in resection. A lower C-Index score (for example CI = 1) equates to a more centrallly located tumour, therefore higher complexity PN, compared to a high C-index score (for example CI > 1) which would suggest a more exophytic tumour ameanable to PN [27]. The C-Index system is intended to complement TNM-based pathological staging and as a measured value it can quantify renal mass centrality [27].

SURGICAL OPTIONS FOR PARTIAL NEPHRECTOMY

Warm Ischaemia Time (WIT)

Renal ischaemia during PN partial nephrectomy is applied to avoid damage to the organ being treated. In general the technique used for PN includes exposure of renal vascular pedicle (vein and artery), wide tumour excision with renal-pedicle clamping following by closure of the renal defect [28]. Warm ischaemia time (WIT) from clamping of vessels at the renal hilum, is a widespread technique in PN aiding a bloodless field and meticulous dissection of tumour [21]. Warm ischaemia, where the kidney is not cooled to below body temperature (37.5°C) is the predominantly used technique in minimally invasive surgery. The major disadvantage of this technique is that it inflicts a theoretical ‘time-pressure’ on the operating surgeon to minimise WIT and complete resection within a reasonable time. The duration of safe WIT before renal function becomes irreversibly impaired is controversial. Becker *et al*. [29] conclude that clinical data suggests a safe WIT of up to 20 minutes whereas Thompson *et al*. [30] gives the value of 25 minutes but that there is a clear correlation between increasing WIT and decline in renal function. These results are to be kept in mind when assessing the relative merits of each partial nephrectomy approach.

Open Partial Nephrectomy (OPN) Vs. Laparoscopic Partial Nephrectomy (LPN)

A very large cohort study by Gill *et al*. [13] involving 1,800 patients at 3 large referral centres compared OPN with LPN for single tumours (T1) 7cm or less. The cases were analysed using a multivariable analysis with covariates of age, tumour size, contralateral kidney function and bilateral disease status. Numerous statistically significant results emerged as could be expected with such a high-powered study. In the LPN group the WIT was 69% longer (95%CI 62%-77%) with a mean of 30.7 minutes compared to 20.1 in the OPN cohort. Note cold ischaemia was rarely used in both the LPN and OPN cohorts. Additionally there was greater post-operative morbidity in terms of urological and non-urological complications. However there were equivalent results in renal functional outcomes at 3 month follow up and also in 3-year cancer specific survival. Moreover, the LPN approach offered the advantage of decreased operation time, estimated blood loss and hospital length of stay.

A study of 200 patients matched for age, sex and tumour size have been followed for a mean of 3.6 years [31]. Again, surgical and hospital length of stay times were lower in the LPN group. Ischaemia times were lower in the LPN cohort but were primarily WIT compared to cold ischaemia time in the OPN cohort. In this study there were no significant differences in complication rate or in follow up renal function (eGFR) or estimates of 5-year recurrence free survival.

While peri-operative outcome measures may differ with OPN vs. LPN it does appear that long term outcome measures of renal function and disease free survival are comparable between the two approaches.

Open (OPN) Vs. Robotic (RPN)

A single centre retrospective study in South Korea by Lee at al compared OPN to RPN for small renal masses (<4cm) in size in 303 patients, 234 in the OPN series and 69 in the RPN series [32]. The two cohorts were not significantly different in terms of age, sex, tumour size and location. While RPN was associated with longer operating time (192.42mins vs. 142.77mins; P<0.001) and warm ischaemia time (22.99mins vs. 18.14mins, P<0.001), the length of hospital stay (6.20 days vs. 8.90 days, P<0.001) and amount of post-operative analgesia was reduced (P<0.001) [32]. There were no statistically significant differences in pathological outcome including positive resection margins, postoperative renal function as measured by serum creatinine and eGFR or in post-operative complications. The authors note that the RPN series was performed as the surgeons were advancing along the robotic learning curve and the latest 30 in the series had a mean ischaemia time of 19.5 minutes.

