

# Current Status of Nephron-Sparing Surgery (NSS) in the Management of Renal Tumours

Vivek Venkatramani<sup>1</sup> · Sanjaya Swain<sup>1</sup> · Ramgopal Satyanarayana<sup>1</sup> · Dipen J. Parekh<sup>1</sup>

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**Abstract** Nephron-sparing surgery has emerged as the surgical treatment of choice for small renal masses over the past two decades, replacing the traditional teaching of radical nephrectomy for renal cell carcinoma. With time, there has been an evolution in the techniques and indications for partial nephrectomy. This review summarizes the current status of nephron-sparing surgery for renal carcinoma and also deals with the future of this procedure.

**Keywords** Nephron-sparing surgery · Renal tumours · Renal cell carcinoma

## Introduction

Renal cell carcinoma (RCC) accounts for about 3% of all adult malignancies, occurring at a rate of 4.4 to 11.1/100,000 person-years [1, 2]. It is the most lethal of urological malignancies with close to 40% of patients dying as a result of their cancer [3]. RCC was initially found to be resistant to systemic treatment, and surgical management was the only possibility of cure for localized tumours. As a result, Robson's classic radical nephrectomy (RN), which involved complete excision of the contents of Gerota's fascia including the kidney and adrenal gland, with early vascular control and lymphadenectomy from the crus of the diaphragm to the aortic bifurcation, remained the mainstay of treatment for almost 50 years [1, 2]. Robson was able to demonstrate an overall 5-year

survival of 52% in the large symptomatic masses that predominated at that time, and radical nephrectomy remained the standard to which all treatments for RCC were compared [2].

## Evolution of Nephron-Sparing Surgery

Partial nephrectomy (PN) was first described by Wells in 1884, for a perirenal fibrolipoma [1]. Subsequently in 1887, Czerny described its use for a malignant renal angiosarcoma [4]. In the 1950s, Vermooten strengthened the rationale for PN when he showed that a 1-cm margin was adequate for local tumour control [4]. However, the high morbidity associated with the procedure in the form of bleeding and urinary fistula, coupled with the success of Robson's RN, led to a poor adoption of PN by the urological community [4]. At this time, PN was relegated to absolute indications wherein radical nephrectomy would render the patient anephric or dialysis dependent, for example, tumours in a solitary kidney or bilateral renal tumours.

Evolution in surgical techniques for open stone surgery and renal trauma in the 1960s and 1970s, with the development of renal cooling, reno-protective techniques and renorrhaphy, coupled with greater knowledge of the renal vascular and collecting system anatomy, led to resurgence in interest in PN for renal masses [4]. Simultaneously, the development of modern imaging techniques including ultrasound (US) and computed tomography (CT) led to the detection of a new class of small, incidentally detected renal lesions (small renal masses—SRM) for whom traditional RN seemed an overkill [5]. Further understanding of the biology of cancer in general, and a move away from the Halstedian concept of wider excisions, also strengthened interest in PN. In 1993, Licht and Novick reported their experience of 241 cases with a normal

✉ Dipen J. Parekh  
parekhd@med.miami.edu

<sup>1</sup> Department of Urology, University of Miami Miller School of Medicine, Miami, FL, USA

contralateral kidney that underwent renal tumour resection alone [6]. The median tumour size was 3.5 cm, and they demonstrated only two local recurrences with a 95% survival at 3 years [6]. The term ‘nephron-sparing surgery’ (NSS) was coined, and a new era in the management of RCC dawned.

## Rationale for NSS

### Renal Tumour Biology

While the traditional large symptomatic renal masses were often lethal, >70% of tumours diagnosed today are small and incidentally detected on imaging for other indications. Despite improvements in imaging modalities, they remain non-specific for the diagnosis of malignancy and nearly 20% of SRMs are found to be benign on histopathology with diagnoses including oncocytoma, angiomyolipoma, metanephric adenoma or hemorrhagic cyst [7]. The incidence of benign tumours increases from 7% for tumours >7 cm to 38% for tumours <1 cm [8]. However, Nguyen and Gill have shown that up to 5% of tumours <2 cm can metastasize, thereby underscoring the importance of NSS as a perfect means of achieving tumour control with maximum organ preservation [9].

