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TOPIC PAPER

Do we know (or just believe) that partial nephrectomy leads to better survival than radical nephrectomy for renal cancer?

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Abstract
Purpose Partial nephrectomy (PN) has become the gold standard for treating small renal masses amenable to such an approach. Surprisingly, the single randomized controlled trial of PN versus radical nephrectomy (RN) indicated an overall survival benefit for RN over PN. Recent studies have shed light on this discordance, and this review will attempt to discern what is *known* at present.
Results Multiple retrospective observational studies have demonstrated superior outcomes with PN compared with RN. Whether the observed survival benefit with PN is the result of renal functional advantages or the result of selection bias and other unmeasured variables is up for discussion. A meta-analysis of 21 studies including the EORTC 30904 found a 19 % reduction in all-cause mortality ($p = 0.0001$) and 29 % reduction in cancer-specific mortality ($p = 0.0002$) with PN versus RN. Recent analysis of SEER-Medicare data revealed that patients undergoing RN had similar survival when compared with non-cancer controls, further supporting concerns about selection biases in prior observational series.
Discussion Although PN is clearly of benefit for those likely to experience end-stage renal disease with RN, a survival benefit with PN in the elective setting is not proven at present. While experts may still *believe* PN to improve survival for these patients, the only level I evidence in the field would suggest otherwise, and selection bias is undoubtedly responsible for a significant part of the improved survival observed in retrospective studies. Given recent evidence, any further push to limit the role of RN should be tempered until we *know* PN is indeed superior.

Keywords Kidney neoplasms · Nephrectomy · MIS · Nephrometry · Renal cell carcinoma

Abbreviations

PN	Partial nephrectomy
RN	Radical nephrectomy
GFR	Glomerular filtration rate
CKD	Chronic kidney disease
RCT	Randomized controlled trial
RCC	Renal cell carcinoma
SRM	Small renal masses
OS	Overall survival
ACM	All-cause mortality
CSM	Cancer-specific mortality
HR	Hazardous ratio
ESRD	End-stage renal disease
CAD	Coronary artery disease
RFD	Renal functional decline

Introduction

Renal cell carcinoma (RCC) is the third most common genitourinary cancer and most commonly treated with surgical excision of the primary tumor [1]. The incidence of RCC is increasing and is likely due to earlier detection, as the majority of renal masses are diagnosed as cT1 tumors

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(localized, <7 cm) [2, 3]. Historically, the treatment modality used for the vast majority of small (<4 cm) renal masses (SRM) was radical nephrectomy (RN). Partial nephrectomy (PN), designed to preserve renal parenchyma and function, was pioneered for patients who would require renal replacement after RN [4]. In the past decade, utilization of PN has increased in tertiary care centers and the community setting, in large part based on the belief that PN is "better" than RN [5–7]. This has been supported by an extensive literature of retrospective studies demonstrating renal functional and overall survival (OS) benefits with PN over RN, along with at least equivalent oncologic outcomes [6–14]. Backed by these data, both the AUA and EAU make strong recommendations regarding PN in their guidelines for SRM amenable to such an approach [15, 16]. With the support of robust literature and clinical guidelines and calls that PN is under-utilized worldwide [3], the use of PN has expanded greatly [17]. Surprisingly, the only level I evidence available on this topic, a European trial that did not meet accrual goals, revealed that PN provided no survival benefit compared to RN [18]. Considering the conflicting literature, the question remains for urologic surgeons, what benefits are afforded by PN (relative to RN): Preserved renal function? Reduced cardiovascular events and mortality? Improved overall survival? Better cancer-specific survival? This review highlights pertinent literature on the topic, attempting to draw it into a clear synthesis of the currently available information.

Methods

A comprehensive English-language literature review was performed using MEDLINE/PubMed to identify articles and guidelines pertinent to cancer-specific mortality (CSM), all-cause mortality (ACM), and renal functional outcomes for PN and RN. Combination of the MeSH search terms: kidney cancer, partial nephrectomy, radical nephrectomy, overall survival, cancer-specific survival, renal function, and chronic kidney disease was used.

