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Collaborative Review – Kidney Cancer

The Expanding Role of Partial Nephrectomy: A Critical Analysis of Indications, Results, and Complications

Karim Touijer [a,*], *Didier Jacqmin* [b], *Louis R. Kavoussi* [c], *Francesco Montorsi* [d], *Jean Jacques Patard* [e], *Craig G. Rogers* [f], *Paul Russo* [a], *Robert G. Uzzo* [g], *Hendrik Van Poppel* [h]

[a] *Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*
[b] *Department of Urology, University of Strasbourg, Strasbourg, France*
[c] *Smith Institute for Urology, The North Shore-Long Island Jewish Health System, New York, NY, USA*
[d] *Department of Urology, Universita' Vita Salute San Raffaele, Milan, Italy*
[e] *Department of Urology, University of Rennes, Rennes, France*
[f] *Vattikuti Urology Institute, Henry Ford Hospital, Detroit, Michigan, USA*
[g] *Department of Urologic Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA*
[h] *Department of Urology, University Hospital, KU Leuven, Leuven, Belgium*

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Abstract

Context: The gained expertise in the surgical technique of partial nephrectomy (PN) with excellent oncologic outcome and reduced morbidity has contributed to more frequent use of PN in many centres of reference, and the recent evidence favouring PN over radical nephrectomy (RN) in the prevention of chronic kidney disease and possibly linking it to a better overall survival (OS) will constitute a strong argument for wider use of PN.

Objective: To objectively analyse the advantages of PN over RN and to evaluate the risk–benefit ratio of expanding the indications of PN T1b renal cortical tumours.

Evidence acquisition: Literature searches on English-language publications were performed using the National Library of Medicine database. The queries included the keywords *partial nephrectomy* and *nephron sparing surgery*. Eight hundred four references were scrutinised, and 175 publications were identified and reviewed. Sixty-nine articles were selected for this review. These references formed the basis for this analysis and were selected based on their relevance and the importance of their content.

Evidence synthesis: The use of PN has been steadily increasing, particularly in tertiary care centres. This trend is now strengthened by evidence supporting the role of PN in reducing the risk of chronic kidney disease in patients with renal masses $\leq$4 cm. A wider use of PN for larger tumours, granted technical feasibility, is supported by the preliminary evidence, suggesting an OS advantage favouring PN over RN. However, the potential for selection bias and residual confounding factors may contribute to the observed difference. In the carefully selected patients with tumours >4 cm, PN obtained equivalent oncologic outcome to that achieved after RN. Although higher morbidity rates were seen after PN, the complication type and severity were not prohibitive.

Conclusions: The available evidence supports elective PN as the standard surgical treatment for renal cortical tumours $\leq$4 cm. For larger tumours, PN has demonstrated feasibility and oncologic safety in the carefully selected patient population studied.

* Corresponding author. Memorial Sloan-Kettering Cancer Center, Sidney Kimmel Center for Prostate and Urologic Cancers, 353 East 68th Street, New York, NY 10021, USA. Tel. +1 646 422 4486; Fax: +1 212 988 0768.
E-mail address: touijera@mskcc.org (K. Touijer).

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1. Introduction

Historically, the report by Robson et al [1] established radical nephrectomy (RN) as the standard treatment for localised renal cell carcinoma (RCC). The cancer-specific survival (CSS) for early-stage cancers following RN was good, with a low rate of local recurrence. Partial nephrectomy (PN) or nephron-sparing surgery was reserved for patients with a tumour in a solitary kidney, bilateral renal tumours, or renal function impairment.

In recent years, a number of developments have placed this paradigm under pressure to change. The widespread use of modern cross-sectional imaging has led to an increase in diagnosis of renal incidentalomas—that is, tumours that tend to be smaller, earlier stage, and possibly of lower grade. Concerns over treatment mismatch, with RN being perceived as an overly aggressive therapeutic option, opened the opportunity for the elective PN.

The knowledge that renal cancer does not represent a single disease but a compendium of a complex family of tumours, each with a unique histology, cytogenetic background, and variable metastatic potential ranging from the benign oncocytoma to the indolent papillary and chromophobe carcinomas to the more malignant conventional or clear-cell carcinoma [2] calls into question the rationale of RN for the 20–30% of patients with a benign or low-malignant-potential renal tumours.