### Oncological Efficacy of NSS

A number of studies in the late 1990s and early 2000s demonstrated that NSS provided equivalent oncological outcomes to RN for tumours <4 cm [1]. Long-term results published by Fergany et al. revealed cancer-specific survival of 98% at 5 years and 92% at 10 years for patients who underwent PN for tumours <4 cm, regardless of the indication for surgery (i.e. absolute or elective) [10]. Numerous other investigators found no difference in disease-specific survival, progression-free survival or recurrence-free survival between RN and NSS, especially in tumours <5 cm [1]. A disease-specific survival of 90–100% was found in several series for elective NSS for SRMs [1].

Initial objections to NSS for elective indications included the possibility of multifocal RCC and the risk of positive surgical margins and subsequent tumour recurrence. Many studies have since demonstrated that gross resection of all tumour, as assessed intraoperatively by the surgeon, with microscopically negative margins, allows excellent local control without increased risk of recurrence, even without the need for a 1-cm margin of normal renal parenchyma [7, 11]. Routine frozen section of the resection bed is also no longer recommended [11]. This finding also allowed surgeons to offer NSS to patients with perihilar, sinus or endophytic tumours in whom the 1-cm margin was previously a barrier.

Investigators from Mayo Clinic and MSKCC reported that a positive surgical margin (5.5% in a series of 1344 patients) had no association with an increased risk of tumour recurrence or metastatic disease [12]. Other studies showed similar outcomes, and currently patients with a positive margin can be safely observed with regular surveillance imaging without the need for a ‘completion’ nephrectomy [7, 12].

Multifocal RCC can occur sporadically or as part of familial renal cancer syndromes like von Hippel-Lindau (vHL) disease. Nephron-sparing surgery in these cases has shown to be safe and effective with minimal risk of recurrence, and multifocal RCC should no longer trigger RN [1, 4]. In these cases, even simple enucleation of tumours has demonstrated almost equivalent efficacy to PN; however, full efforts must be made to achieve complete tumour resection when feasible [13]. The use of intraoperative US by surgeons to identify multifocal disease and allow complete resection of all tumours in a kidney has also been reported [4].

### Medical Renal Disease and Preservation of Renal Function

In contrast to renal donors, a population to which they are often compared, patients with RCC are generally older and often have comorbidities with the potential to worsen renal function like obesity, hypertension or diabetes mellitus. Additionally, beyond the age of 60 years, studies have shown a progressive reduction in the number of nephrons and glomerular filtration rate (GFR) [14]. Pathological studies of the non-neoplastic portion of nephrectomy (PN or RN) specimens have further demonstrated a high degree of unsuspected underlying renal disease in patients with RCC, with Huang et al. showing that almost 26% had preexisting chronic kidney disease (CKD) [15, 16]. These findings indicate that many patients with RCC do not have the renal reserve to tolerate an RN and would be better served with NSS.

Chronic kidney disease, defined as a GFR <60 ml/min/m<sup>2</sup>, is a growing health problem all over the world, and it is estimated that by the year 2030, 2 million adults in the USA will require renal replacement therapy [7]. CKD has been shown to be an independent risk factor for cardiovascular disease, and studies have shown an increased mortality and hospitalization risk as GFR declines [7]. Studies from Mayo Clinic and MSKCC further showed that patients undergoing RN were more likely to have a serum creatinine >2 mg% and proteinuria postoperatively [17, 18]. Similarly, Huang et al. showed in a series of 662 patients with a normal serum creatinine and RCC who underwent PN or RN that even on multivariate analysis, RN was an independent risk factor for the postoperative development of CKD [16]. Furthermore, Thompson et al., from Mayo Clinic, discovered that in patients younger than 65 years at the time of surgery, RN was associated with

an increased risk of death, even after controlling for common comorbid illnesses and tumour histology [19].