Survival outcomes

In an effort to preserve renal parenchyma, PN was originally offered to selected patients with bilateral RCC, a solitary functioning kidney, and those in whom the risk of renal replacement therapy after RN was high based on preoperative renal dysfunction or disease that posed a threat to future renal function [19, 20]. Utilization of PN has increased beyond these imperative settings emerging into the community setting; however, large volume centers still remain the highest utilizers of PN [7, 21]. Retrospective studies emerged to validate PN as an attractive alternative to RN for patients with a clinically localized SRM and a normal contralateral kidney [22–24]. In single-institution, multi-center, and population-based studies, improvements in OS have been consistently demonstrated with PN (Fig. 1a) [25]. In fact, prior attempts to find situations in which RN resulted in improved survival in certain patient subsets have failed [13, 26] [unpublished data].

Cancer-specific survival for elective PN has been reported to be close to 95 % for clinical and pathologic T1a RCC in most retrospective series [27] and exceeds the survival rates reported in series of patients undergoing RN for clinical T1 tumors. Selection bias clearly plays a dominant role in this observed difference in outcomes as PN cannot be an oncologically superior operation to RN. Tumors undergoing RN in comparative studies were larger, more likely to be cancer, and more often high-grade and/or higher-stage [22–25]. These differences notwithstanding, PN has become the de facto clinical standard for renal masses amenable to such an approach [15].

A single randomized clinical trial (RCT) addresses the question of PN and RN in the elective setting [13]. This European trial (EORTC 30904), opened in 1992, was slow to accrue patients and closed in 2003 prior to meeting its accrual goal of 1,300 patients. During a >10-year period, 541 patients with tumors ≤5 cm were enrolled, including 268 and 273 randomized to receive PN and RN, respectively. Intention to treat analysis showed 10-year OS rates of 75.7 and 81.1 % for PN and RN, respectively, with an estimated HR for ACM of 1.50 (95 % CI 1.03–2.16) (Fig. 1b). The test for non-inferiority (primary outcome as designed) was not significant ($p = 0.77$), but the test for superiority (of RN) was significant ($p = 0.03$). Smaller subgroup analyses of patients with RCC and those clinically and pathologically eligible for comparison showed less pronounced differences and failed to reach statistical significance. Regardless, patients undergoing PN were not observed to have improved OS in this prospective, randomized trial. With regard to CSM in EORTC 30904, only 12 patients died of kidney cancer: 8 in the PN group and 4 in the RN group ($p = 0.07$). While this study represents the only level I evidence to date, it does have several notable limitations. PN utilization during the accrual period was not as high as it is today [28], and the study had poor accrual overall and was, therefore, ended early. Additionally, there was imperfect compliance with the assigned intervention, with 14.6 % of patients assigned to PN undergoing RN (as a result of intraoperative pathologic disease characteristics) and 5.9 % of those assigned to RN undergoing PN (due to patient decision). The authors have subsequently commented that 15 % crossover from PN to RN should not be viewed as a defect, but rather a real-world feature of the trial. We would concur that this fact may indicate that some