The gained expertise in the surgical technique of PN with excellent oncologic outcome and reduced morbidity contributed to more frequent use of PN in many centres of reference. Hypothetically, one can also debate that the advent of minimally invasive approaches in the treatment of renal cortical tumours might have led open PN to an expansion of indications and a shift on the surgical complexity scale towards more challenging lesions. Finally, the recent evidence favouring PN over RN in the prevention of chronic kidney disease and possibly linking it to a better overall survival (OS) will constitute a strong argument for wider use of PN.

The scope of this analysis is to evaluate, based on the published information, the current status of PN—its utilisation and the rationale for its use as the standard treatment—and to explore whether expanding the indications to include larger tumours and more complex PN procedures maintains the nephron-sparing benefits without jeopardising the oncologic and morbidity outcomes.

2. Evidence acquisition

Literature searches in English-language publications were performed using the National Library of Medicine database. The queries included the keywords *partial nephrectomy* and *nephron sparing surgery*. A free-text strategy was applied without limitation of the year of publication. Eight hundred four references were scrutinised, and 175 publications were identified and reviewed. Links to related articles and cross-reading of citations in related articles were surveyed. Sixty-nine articles were selected for this review, and these references formed the basis of this analysis. The aim of this review is not a meta-analysis of published literature on PN but rather a critical analysis and discussion of the current status and main points of controversy regarding the use of PN for the treatment of renal cortical tumours. This review is the result of an interactive peer-reviewing process by an expert panel of coauthors, discussing a set of relevant "topics" in PN. The articles forming the basis of this review were selected based on their relevance and the importance of their content; articles with a clear, specified end point addressing a given "point of discussion" were given priority over general, retrospective descriptions of experience with PN.

3. Evidence synthesis

3.1. *The use of partial nephrectomy*

Over the past 2–3 decades, the incidence of kidney cancer has steadily increased both in Europe and in the United States [3]. Greater access and utilisation of modern medical imaging has contributed not only to this rise in overall incidence but also to a downstage migration of the disease. A great proportion of these newly diagnosed renal cortical tumours are small (<4 cm), low-stage incidentalomas, often associated with a better prognosis [4–6]. Although understandably a rise in incidence will be associated with an increase in surgical demand and delivery, the question of pertinence is, how did the urologists adapt to kidney cancer as the disease presents today?

Five reports addressing this issue have been selected for review. The cumulative study period spans 1988–2007. All reports showed an increasing, albeit slow utilisation trend of PN. Studies based on national registry data (Surveillance, Epidemiology, and End Results [SEER] or Nationwide Inpatient Sample) queries in the United States between 1988 and 2002 have shown that PN remained relatively uncommon, representing <10% of the overall nephrectomies performed between 1988 and 2002 [7–9]. These studies indicated that urban, high-volume, and teaching hospitals were more likely to perform PN; patients of a younger age, male gender, and smaller tumours were more likely to receive PN. Recent year of diagnosis was also an independent determinant of PN use [7–9].

Reports based on tertiary care centre experiences both in Europe and in the United States reported a relatively higher use of PN. Combined data from six tertiary care centres in Europe demonstrated that in the period between 2004 and 2007, PN represented 50% of the overall nephrectomy activity. PN was used in 86% of the tumours <2 cm, 69% of the tumours between 2.1 cm and 4 cm, and 35% in those between 4.1 cm and 7 cm [10]. In the Memorial Sloan-Kettering Cancer Centre (MSKCC) experience between 2000 and 2007, PN accounted for 56% of the nephrectomies for renal cortical neoplasms. For a tumour ≤4 cm electively treated, the PN utilisation steadily increased from 69% in 2000 to 89% in 2007; similarly, PN for a 4-cm to 7-cm electively treated tumour represented 20% in 2000 and 60% in 2007. At MSKCC, the trend towards higher use of PN over RN was seen regardless of whether the PN were performed open or laparoscopically [11]. Both the European and MSKCC tertiary care–based studies reported smaller tumour, younger age, male gender, and contemporary year of surgery as independent predictors of PN [10,11].