There is therefore strong data to suggest that routine RN for SRMs should be avoided in order to preserve the renal and cardiovascular health of the individual. Emphasis should be laid on increasing the utilization of NSS in these cases, as studies have demonstrated a statistically significant decrease in the risk of CKD after NSS [2].

## Indications for NSS

### Standard Indications for NSS

Indications for NSS can be classified as absolute, relative or elective [1].

Absolute indications include RCC in patients with an anatomically or functionally solitary kidney, bilateral tumours or patients with CKD [1]. In all cases, the tumours should be amenable to complete excision by a PN.

Relative indications include patients with suspected RCC in whom the normal kidney is threatened by local, systemic or genetic conditions that could affect renal function. These include a variety of conditions like nephrolithiasis, chronic pyelonephritis, hypertension, diabetes mellitus and other causes of glomerulopathy. In these cases, the risk-benefit ratio of NSS must be assessed individually vis-à-vis the risk of progression of the renal disease [1].

Elective indications include the group of patients with a contralateral normal kidney. As has been seen, NSS remains the procedure of choice even in this group of patients for a tumour size <4 cm [1, 4, 13].

**T1b Tumours** Numerous studies have emerged to show that elective PN can achieve equivalent oncological outcomes to RN for selected T1b tumours [13, 20]. A report combining the Mayo Clinic and MSKCC databases showed no differences in survival between PN and RN in 1159 patients with T1b tumours [21]. These studies have also shown better preservation of renal function in patients undergoing PN [22]. While laparoscopic and robotic approaches have been reported with success in experienced hands, open PN remains the technique of choice for T1b tumours [22]. Current recommendations therefore suggest that whenever technically possible, tumours between 4 and 7 cm should also be offered NSS [13, 22, 23].

### Expanding Indications for NSS

1. *T2 tumours*: In a study using the SEER database, Hansen et al. demonstrated no significant difference in cancer-specific mortality among patients who underwent PN or RN for tumours larger than 7 cm [24]. Other studies have also corroborated this finding [25, 26]. Kopp et al. further

demonstrated a lower decline in GFR following PN in this cohort; however, this was not seen in patients with more complex and endophytic tumours in whom less parenchyma may be preserved [26]. More surgeons are now offering NSS for T2 tumours if surgically feasible [23, 25].

2. *Downstaging of tumours with targeted therapy*: Targeted therapy has shown efficacy in the downstaging of locally advanced tumours including those with caval thrombi in anecdotal reports [27]. Current evidence suggests that targeted therapy could be effective in downstaging tumours to allow NSS, especially in those with absolute indications [28, 29]. A phase II trial of 25 patients using 8 weeks of neoadjuvant pazopanib in localized RCC (median tumour size 7.3 cm) showed that NSS was possible in 6 out of 13 patients in whom it was not possible at baseline [30]. A reduction in tumour volume was noted in 92% of cases [30]. This potentially opens up a whole new avenue of patients who would be made eligible for NSS.

## Tumour Nephrometry Systems

Multiple scoring systems have been described to better characterize renal lesions with respect to the probability of sparing uninvolved renal parenchyma during PN [31]. A renal CT scan is a prerequisite of imaging renal masses, and most scoring systems are based on this study. With a number of minimally invasive techniques available for management of RCC, these systems aim to provide a standard way of reporting anatomical tumour features in order to determine surgical complexity in order to ease comparison [32]. The most commonly used score is the R.E.N.A.L score devised by Kutikov et al. (Table 1) [33]. Others include the PADUA score and the c-index [32]. All these scores have demonstrated excellent interobserver reliability, and their use in combination with BMI and the Charlson comorbidity index has been shown to improve the predictive ability for complications [32]. They may also allow better preoperative planning and patient counselling in the future.