Robotic (RPN) Vs. Laparoscopic (LPN)

There are a few papers in the literature that compare the outcomes of laparoscopic and robot-assisted approaches to partial nephrectomy. A large, multi-institution retrospective review by Benway *et al*. of 247 cases across 3 academic centres evaluated 129 RPN and 118 LPN procedures performed by 3 surgeons experienced in minimally invasive procedures [33]. Both groups were equivalent with respect to age, gender, BMI, ASA score and tumour size, although no statistical evidence is provided. The most significant result was the shorter WIT in the RPN group (19.7 vs. 28.4 minutes; P<0.0001) and for the subset of "complex" tumours (defined as those requiring repair to the collecting system) the difference was also significant (25.9 vs. 36.7 minutes; P=0.0002). There were also small but significant reductions in estimated blood loss (EBL) and hospital stay in the RPN group. Length of operation, positive margin rates and post-operative complications were similar between the two cohorts.

A single surgeon, single institution, case matched retrospective cohort study by Haber *et al*. of 150 patients yielded slightly differing results [34]. The 75 patients in each cohort had no significant difference in age, gender, BMI, ASA score, pre-operative eGFR or tumour size. This study showed no difference in WIT and indeed a higher EBL in the RPN group (323 vs. 222 ml; P=0.01). No significant difference was found in operation time, length of hospital stay, post-operative change in renal function and complications.

A very recent retrospective analysis from the same group as the Haber study by Long *et al.* compared RPN and LPN in 381 patients for "complex renal masses" defined as RENAL score greater than or equal to 7 [35]. Again the cohorts were demographically and medically similar with only a marginally lower pre-operative eGFR in the LPN group (81.1 vs. 86.1; P=0.02). The significant results were that the LPN cohort had a higher decrease in eGFR post op (16.0% vs. 12.6%; P=0.03), though the mean follow up is less for the RPN group. The LPN cohort also had an increased rate of conversion to RN (11.5% vs. 1%; P<0.001). The authors attribute this to robotic instruments being better articulated. All other major parameters were similar between the cohorts including WIT, EBL and post-operative complications.

These papers certainly would suggest the superiority of the robotic approach. Aron [36] and

Benway [33] highlight the technical challenges of LPN particularly with regard to tumour dissection and intracorporeal suturing have limited its dissemination. With the robotic advances in stereoscopic vision and "wristed" instrumentation, RPN may become the preferred and more widely used minimally invasive surgical technique, as is the case for radical prostatectomy. However, Aron illustrates, the time pressures of the PN procedure once hilar clamping is performed magnify the problems that occur with robot malfunction. Since WIT is a limiting factor, LPN is considered a challenging method even for an experienced surgeon [23]. Well-trained assistants and staff are required for safe operation of RPN.

The retrospective nature of these studies introduces an inherent selection bias in the two cohorts. It is interesting to note that in the Lee [32] and Long [35] studies, the RPN cohort had a significant higher BMI than the other cohort, this may reflect some underlying bias. As yet no prospective randomised comparisons between the three known PN techniques are in the literature.

CURRENT OPTIONS FOR INDUCING ISCHAEMIA IN PARTIAL NEPHRECTOMY

It has long been recognised that the most important factor governing the return of renal function remains the duration of WIT or the amount of time during which renal blood flow is interrupted [37]. The traditional method to produce operative ischaemia is either by cross clamping of renal vascular pedicle (warm ischaemia) or by cooling methods (cold ischaemia). Although the safe duration of induced ischaemia remains controversial, recent studies suggest partial nephrectomy without clamping for suitable tumours may reduce the risk of acute renal failure (ARF) or CRI [38].

Cold ischaemia adopts the method of global cooling of the kidney, as the hypothermic effect protects renal tissues from ischaemic insults [39]. Renal metabolic activity is suspended below 20°C and the optimal temperature for effective renal hypothermia for PN is less than 15°C [39]. This has been observed and used in kidney transplantation although data relevant to short periods of ischaemia in human kidneys is inconclusive [40, 41]. The most common option for cold-ischaemia is to use superficial sterile ice during OPN, and to trans-arterial (TAP) and trans-ureteral (TAU) perfusions during LPN. The other advanced method is to use Freka-Gelice (FG), a new gel like cooling material which is currently on trial [39]. In a series of 660 OPNs by Lane *et al.* the efficacy of cold ischaemia vs. warm ischaemia was analysed [40]. Results showed an equivocal median decrease in eGFR with warm vs. cold ischaemia at 3 months (22% vs. 21%; p = 0.7) [40]. It concluded that within the normal conventions of PN, ischaemia time was not an independent predictor of post-op renal function [40]. Kijvikai *et al.* formulated a method that can be used in LPN that allows effective renal cooling (<20°C) and a hypothermic window for the entire ischaemic time (average 30.4 minutes) [15].