Given that laparoscopically, PN is a technically more challenging procedure than RN, it has been a concern that the advent of laparoscopy will lead to more RN for small lesions that would otherwise be amenable to open PN, thereby reducing the use of PN. This argument is difficult to prove or disapprove. There is a stark contrast between the believed [12] and actual utilisation of laparoscopy in the treatment of renal tumours. In the United States, based on a nationwide inpatient sample study between 1991 and 2003, laparoscopy constituted only 4.9% of all nephrectomies, with a peak utilisation in 2003 of 16% for all radical and partial nephrectomies for RCC [13]. In 2003, kidney donors and patients with benign renal disease were more likely to have a laparoscopic nephrectomy than those with malignant kidney disease (33% vs 22% and 16%, respectively) [14]. In another population-based study, the use of both open PN and laparoscopic RN increased gradually between 1997 and 2002; however, open RN remained the predominant therapy for older men with kidney cancer treated in the United States during the above timeframe. Overall, of the 5483 cases identified in this study, 11.1% underwent PN (0.8% laparoscopically), and 88.9% underwent RN (9.4% laparoscopically). The surgeon-attributable variance in this study exceeded that of patient and tumour characteristics [15]. In a report from Washington University (a centre with a pioneering experience in renal laparoscopy) between 1997 and 2001, renal tumours $\leq$4 cm were treated by open PN (48%), laparoscopic RN (23%), open RN (16%), and laparoscopic PN (14%). During the study period, a trend towards less open RN and more laparoscopic PN and RN was observed; in 2001, more than one-third of these tumours were treated by laparoscopic RN (36%), laparoscopic PN (35%), or open PN (29%); open RN represented 2% of cases [16].

In the interpretation of these data, one can conclude that the overall utilisation of PN is on the rise. However, a number of issues remain. Although much has been written about PN, its use remains for the most part clustered in high-volume tertiary care centres and has not diffused widely to the greater urologic community. If a treatment has to establish evidence supporting its superiority, wide acceptance, and ease of reproducibility to become the standard of care, the present underutilisation of PN weakens its case [7–11].

The practice patterns reported above confirm that older patients are less likely to receive PN, indicating that perhaps PN is perceived as associated with higher complications and is therefore withheld from older patients more likely to have serious comorbidities. Such a thought process goes against the one supporting more PN in the elderly, as this patient population is the one in need for the most nephron sparing to avoid chronic kidney disease.

In recent years, the utilisation of laparoscopy has been steady but slow. Up to 2003, population-based studies had shown that laparoscopic RN represented a small proportion of the nephrectomies performed for RCC and would therefore not constitute a major contributing factor in the underutilisation of PN. Utilisation data beyond 2003 are currently not available; the impact of the incremental experience and integration of robotic technology is awaited. Early retrospective data about robot-assisted laparoscopic PN are emerging; prospective confirmation is awaited.

3.2. *Partial nephrectomy, chronic kidney disease, and overall survival*

3.2.1. *Partial nephrectomy and chronic kidney disease*

Chronic kidney disease is now recognised as a concerning public health problem worldwide. In the United States, its incidence is rising, and the number of individuals with renal failure requiring dialysis or renal transplantation is expected to surpass 650 000 by the year 2010 [17]. According to the US National Kidney Foundation, chronic kidney disease is defined as either kidney damage for >3 mo as confirmed by renal biopsy or markers of kidney damage with or without a decrease in glomerular filtration rate (GFR) or GFR <60 ml/min per 1.73 m^2 for >3 mo with or without kidney damage [18].

A GFR <60 ml/min per 1.73 m^2 is only the selected cut-off value for the definition; the severity of chronic kidney disease spans a spectrum based on the different stages of GFR potential loss [19]. In a community-based study on 1 120 295 adults who received their care in a large integrated health care system, chronic kidney disease was found to be an independent risk factor for the development of cardiovascular events (coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease), hospitalisation, and death [19]. The cellular mechanism by which a reduced GFR affects the cardiovascular system is not yet elucidated.