## Surgical Technique

### Principles of Surgery

Partial nephrectomy is a technically challenging surgery, and more extensive imaging studies are required preoperatively. The usefulness of a triphasic renal protocol CT scan with 3-D volume rendering and CT angiography for accurately demonstrating the renal parenchyma and vascular anatomy has been shown in a number of studies [1, 34].

**Table 1** R.E.N.A.L score (Kuttikov and Uzzo) [33]

Points	1	2	3
(R)adius (maximal diameter in cm)	≤4	>4 but <7	>7
(E)xophytic/endophytic properties	≥50%	<50%	Entirely endophytic
(N)earness of the tumour to the collecting system or sinus (mm)	>7	>4 but <7	>7
(A)nterior/Posterior	No points given. Mass assigned descriptor of a, p, x		
(L)ocation relative to the polar lines* *suffix “h” assigned if the tumour touches the main renal artery or vein	Lesion entirely above or below upper and lower polar lines	Lesion crosses polar line	>50% crosses polar line/mass crosses midline/mass lies completely between polar lines

Scores: 4–6, low complexity; 7–9, moderate complexity; 10–12, high complexity

Whatever the approach, the basic surgical principles of NSS involve the following:

- Early vascular control
- Minimizing renal ischaemia
- Complete circumferential tumour excision with negative margins
- Precise closure of the collecting system
- Careful haemostasis
- Closure of the renal defect [1, 34]

Open PN involves an extraperitoneal flank approach with or without rib resection to resect the tumour [1, 34].

As surgical technique and experience have improved, perioperative complications have reduced in incidence. Urinary leak or fistula remains the most troublesome surgical complication with an incidence ranging from 1.4 to 17.4% [1]. Factors associated with urinary leak include larger tumours, endophytic location and repair of the collecting system intraoperatively [34]. Intraoperative injection of methylene blue via a ureteral catheter can help identify entry into the collecting system and aid in repair [1]. Most urinary leaks resolve spontaneously in 6–8 weeks, but stenting or percutaneous drainage may be required in a small percentage [34]. Postoperative haemorrhage has been reported in about 2% of cases [1]. Delayed bleeding is usually due to formation of a pseudoaneurysm or arteriovenous fistula, and selective renal arteriogram with coil embolization is usually successful in controlling this complication [34]. Careful technique with avoidance of large haemostatic sutures into the renal sinus can help minimize this [34].

### Renal Ischaemia

During PN, the renal vessels are often clamped in order to reduce bleeding and improve visualization of the tumour bed in order to facilitate complete tumour excision and ligate vascular structures or repair the collecting system [34]. As the kidney has an aerobic metabolism, it has been assumed that

it is sensitive to ischaemia [34]. Our understanding of renal ischaemia has been based on animal studies, the background of renal transplantation and retrospective human studies where confounding factors like blood loss and surgery play a role [35]. Based on these data, limits of 20 to 35 min for warm and cold ischaemia were proposed [1, 34, 36]. However, recent evidence throws some doubt on this practice. Parekh et al. studied the renal response to ischaemia using biomarkers and renal biopsy in 40 cases of open PN. The mean ischaemia time was 37.4 min. While there was a small, temporary increase in the serum creatinine, they observed that serum cystatin C remained stable and renal functional changes did not correlate with ischaemia time. The structural changes observed on renal biopsy were much less significant than those observed in animal studies with similar ischaemia times, calling into question the extrapolation of data from animal studies. They therefore concluded that human kidneys could safely tolerate 30–60 min of ischaemia without functional loss [35]. Their 1-year data further showed no correlation between ischaemia time and the change in renal function [37]. Other contemporary reports also suggest that the volume of renal parenchyma preserved and preoperative renal function are the most important factors affecting long-term renal function following PN, with ischaemia time probably only affecting short-term renal function [38]. These studies suggest that the utilization of partial nephrectomy can be safely expanded without undue fear of renal ischaemia, further enabling optimal oncological outcomes to be achieved.