The degree of surgical exposure to the kidney is greater in OPN, compared to LPN and RPN, which can allow for a 'manual compression' technique. One method is to apply a 'lasso' proximal to the renal tumour, in relation to the renal hilum, with umbilical tape (or similar) which is then compressed with a Kelly Mosquito clamp (or similar) [42]. No hilar dissection for renal vascular structures is performed. Tumour resection with adequate margin is then carried out, with the tape 2 to 3cm from the resection margin. Tension can be adjusted according to bleeding but care is taken to avoid excessive strain on the renal parenchyma. A retrospective case-control, single surgeon study by Ko *et al*. [42] compared two matched cohorts of 40 OPNs with either manual parenchymal compression (Group 1) or either conventional vascular hilar clamping (Group 2). Operative time was significantly higher in Group 2 (132.4±17.7 vs 151.4±21.4 minutes: p = 0.031) in addition to EBL, which was slightly higher in this group (173.7±11.5 vs. 211.2±43.8 ml; p = 0.06). Comparison of pre-operative and post-operative serum creatinine levels at 30-days demonstrated a statistically significant trend between the two groups, with a trend of more elevated levels in Group 2 (p<0.001). All serum creatinine levels were within normal limits.

Wszolek at al published a case series of 104 PNs (29 with hilar clamping vs. 75 non- hilar clamping), which showed that non-hilar clamping PN partial could diminish morbidity and mortality especially in patients with solitary kidney [37]. The two groups had similar pre-operative eGFR and the non-clamping group had a smaller per cent decrease in late eGFR, measured around 6 months post-op, compared to the clamping group (11.8% vs. 17.7%; p = 0.002) [37].

Selective clamping of renal parenchyma around the tumour rather than hilar vessel clamping allows for resection of tumour with an adequate surgical margin and a relatively bloodless field [16]. This technical modification is performed using a Satinsky or a curved

DeBakey aortic clamp (or similar) [16, 28]. The rationale is that renal ischaemia is restricted to normal tissue immediately adjacent to the tumour and has been suggested to reduce the incidence of temporary dialysis or development of CRI during follow-up periods [16, 28, 43]. This technique is generally restricted to OPN. A modification of this open technique is manual digital pressure that is applied around the tumour, similarly to a clamp, to aid a bloodless field during excision and closure of the renal defect.

A non-randomized study by Nguyen *et al.* analysed 100 consecutive LPNs the initial 50 of which patients underwent standard LPN and the final 50 patients had 'early unclamping' LPN [17]. WIT was reduced by more than 50% in the early-unclamping compared to the standard LPN group (13.9 vs. 31.1 minutes; $p < 0.0001$) [17]. Baumert *et al.* compared a similar early unclamping technique, which involved unclamping of renal vessels after one or two running sutures of the renal defect, to standard LPN in 40 patients in total [44]. Results were similar in that WIT was reduced with the modified closure and early-unclamping was significantly less than the control group (27.2+/-5 min vs. 13.7 +/-4min; $p < 0.01$) [44]. A reduced median WIT of 16 minutes (11 to 25) using early-unclamping has been achieved in RPN [20].

Orvieto *et al.* have introduced a LPN method that uses the application of absorbable clips in replacement for knot-tying when suturing the renal defect [18]. Despite being a reproducible and potentially time-saving technique median WIT was a respectable 33.1 minutes (range 13 – 55) [18]. Radiofrequency coagulation alongside non-clamping has been successful for exophytic and small tumours (median nephrometry score = 5) undergoing LPN [19].

'ZERO-ISCHAEMIA'

It is well recognised that longer duration of renal ischaemia during PN negatively effects post-operative renal function [30]. As previously discussed ischaemia time varies according to operative method chosen, with more technically challenging minimally invasive surgery such as LPN and RPN.