From a urologic standpoint, single-institution reports retrospectively comparing PN to RN in patients with a normal contralateral kidney and using postoperative serum creatinine levels as the end point have shown a higher likelihood of renal function impairment after RN. In the MSKCC series comparing 117 patients treated by PN to 173 who underwent RN, the mean postoperative serum creatinine was 1.0 mg/dl (range: 0.5–1.9) and 1.5 mg/dl (range: 0.8–3.8), respectively ($p < 0.001$). None of the patients in either group required acute or chronic dialysis [20]. The Mayo Clinic experience using a matched comparison of PN and RN has shown a higher risk for proteinuria (defined as a protein-to-osmolality ratio of 0.12 or higher) and chronic renal insufficiency (defined as serum creatinine >2.0 mg/dl) after RN (risk ratio: 3.7; 95% confidence interval [CI], 1.2–11.2; $p = 0.01$) [21]. With some limitations, these reports have established the negative impact of RN on long-term renal function and questioned the idea that patients who undergo RN for renal cortical tumours can be perfectly safe with one kidney. This concept was challenged further by Huang et al, who in a retrospective analysis based on 662 patients undergoing elective partial or radical nephrectomy for a <4-cm renal mass demonstrated that with a normal preoperative serum creatinine and a healthy-appearing contralateral kidney on imaging, 171 (26%) patients had preexisting chronic kidney disease at baseline before surgery (GFR <60 ml/min per 1.73 m^2). After surgery, the 3-yr and 5-yr probability of freedom from chronic kidney disease were 80% (95% CI, 73–85) and 67% (95% CI, 57–75), respectively, after PN and 35% (95% CI, 28–43) and 23% (95% CI, 16–30), respectively, after RN ($p < 0.0001$). For more severe chronic kidney disease, the 3-yr and 5-yr probability of freedom from new onset GFR <45 ml/min per 1.73m^2 were 95% (95% CI, 91–98) and 93% (95% CI, 87–96), respectively, for patients treated by PN compared to the respective values of 64% (95% CI, 56–70) and 57% (95% CI, 50–64) for those who underwent RN ($p < 0.0001$). Multivariable analysis indicated that RN remained an independent risk factor for the development of new-onset chronic kidney disease (hazard ratio [HR]: 3.82; 95% CI, 2.75–5.32; $p < 0.0001$) [22].

The mechanism by which PN offers an advantage over RN in preventing chronic kidney disease in patients with renal masses <4 cm is certainly the result of a greater preservation of the nephron capital. Studies looking at the independent predictors of renal function outcome after PN have shown that larger renal volume reduction, or percent of parenchyma resected, adversely influence renal function after PN. Other predictors are either patient dependent (preoperative estimated GFR, solitary kidney status, older age, and male gender) or technique dependent (length of ischaemia time) [23–25].

Based on historical animal models, it has been believed that 30–90 min of warm ischaemia can be safely tolerated [26–29]. However, extrapolation of such findings to guide nephron-sparing surgery in humans may not be totally accurate. A multi-institutional retrospective study looking at postoperative renal function after PN in 537 patients with a solitary kidney and baseline renal insufficiency indicated that the rate of chronic renal insufficiency (defined as postoperative serum creatinine levels >2.0) were 26% when no ischaemia was used, 30% after warm ischaemia, and 41% after cold ischaemia. The authors recommended a warm ischaemia time cut-off of 20 min to decrease the risk of acute and chronic renal failure in this very distinct patient population [30]. Clinically, it has been difficult to reliably differentiate between renal impairment secondary to ischemic injury and parenchymal loss. Renal parenchymal transit time of radiotracer during mercaptoacetyltriglycine-3 (MAG-3) renal scintigraphy has been proposed as a marker for renal ischaemia but has not gained wide acceptance [31]. Porpiglia et al evaluated the impact of warm ischaemia times >30 min on renal function as measured by (1) total daily proteinuria, (2) proximal tubular enzymes, (3) serum creatine and cystatin C, (4) creatinine clearance using the Cockcroft-Gault equations, (5) estimation of GFR using radionuclide chromium 51–ethylenediaminetetraacetic acid (^{51}Cr-EDTA), and (6) renal scintigraphy with technetium 99m–mercaptoacetyltriglycine (^{99m}Tc-MAG3). Measurements were performed at baseline and at different time points postoperatively in 18 patients treated with laparoscopic PN: No statistically significant difference was seen in the proximal tubular enzyme measurements, serum creatinine, serum cystatin C, creatinine clearance, or GFR. The proteinuria, although increased in the first postoperative week, normalised at the 1-yr measurement. Assessment of the operated kidney by ^{99m}Tc-MAG3 showed a significant difference, influenced by the maximum thickness of resected healthy parenchyma and the duration of warm ischaemia on multivariate analysis [32]. Funahashi et al have demonstrated on 32 patients undergoing PN a correlation between a warm ischaemia time of 25 min or longer and decreased effective renal plasma flow and tracer uptake on ^{99m}Tc-MAG3 renal scintigraphy performed preoperatively, at 1 wk, and at 6 mo postoperatively [25].

