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Commentary

Radical Nephrectomy is the Treatment of Choice for Complex, Localized Renal Tumors

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Radical nephrectomy has historically been the gold standard of surgical treatment for suspected renal cell carcinoma (RCC). Over the years this paradigm has evolved as partial nephrectomy (PN) was shown to be a feasible technique in well-selected patients that preserved functional renal parenchyma without sacrificing oncologic efficacy [1]. Over the past 2 decades, minimally invasive techniques have further propelled the utilization of PN. There is virtually no debate among surgeons that most clinical T1a renal masses should be managed with PN, a consensus which is clearly reflected in the guidelines provided by the American Urological Association, the European Association of Urology, and the National Comprehensive Cancer Network [2–4]. Moreover, PN should be prioritized when feasible in patients with a solitary kidney, bilateral renal tumors, familial RCC syndromes such as von-Hippel Lindau, and those with pre-existing chronic kidney disease or proteinuria [2]. As urologists have gained more experience, PN has been extended to larger clinical T1b-T2 masses and anatomically complex tumors. A recent analysis of the National Cancer DataBase (NCDB) examining the utilization of PN among patients with clinical T1a-T2a masses found that the proportion of patients undergoing PN increased significantly from 2004–2014 (30.8% in 2004 to 56.7% in 2013; $p < 0.001$) [5]. Notably, PN was performed for 11% of cT2a masses in 2013, compared to 3.2% in 2004 [5]. Retrospective cohort studies and database analyses suggest that PN can be safely undertaken in this setting in well-selected patients. However, these data lack the granularity to endorse widespread adoption of this technique. Herein, we argue that radical nephrectomy should remain the treatment of choice for large, complex renal masses.

COMPARING SURVIVAL AND ONCOLOGIC OUTCOMES FOR PN AND RN

There are few controversial topics regarding surgical management of urologic malignancies that have the benefit of randomized trials to help urologists

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address the questions at hand. Fortunately, the debate over partial versus radical nephrectomy is one such beneficiary. The EORTC 30904 Trial was a multicenter, randomized trial evaluating PN versus RN in patients with unilateral renal tumors ≤ 5 cm and a normal contralateral kidney [6]. The primary endpoint of the study was overall survival (OS), with cancer-specific survival, progression and surgical side effects as secondary endpoints. Patients treated with RN had better overall survival than those treated with PN. The 10-year OS for the RN and PN groups was 81% and 75%, respectively (HR 1.51, 95% CI 1.03–2.16). As one would expect in this cohort of patients with small renal masses, the incidence of renal cancer death was low (2.2% of patients). However, cancer-specific mortality (CSM) was lower in patients who underwent RN compared to those who underwent PN (4 deaths vs 8 death, respectively). While patients in the PN group had a lower incidence of new onset post-operative CKD, this did not translate into a higher overall mortality for RN group. A recent subgroup analysis of this trial found no difference in all-cause mortality between treatment modalities when patients were stratified by baseline renal function, co-morbidities, and performance status [7]. The limitations of this study are well known and should be acknowledged, most notably the poor accrual leading to it being underpowered. Despite this, the EORTC 30904 study provides level I evidence that RN is not necessarily harmful to patients with cT1 renal masses with a normal contralateral kidney.

Radical nephrectomy, by definition, entails complete surgical extirpation of the known or suspected renal malignancy. PN, therefore, cannot be superior to RN with regards to cancer control. While long-term data on oncologic efficacy of PN for cT1a renal masses suggest excellent CSM [8], the evidence is less robust for PN in the setting of larger tumors. Shah et al. examined survival outcomes of patients with a positive surgical margin (PSM) after PN for "high-risk" tumors (defined as pT2-T3a or Fuhrman grade III or IV) in a contemporary, multi-institutional cohort [9]. The overall incidence of PSM was 7.8%. At a median follow-up of 33 months, 6% of all patients had suffered a recurrence, and a positive surgical margin conferred a 2-fold increase in the risk of developing a recurrence (HR 2.08 95%CI 1.09–3.97; $p = 0.03$). Most striking from these data is that high-risk patients with a PSM had a significantly higher risk of recurrence compared to both low-risk patients with a PSM and high-risk patients without a PSM (HR 7.48 95%CI 2.75–20.3, $p < 0.001$).