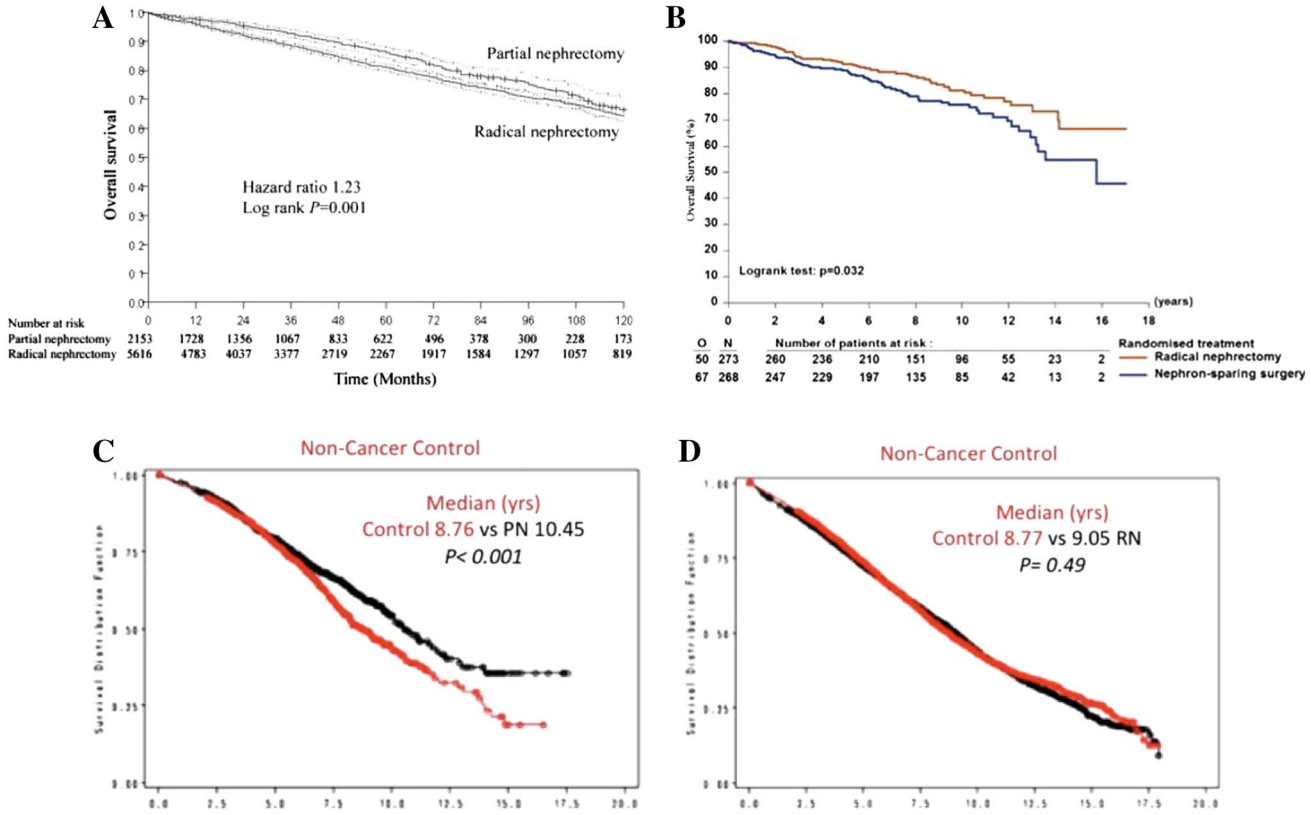

Fig. 1 Kaplan–Meier survival curves depicting overall survival curves of a matched cohort of patients with clinical T1a tumors undergoing PN and RN in a representative observational study (**a**) [24], in the single randomized controlled trial (**b**) [18], and in a SEER-Medicare dataset comparing PN (**c**) and RN (**d**) with non-cancer controls [43]. All figures are reprinted with permission

surgeons enrolled patients on trial with tumors of intermediate to high complexity that were potentially less amenable to PN, making the study applicable to environments in which surgeons are pushing the limits of PN.

With conflicting literature and little data integrating the disparate studies that compare the effectiveness of PN and RN, Kim et al. [29] performed a systematic review and meta-analysis for three endpoints: ACM, CSM, and incidence of severe chronic kidney disease (CKD). After review of 665 studies, 36 were identified as eligible for systematic review. These studies included >41,000 patients undergoing PN (23 %) or RN (77 %). In a pooled estimate that included one prospective (EORTC 30904) and 20 retrospective studies, PN correlated with a 19 % reduction in ACM (HR 0.81, 95 % CI 0.76, 0.87; $p < 0.00001$) compared with RN. PN was also associated with a 29 % reduction in CSM (HR 0.71, 95 % CI 0.59, 0.85; $p = 0.0002$) compared with RN, also based on data from 1 prospective and 20 retrospective studies. Although the authors conclude that "the lower CSM for PN represented an unanticipated finding," we are less surprised given the large selection bias at work in retrospective surgical series in which the tumors selected for treatment with PN are likely also those with lower tumor complexity (RENAL score), less access to the renal vasculature, and lower associated oncologic risk. While the pooled estimates do show a benefit of PN over RN, the authors appropriately conclude that "the available evidence is of low quality" and patients should be "made aware of the uncertainty of the evidence."