If from the above data one can deduct that for renal cortical tumours <4 cm RN as opposed to PN leads to a higher likelihood of chronic kidney disease, and chronic kidney disease is associated with a higher risk of cardiac events, hospitalisation, and death, then the logical question is, do patients treated by RN have a higher risk of cardiac events and lower survival rates?

3.2.2. *Partial nephrectomy versus radical nephrectomy: impact on overall survival*

In a large retrospective study based on information from the SEER-linked Medicare database on 10 886 patients (>65 yr of age) who underwent either PN (7%) or RN (93%) for kidney cancer, Miller et al compared the frequency of cardiovascular morbidity after PN and RN. To control for secular trends in the indications with regards to PN, the authors did subset analyses based on the period of treatment between the years 2000 and 2002; no association was observed between treatment and postoperative cardiovascular morbidity [33].

Huang et al addressed the issue of cardiovascular events and OS by analysing a population-based cohort of 2991 patients older than 65 yr of age treated by partial (19%) or radical nephrectomy (81%) for renal cortical tumours <4 cm from the SEER–Medicare-linked data registry for the period between 1995 and 2002. When controlling for demographic characteristics and patient comorbidities, the type of surgery was not a statistically significant predictor of cardiovascular events or cardiovascular death, although the HR for cardiovascular events was 1.21 ($p = 0.1$). RN, however, was associated with an increased risk of death from any causes (HR: 1.46; $p < 0.001$). The authors note that of the deaths attributed to cancer in their dataset, 1.4% occurred after PN, 4% after RN [34].

In the Mayo Clinic series, a retrospective analysis based on 648 patients treated with PN or RN between 1989 and 2003 for renal masses <4 cm, the type of surgery was not significantly associated with an increased risk of death from any cause (relative risk: 1.12; $p = 0.5$). However, in a subset analysis limited to patients younger than 65 yr of age, RN was associated with a decreased OS (relative risk: 2.34; 95% CI, 1.17–4.69; $p = 0.016$) [35].

In a population-based cohort of 7769 patients matched for age, tumour size, and year of surgery, RN was associated with a 1.23-fold increase in overall mortality than PN ($p = 0.001$). The 5- and 10-yr survival rate of PN versus RN was, respectively, 89.3% versus 84.4% and 71.3% versus 68.2%, resulting in an absolute survival difference of 4.9% and 3.1%. In a competing risk analysis adjusting for patient age and tumour characteristics, RN was associated with a higher rate of non–cancer-related mortality. Although adjusting for tumour size, neither analysis adjusted for the imperative versus elective indication of PN; the latter may favour PN further with regards to OS [36].

In summary, there is compelling evidence to support the advantage of PN over RN in reducing the risk of chronic kidney disease and promoting the awareness of the importance of kidney preservation. However, in the analysis of the above data, the following limitations have to be highlighted. Because of their retrospective nature, the studies comparing PN to RN are subject to selection biases. As listed above, in the practice pattern based on centres of reference and large cross-sectional national databases, older patients are more likely to receive RN than younger and healthier patients. Granted, most analyses comparing the outcomes of PN and RN have controlled for age and comorbidities, but they did not account for other confounding factors that were recognised by the surgeon preoperatively and dissuaded him or her from using PN; factors such as the interplay of the different comorbidities on the overall individual patient's health are often not captured retrospectively.

In the general population, chronic kidney disease has been shown to be associated with an increased risk of cardiovascular events and death. The process is a chronic deterioration of health, and the exact mechanism remains unknown. In the nephrectomy population, RN has been recognised as a predisposing factor of chronic kidney disease, but not enough evidence exists to support the inference that RN increases the risk of cardiovascular events or even reduces survival. Information from retrospective subset analyses is less likely to provide reliable evidence and is, at best, hypothesis generating.