The concept of 'zero-ischaemia' PN was first explored by Gill *et al*. [21]. In a prospective study of 13 LPN and 3 RPN they demonstrated that a combined technique of selective branch microdissection of renal artery/vein and pharmacologically induced hypotension, without renal hilum clamping, was successful for resection of laterally based T1 renal tumours [21]. This technique requires: a pre-operative contrast computer tomography (CT) or MRI scan with 3D reconstruction of extra-renal hilar anatomy; micro-dissection and neurosurgical bulldog clamps for tumour feeding arterial braches and pharmacologically induced hypotension. This initial study showed 100% negative surgical margin for all cases [21]. No difference was found between pre- and post-operative serum creatinine and eGFR [21], but due to the short interval between samples (median 3 days) this was statistically insignificant and longer follow-up of post-operative renal function is needed.

A follow-up prospective cohort study by Ng *et al*. compared a technique of anatomic vascular micro dissection (VMD) to a non-VMD technique in a total of 44-patients in 2 matched cohorts undergoing LPN or RPN for medially located renal tumours [22]. Anatomic VMD specifically involves microsurgical clipping of one or more tumour-specific, higher order renal branches [22].

The tumour characteristics in the group 1 (VMD technique) compared to group 2 (non-VMD) were larger in size (4.3 vs. 2.6cm; $p = 0.011$) had higher RENAL score scoring tumours (median 8 vs. 6; p 0.013) and a shorter tumour-to-hilum distance (1.46 vs. 3.26 cm; $p = 0.0002$) [22]. WIT time and positive tumour margin rate was zero in all cases in both groups [22]. It demonstrated that anatomic VMD is technically feasible for hilar and medially located renal tumours (median RENAL score 8.0) [22]. Median change in pre- and post-operative creatinine (0.2 vs 0.1; $p = 0.57$) and eGFR (-10.2 vs -11.2; $p = 0.9$) was measured at 2 months [22]. Despite conclusions from the study that irrespective of central tumour location, renal vein / artery clamping is unnecessary for renal tumours undergoing LPN or RPN there was insufficient long-term outcome data justifying the specific anatomic VMD technique. The study also lacked a description of the zero-ischaemia surgical technique used for the non-VMD cohort. Furthermore, the sample size was small (N=44) and a single experienced surgeon performed all operations. It appears that anatomic VMD is selective for renal tumours with central location and short feeding braches amenable to micro-clipping [22]. Facilities for pre-operative CT or MRI 3D reconstruction imaging also needs to be available to aid the 'vascular road-map' supplying the tumour.

Simone *et al*. conducted a prospective case series of 101 patients that underwent a zero-ischaemia sutureless LPN technique for low RENAL score tumours between 2003 and 2010 [23]. No hilar clamping was performed and excision of tumour was achieved by LigaSureTM (Coviden, Boulder, CO, USA) followed by monopolar and biological coagulation of the surface of the renal defect without primary closure [23]. Cases inclusion criteria were: tumour width ≤4cm, intraparenchymal depth ≤1.5cm with exclusion criteria: >50% endophytic growth and nearness of <0.5cm to urinary collecting system [23].

Median RENAL nephrometry score and PADUA scores were 4 and 6 respectively [23]. The specific sutureless technique was successfully performed in all but four cases (n=97) [23]. Open conversion rate was zero and all cases were performed without hilar clamping and therefore zero-ischaemia [23]. Surgical margins were negative in all cases on histopathology with one case of ipsilateral recurrence of pT1b clear cell RCC on CT at 57 months [23]. Renal function (serum creatinine and eGFR) was measured pre-operatively and at 3 and 12 months post-operation [23]. Median decrease in split eGFR in the treated kidney at 3 and 12 months was 3% (0-9; p = 0.122) and 1% (0-5); p = 0.665) and serum creatinine (mg/dL) level increases were 0.1 (0-0.5; p = 0.104) and 0.09 (-0.2 to 0.5; p = 0.157) respectively [23]. This technique was associated with an 8.9% (n=9) complication rate (Clavien grades 1 - 2), which might be partly attributable to the low nephrometry score of this series [23].

CONCLUSION

Partial nephrectomy is a well-established technique for the treatment of suspicious small renal masses. Nephrometry scoring quantifies anatomical characteristics of masses, thereby guiding surgical resection. Increasing numbers of PNs are being performed *via* minimally invasive techniques such as LPN and RPN, compared to the traditional open technique. Ischaemia time still remains a pertinent factor which influences post-operative renal function. Various reno-protective techniques are available, most utilised are cold ischaemia and early-unclamping. 'Zero-ischaemia' is an exciting new concept that requires further evaluation.

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