Recent work by Tan et al. [30] investigated long-term survival after PN versus RN using sophisticated statistical modeling in an attempt to account for selection bias and residual confounding that limits the conclusions that can be drawn from prior observational studies. Instrumental variable analysis is a statistical method that relies on an "instrument" that is strongly associated with the treatment of interest, but cannot be associated with the outcome of interest (other than through its effect on the treatment of interest) [31]. The authors used the distance between the patient's home and the nearest PN physician as the "instrument," finding this to be strongly associated with PN rates ($p < 0.001$) and not independently associated with OS (HR 1.03; 95 % CI 0.99, 1.07). Assessing patients with clinical T1a renal masses, ACM was 15.5 % better following PN at 8 years of follow-up, which translates into 1 life saved for every 7 patients undergoing PN instead of RN. The authors

suspect that the differences between their findings and the EORTC study are not due to residual bias or confounding, but rather distinct treatment eras. They conclude that "the EORTC study provides mainly historical context, while our findings reflect the current comparative effectiveness of" PN versus RN [30]. Limitations of this study are inclusion of only patients 65 years and older, analysis of only tumors <4 cm in size (whereas larger tumors are also considered for both surgeries), and reliance on the untested assumption that living closer to a PN surgeon is *not* a proxy for higher quality of healthcare overall. Given these limitations, we conclude that even with these data, the level I evidence still stands.

Renal functional outcomes

As the increased utilization of PN has largely been driven by concern regarding the risks of CKD, an understanding of the actual risks of pre-existing medical CKD and surgically induced CKD are of paramount import [32]. The Kidney Disease: Improving Global Outcomes CKD work group recently published new clinical guidelines for the evaluation and management of CKD [33, 34]. In contrast to a work group convened about 10 years earlier that prioritized identification of disease (based on eGFR rather than sCr) [35], this multinational collection of experts has emphasized classification of CKD according to current and future risk of morbidity [34]. This is of great import given the unclear connection between the renal functional implications of nephrectomy on cardiovascular events and ACM.

At diagnosis and prior to surgery, 24–31 % of patients undergoing PN or RN for a renal tumor have CKD (estimated GFR < 60 ml/min/1.73 m^2) [12, 26, 36]. These patients have more to benefit from PN, given their increased risk for complications and decreased OS when compared with patients without pre-operative CKD [32]. Of those without CKD prior to surgery, between 16 and 35 % of patients develop CKD (GFR < 60) and 10–20 % develop CKD stage 3b to 5 (GFR < 45) after PN [36–39]. In contrast, 44–70 % of patients are found to have GFR < 60 and 35–45 % have GFR < 45 after RN [26, 29, 37, 38]. Although the risk of moderate CKD in the elective setting is higher with RN, EORTC 30904 proves that the risk of end-stage renal disease (ESRD) is limited after elective PN (0.8 %) or RN (1.2 %), as has been demonstrated in multiple retrospective studies [18, 26, 36, 40]. Importantly, however, the same claims cannot be made about patients with pre-operative CKD. For example, in a large single-center experience, the risk of ESRD after PN was 0.1, 3.7, and 36 % for patients with normal pre-operative renal function, CKD stage 3, and CKD stage 4, respectively [41].

Attempts to link the poorer renal functional outcomes associated with RN to increased cardiovascular morbidity and mortality have in general met with limited success [10–13]. Of note, this endpoint was not analyzed in the meta-analysis, likely due to the limited and inconclusive findings from this literature [29]. In perhaps the most informative retrospective study, Weight et al. [13] found that the risk of death from cardiovascular causes was associated with pre- and post-operative GFR and pre-existing CAD, but not with surgery type (PN vs. RN) or loss of function from surgery. The reported outcomes from EORTC 30904 support both the prior observations of lesser GFR loss with PN compared with RN and lack of significant differences in cardiovascular mortality between the groups [18, 40]. In fact, death from cardiovascular causes was more common in the PN cohort (9.3 vs. 7.3 %) of the RCT. These data suggested that in contrast to the imperative setting, preservation of renal parenchyma and function in the elective setting (pre-operative GFR > 60 and minimal comorbidity) may have limited impact on survival. Considering the results of the trial regarding OS [18], these findings suggest that reductions in GFR due to surgery may not have the same negative implications as renal dysfunction from medical causes [42].