In the interpretation of these data, one can conclude that serum creatinine levels are a poor reflector of a patient's true renal function. The fact that when estimated by GFR, up to 26% of the patients with "normal renal function" based on serum creatinine do have some degree of chronic kidney disease should prompt a wider preoperative and postoperative use of the estimated GFR (the formulae are readily available online).

In patients with renal masses $<$4 cm, RN leads to a higher likelihood of new-onset chronic kidney disease postoperatively. Potential selection bias and residual confounding factors in the available and reported evidence preclude any valid conclusion as to whether PN is associated with reduced cardiovascular events and higher OS. Prospective, randomised trials are the best fit to test these hypotheses; however, such trials remain difficult to implement.

3.2.3. Expanding the indications of partial nephrectomy: oncologic principles of excision

Initially attempted for small, exophytic, and easily accessible renal tumours, the indications for elective PN have, with growing experience, expanded to tumours of a larger size and in difficult locations. The technical challenge and ensuing morbidity of a PN is dictated by the tumour size, its growth pattern (endophytic vs exophytic), and its location (lower pole vs upper pole vs hilar and centrally located). Given the lack of an objective, reliable, and reproducible index encompassing size, location, and growth pattern to measure the technical complexity of a PN, tumour size is the default parameter and has been widely used in the literature. The use of tumour size is justified by the fact that it is objective, reproducible, and correlates with oncologic outcomes. The 4-cm cut-off as the upper limit of acceptability of PN was determined on the basis of its significant correlation with CSS, favouring tumours of the smaller size [37,38]. In this category, PN was established by retrospective methodologies as a noninferior therapeutic option to RN with regard to oncologic outcomes. Several reports have shown a long-term 5- and 10-yr cancer-free survival rate of 92–100% and acceptably low local recurrence rates [39–42].

Avoiding local recurrences has been paramount to the concept of nephron-sparing surgery. The initially recommended negative surgical margin (NSM) width was 1 cm [43]. However, with the expansion of indications to larger and centrally located tumours, wider safety margins were not always technically feasible, and simple tumour enucleation has been proposed as an alternative [44,45]. In a retrospective review by Carini et al, 71 patients with renal cortical tumours between 4 cm and 7 cm were treated by simple enucleation of the tumour and followed; with a median follow-up of 51 mo, the 5- and 8-yr CSS was 85.1% and 81.6%, respectively. The local recurrence rate, however, was 4.5%; the histologic distribution in this series was 85.9% clear cell, 8.5% chromophobe, and 5.6% papillary [46].

In a smaller study of 44 patients treated by PN for renal cortical tumours with a mean follow-up of 49 mo (range: 8–153), none of the 41 patients with NSM developed local recurrence at the excision; the mean and median size of the healthy renal parenchymal rim surrounding the tumour ensuring a negative margin were 2.5 mm and 2 mm, respectively [47]. One patient with NSM developed tumour implants along the posterior pararenal space and subdiaphragmatic area, whereas one of three patients with positive surgical margins (PSM) on a solitary kidney developed local recurrence and subsequent liver metastases. The positive margin rate in this series was 6.8%.

In a retrospective review of 777 PNs performed at a single centre, Kwon et al reported a PSM rate of 7%. With a median follow-up of 22 mo, the detected local recurrence rate was 4% in patients with PSM versus 0.5% in those with NSM. Recurrence after a PSM were seen only in patients with what the authors determined as high-malignant-potential tumours (clear cell, collecting duct, or the presence of sarcomatoid features) [48]. A report combining the PN experience from two tertiary care centres in the United States examined 77 cases of PSM out of 1390 PN procedures (5.5%) and did not find any significant difference between patients with positive and negative surgical margins with regard to local recurrence and metastatic