Renoprotective strategies involve the use of mannitol infusion and cooling the kidney to 15–20 °C by using ice slush in order to decrease its metabolism and safely allow prolongation of the ischaemia time (if ischaemia time >30 min is anticipated) [34, 39]. Numerous techniques to reduce ischaemia have been described; however, their clinical applicability is debatable. Surgeons at the Lahey Clinic have described a fully perfused PN, but the excess blood loss and technical difficulty of this procedure are significant limitations [36]. An early unclamping technique wherein the renal vascular occlusion is removed following placement of deep parenchymal sutures

was described by Gill et al. [38] Clamping of the renal artery alone has been thought to allow oxygenation of parenchyma by venous backflow; however, animal and clinical studies have shown limited benefit [36]. Manual compression of the renal parenchyma has not been well studied and can potentially cause trauma, while intermittent clamping could be harmful and should be avoided [36]. Eisenberg et al. described a technique of zero ischaemia laparoscopic PN wherein mean arterial pressure was maintained at 50–60 mmHg using pharmacological agents, combined with selective branch microdissection of the renal vasculature in the renal sinus, thereby avoiding global renal ischaemia [40]. However, the possibility of hypotensive injury to the contralateral kidney and other organs, combined with the need for intense invasive monitoring, has restricted the acceptability of this technique [36, 40]. The magnification provided by the robotic system has helped allow dissection of tertiary and quaternary branches of renal vessels that selectively supply the tumour, thereby reducing the need for global ischaemia in hilar tumours [38, 41]. Tumour-specific devascularization can be confirmed with the use of colour Doppler US or the injection of indocyanin green with a robot with near-infrared vision (NIRF technique) [38, 42, 43]. The majority of these techniques remain experimental and have not gained general acceptability in the urological community. We do not suggest that renal ischaemia should not be taken seriously. We believe, however, that the current practice of using ischaemia duration as a dichotomous marker suggesting renal injury and the commonly suggested ‘safe’ ischaemia values of 20 or 30 min and, recently, zero ischaemia is based on flawed evidence. Most urologists are able to perform renal tumour excision and parenchymal reconstruction in a timely manner using renal hilar clamping.

### Status of Minimally Invasive PN

The introduction of laparoscopic partial nephrectomy (LPN) helped reduce the morbidity of an open incision and allowed for faster recovery [44]. Early series, however, revealed a higher rate of complications, as well as a steep learning curve, restricting its use to specialized centres, and favourable, exophytic tumours in patients with normal kidneys [44]. With increasing experience, specialized centres began reporting complication rates and oncological outcomes equivalent to open surgery [44]. The limited movement of laparoscopic instruments made tumour excision, closure of the parenchymal defect and the collecting system very difficult, leading to increased ischaemia times and limiting its use to specialist high-volume centres [45].

Robotic partial nephrectomy (RPN) incorporates improved dexterity of movements with 3D vision, allowing easier retractor setup with minimization of ischaemia time and wider adoption of minimally invasive PN [44]. Studies have demonstrated its feasibility and safety in all types of complex renal

masses and even in solitary kidneys [44, 45]. RPN has been shown to reduce ischaemia times for most surgeons in comparison with LPN [44]. Contemporary series show low margin positive rates and equivalent oncological outcomes compared to LPN and open PN [44]. Early data confirm equivalence to open PN, and it appears to be the true minimally invasive alternative to open surgery, allowing excision of complex renal masses [45, 46]. The limitations of the robotic platform include the lack of tactile feedback and the high cost of the system [44].

### Conclusions

Nephron-sparing surgery is today a standard of care in the management of T1 renal masses whenever technically feasible. However, its utilization among the urological community needs to be improved [47].

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