We have hypothesized that CKD caused by surgery (CKD-S) may not be associated with the same risk of progression and mortality as CKD caused by medical renal disease (CKD-M). In a recent investigation of OS and renal functional decline (RFD) in over 4,000 patients undergoing PN or RN for suspected renal malignancy, CKD-M was defined as pre-operative GFR < 60, and CKD-S was defined as new-onset GFR < 60 present 90 days after surgery in a patient with normal pre-operative GFR [26]. With a median follow-up of 6.6 years, ACM was higher in the CKD-M cohort than in the CKD-S (HR 1.76; CI 1.48–2.10; $p < 0.0001$) and no CKD (HR 1.89; CI 1.5–2.3; $p < 0.0001$) cohorts on multivariable analysis. There was no difference when comparing the CKD-S and no CKD cohorts (HR 0.93; CI 0.76–1.14; $p = 0.6$), providing further evidence that the initial renal functional decline due to surgery in patients with normal baseline function may have limited impact on OS. Also, relevant to this conclusion is the finding that kidney donors do not have an increased risk of ESRD or mortality relative to matched healthy controls, even after >30 years of follow-up [43].

In order to identify predictors of cardiovascular morbidity and mortality, the authors investigated annual RFD and >50 % RFD on ACM. Patients with CKD-S had an annual RFD of 0.7 % and only 2.2 % experienced a >50 % RFD more than 90 days after surgery. In contrast, patients with CKD-M prior to surgery had an annual RFD of 4.7 % and 7.3 % experienced a >50 % RFD > 90 days after surgery (both $p < 0.001$ vs. CKD-S) [26]. Annual RFD > 4.0 % was correlated with

increased ACM (HR 1.43; CI 1.24–1.64; $p < 0.0001$), suggesting that progression of CKD may be another important predictor of morbidity from CKD. The findings of these studies together illustrate that assessment of pre-operative renal function is of paramount importance to proper patient selection for PN versus RN. Patients with CKD-M have the greatest risk for RFD after surgery and have more to gain from PN then patients undergoing elective surgery. The focus of this review notwithstanding, it appears prudent to recommend PN to patients with CKD-M whenever feasible.

Selection bias and appropriate controls

The crux of the argument in favor of PN over RN is that RN leads to compromised survival due to the development and/or progression of CKD. In this way of thinking, PN has less of an impact on renal function and; therefore, less impact on survival. Shuch et al. recently reported data comparing PN and RN patients with matched controls from the SEER-Medicare dataset with results more supportive of a different hypothesis [44]. Two control groups for patients aged >65 years and diagnosed with a single, non-metastatic, localized SRM were prepared: matched patients with low-grade, non-muscle-invasive bladder cancer and patients without any prior cancer diagnosis at the time of matching. The use of these two control groups allowed the authors to assess for potential biases and confounding that may have affected the results of previous retrospective studies. As expected from prior SEER-Medicare analyses, median OS was higher with PN than RN (10.45 vs. 9.05, $p < 0.001$) and lower than that observed with younger cohorts of patients (compare with Fig. 1a).

After matching the PN cohort with individuals within non-invasive bladder cancer and non-cancer controls, the PN cohort was found to have improved OS (10.45-year median) compared with the bladder cancer (8.75 years) and non-cancer (8.76 years) controls, respectively (Fig. 1c). In contrast, the median OS of the RN group (9.05 years) was similar to that observed in the bladder cancer (8.67 years) and non-cancer (8.77 years) controls (Fig. 1d). If RN was harmful (because it leads to new-onset CKD), then OS would have been shorter in comparison with these control groups. If the improvement in survival with PN was due to renal functional outcomes midway between those undergoing RN and those not undergoing renal surgery, OS curves would be predicted to be better than RN and worse than non-cancer controls. What was observed; however, was an improvement in survival for PN versus bladder cancer controls (HR 1.26, $p < 0.001$) and non-cancer controls (HR 1.36, $p < 0.001$) [44]. A better explanation for this paradoxical finding is that selection bias and unmeasured confounding are responsible for the differences between cohorts.

Conclusion

For years, kidney surgery experts have assumed that PN is better than RN based on retrospective observational studies showing improved renal functional outcomes and better OS. The only RCT in this field found no survival benefit with PN in the elective setting. Selection bias and unmeasured confounding are more likely explanations of the improved survival observed with PN in the elective setting. The finding that surgically induced reductions in GFR may have less impact on survival than CKD caused by medical diseases provides a biologic explanation for these seemingly disparate findings. Patients with CKD-M clearly have poorer survival than those with normal renal function prior to surgery and remain prime candidates for PN whenever feasible. The authors *believe* that what is *known* at the present time is that PN appears to have less of a benefit over RN than once believed and that additional high-quality studies and RCTs will help provide a better understanding of this question.

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Conflict of interest The authors have no conflicts of interest.

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