Table 1 – Summary of partial nephrectomy results

Authors	Study period	Single vs multi-institution	Laparoscopic vs open	Patients, *n*	Clear-cell histology, %	Fuhrman grade ≥3, %	Mean tumour size, cm	Mean follow-up, mo	Local recurrence, %	DSS, %
Antonelli et al [54]	1983–2007?	Single	Open	52	80.8	25	–	54.3	1.9	93
Becker et al [42]	1975–2004	Single	Open	69	79.7	7.2	5.3	71	0	100
Dash et al [55]	1998–2004	Single	Open	45	100	20	4.8	21*	–	–
Leibovich et al [56]	1970–2000	Single	Open	91	63.7	25	4.9	106	5.5	98.3
Pahernik et al [57]	1979–2006	Single	Open	102	71.6	10.8	5.0	56.4	1	95.8
Patard et al [58]	1984–2005	Multi	Open	247^	–	28.7	–	36	1.3	–
Patard et al [52]	1984–2001	Multi	Open	65	–	10.9	5.3	62.5	3.6	93.8
Peycelon et al [59]	1980–2005	Single	Open	61^^	77.1	24.6	5.6	70.7*	9.84	81
Simmons et al [60]	1999–2005	Single	Lap	31**	55	33	6	–	–	–
Joniau et al [69]	1997–2005	Single	Open	67	55.2	53.7	4.5*	40.2*	4	99

DSS = disease-specific survival.
* Median.
^ Data available on a subset of this number.
^^ 16 tumours were >7 cm.
** 31 out of 58 patients had a diagnosis of cancer.

disease. The authors concluded that a PSM after PN does not portend an adverse prognosis [49].

In the laparoscopic literature, the issue of PSM was addressed in two large multi-institutional studies. The first reports on 511 PN procedures with PSM in nine patients (1.8%). Two of the nine patients subsequently underwent laparoscopic RN with no evidence of any residual cancer. One of the seven patients on surveillance had von Hippel-Lindau disease and died of metastatic RCC; the remaining six patients were free of disease, with a median follow-up of 32 mo (range: 6–76). Frozen sections of the tumourectomy bed were obtained in eight out of the nine cases, and all were negative [50].

The second study encompasses the laparoscopic PN experience of 17 centres in Europe and the United States. Out of 855 PN procedures, there were 21 cases of PSM (2.4%). This study demonstrated variability in the different practices with regard to frozen sections: Ten centres performed intraoperative frozen sectioning of the excised tumour based on the macroscopic examination of the specimen, five centres always performed random biopsies of the tumourectomy bed, and two centres never obtained any frozen sections. Only seven patients with PSM were followed expectantly; the other 14 patients underwent laparoscopic RN, 2 patients with a PSM had angiomyolipoma on the RN specimen [51].

In summary, the interpretation of the available evidence regarding the PN technique of excision and PSM may allow the following conclusions. A 1-cm margin of healthy parenchymatous rim throughout the specimen is not always possible, particularly at the deep margin of excision. In light of the available information, such a wide margin is not needed. In addition, with PN offered for larger and more endophytic, centrally located, and juxtahilar tumours, the excision at the deep margin may often be limited to an enucleation. Although a complete enucleation may not increase the risk of local recurrence, it could if commonly practiced subject patients to higher PSM rates.

The data on the prognostic significance of PSM are conflicting. Ensuring NSM during PN is a fundamental principle of oncologic surgery and is better accomplished by the surgeon at the time of tumour excision—hence the importance of a bloodless field. Fresh frozen section examination on random biopsies of the PN bed is random at best, uninformative, and potentially misleading. With regard to intraoperatively unsuspected PSM determined by cancer on ink on the surgical specimen, the available data seem to favour vigilant surveillance, as often there is no evidence of residual disease on RN.

3.2.4. *Partial nephrectomy for renal tumours >4 cm: oncologic safety and morbidity profile*

Challenging the 4-cm cut-off as the upper limit for PN has proven reasonable from a technical feasibility and oncologic safety perspective. Patard et al used data from seven centres in Europe and the United States to compare the specific survivals after PN (379) and RN (1075). In 544 patients with available recurrence data (37.4%), there were no significant differences in local or distant recurrence for PN or RN for T1a (0.8% and 2.4% vs 0.6% and 4.6%, respectively; $p = 0.6$) and T1b tumours (3.6% and 7.1% vs 2.3% and 15.6%, respectively; $p = 0.5$). In the patients with tumours >4 cm with comparable characteristics, the disease-specific survival (DSS) between PN and RN was not significantly different ($p = 0.8$), although patients with T1b tumours had a slightly higher recurrence-free rate, suggesting the impact of patients selection [52].

Becker et al described their experience with elective PN for malignant renal cortical tumours >4 cm. Of the carefully selected 69 patients with peripherally located tumours, 55 (79.7%) had clear-cell pathology, the mean pathologic tumour size was 5.3 cm (range: 4.1–10 cm), and four patients (5.8%) experienced disease recurrence at a median follow-up of 5.8 yr [53]. Several other studies have confirmed that elective PN in carefully selected patients can achieve oncologic outcomes equivalent to RN in the treatment of T1b renal cancers [42,52,54–60] (Table 1).

PN is a technically more complex operation than RN and has been shown to be associated with a higher rate of complications when performed for tumours <4 cm in size

[61–66]. The best available evidence on this subject is the prospective, randomised European Organisation for Research and Treatment of Cancer intergroup phase 3 study that compared the complications of elective PN ($n = 268$) and RN ($n = 273$) in patients with renal cortical tumours $\leq$5 cm from 40 institutions. In this study reported by Van Poppel et al, PN was associated with a higher risk of severe perioperative bleeding (3.1% vs 1.2%), reoperation (4.4% vs 2.4%), and having abnormal computed tomography imaging postoperatively (5.8% vs 2.4%). The rate of urinary fistulas as a procedure-specific complication was 4.4% [67]. Patard et al, in a retrospective, multicentre experience, compared the morbidity of PN for tumours below and above the 4-cm cut-off, demonstrating a significantly higher risk for haemorrhage, blood transfusion, and urinary fistulas in the group with tumours >4 cm. These differences, however, did not result in a significantly higher rate of medical and surgical complications [58]. The Becker et al study, which was aimed more at the oncologic outcome, reported a 13% complication rate, with haemorrhage requiring reinterventions in 2.9% of patients and urinary fistulas in 10% of the cases managed by ureteral stent placement or percutaneous nephrostomy [42].

In the laparoscopic experience, tumour size >4 cm was not associated with an increased risk of intraoperative complications or postoperative genitourinary complications. Although these findings demonstrate surgical expertise, careful patient selection is a major component of the relatively reduced morbidity [60]. Gill et al reported a comparative analysis of 771 laparoscopic versus 1028 open PN procedures performed consecutively for renal masses <7 cm between 1998 and 2005. The multivariate analysis demonstrated that the laparoscopic approach was associated with a higher risk of urologic and nonurologic complications, postoperative haemorrhage, and the need for subsequent procedures. Although this paper is important, its methodologic design introduces a number of biases that may preclude any comparative conclusions. The study compares the results of two surgical techniques at different levels of their respective learning curves: one (open) at the established and mature phase, the other (laparoscopic) including the initial pioneer phase of trials and tribulations with the technique. The data collection is not uniform for either group [68].

In summary, the indications of PN are expanding to larger and more complex tumours. The oncologic outcome after surgery for larger tumours is often not determined by the local tumour control but rather by undiscovered metastatic disease. Therefore, given the negative impact of RN (as shown above), PN seems defendable when technically feasible and is oncologically safe even for larger tumours.

4. Conclusions

In recent years, the use of PN to treat small renal cortical tumours has been gradually increasing. However, this utilisation remains largely clustered to tertiary care centres and centres of reference. Younger patients and those of male gender are more likely to receive PN. Similarly, serum creatinine levels do not reliably reflect a patient's renal function; estimated GFR provide a more accurate assessment.

RN is associated with a higher risk of developing chronic kidney disease. Selection biases and subset analyses preclude any determination that RN leads to higher mortality rates than PN. The oncologic safety of PN was built upon the principle of complete tumour excision with NSM. Vigilant surveillance of patients with PSM is recommended.

From an oncologic perspective, the existing evidence supports the indication of PN in carefully selected patients with T1b tumours. The data on the morbidity associated with such an expansion show higher but not prohibitive complication rates.

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Study concept and design: Touijer, Jacqmin, Kavoussi, Montorsi, Patard, Rogers, Russo, Uzzo, Van Poppel.
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Analysis and interpretation of data: Touijer, Jacqmin, Kavoussi, Montorsi, Patard, Rogers, Russo, Uzzo, Van Poppel.
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