Tumor upstaging following PN is another concern that needs to be addressed. Mouracade et al. reported on factors that were predictive of upstaging cT1 renal masses to pT3a tumors [10]. On multivariate analysis, the authors found that tumors with moderate and high complexity RENAL nephrometry scores were significantly more likely to be upgraded from cT1 to pT3a on final pathology. Moreover, patients who were upstaged to pT3a had significantly higher rates of PSM than patients who remained pT1 (18.6% vs 5.8%, $p < 0.01$). This questions the pervasive dogma that positive margins after PN are clinically inconsequential. When considering surgical options for large, complex tumors with inherently aggressive biology, we must be cognizant that a positive margin in this setting is not acceptable.

DOES PN REALLY PROVIDE DURABLE BENEFITS IN LONG-TERM RENAL FUNCTION?

Those who advocate for nephron-sparing surgery when at all feasible highlight the ensuing sequelae of chronic kidney disease – namely cardiovascular and metabolic morbidity – as the chief reason to preserve renal parenchyma at all costs. The significant increase in cardiovascular events and mortality has been well-documented in the literature regarding medical CKD [11]. Hence, it is logical to extrapolate these data to nephrectomy patients with the laudable goal of reducing morbidity and mortality. But has it been shown to be true? Smaldone et al. examined over 5,000 Medicare beneficiaries who underwent RN or PN for renal masses ≤ 4 cm. The authors found that PN afforded a protective effect in the short term, with a longer OS at 1 and 3 years post procedure [12]. However, this treatment benefit disappeared at 5 and 10 years of follow-up. This time varying protective effect of PN is contrary to the assertion that nephron preservation prolongs survival by reducing the long-term detrimental physiologic effects. One could conclude that patients with severe co-morbidities or more aggressive tumors die earlier and the surviving patients are not harmed by reductions in GFR.

The concept that CKD induced by systemic diseases such as hypertension, diabetes, and glomerular nephropathies is distinct from CKD that develops as a result of surgical removal of renal parenchyma is an intriguing one. Long-term follow-up on donor nephrectomy patients has shown that kidney transplant donors have survival outcomes similar to

age-matched controls with two functioning kidneys [13]. This population represents an exquisitely healthy group that cannot be easily compared with kidney cancer patients. However, these data have led investigators to hypothesize that reductions in GFR from a nephrectomy for RCC may not correlate with worse clinical outcomes. Lane et al. evaluated this by stratifying patients according to CKD status: no CKD, surgically-induced CKD (CKD-S), and pre-existing medical renal disease prior to nephrectomy (CKD-M/S) [14]. Non-renal cancer mortality did not differ significantly in patients with no CKD and in those with CKD-S (HR 1.07 95% CI 0.86–1.32, $p = 0.5$). Interestingly, the new baseline GFR in CKD-S patients remained stable over time, whereas patients with CKD-M/S experienced progressive declines in GFR [14]. This study highlights two important aspects of the debate surrounding PN and RN. First, it confirms that patients with pre-existing CKD are vulnerable to continued loss of renal function following nephrectomy and PN should be prioritized when possible. Second, it suggests that RN can be safely undertaken without inducing an irreversible course toward clinically significant CKD.

PATIENT SELECTION AND WEIGHING RISK VS. REWARD

A major concern when evaluating the literature comparing RN and PN is the inherent selection bias for healthier patients with clinically less-aggressive tumors to PN. With the exception of the aforementioned EORTC 30904 trial, we rely on retrospective data to inform us on this topic. A recent meta-analysis comparing RN and PN for cT1b-T2 renal tumors favored PN for OS, CSS, and preservation of renal function [15]. However, PN patients were an average of 3 years younger than RN patients, and the analysis was unable to control for multiple parameters that may influence survival outcomes, including ASA, ECOG and competing co-morbidities. Importantly, RN patients had a significantly higher rate of malignant histology in the surgical specimen, as compared to PN patients [15]. This selection bias is further illustrated by Shuch et al., who compared individuals who underwent RN or PN to age-matched controls without a cancer diagnosis in the SEER database [16]. No difference in OS was found between RN patients and the non-cancer controls. Patients who underwent PN actually had better OS than the non-cancer controls (HR 1.26, 95%CI 1.10–1.44; $p < 0.001$). Clearly, these data inform us that selection bias is widespread and caution should be utilized when drawing conclusions regarding the superiority of PN, especially when using administrative databases.

While the clinical benefits of nephron preservation remain subject to rigorous debate, the inherent perioperative risks associated with PN cannot be overlooked. PN exposes patients to complications that do not occur with RN, including post-operative urine leak, pseudoaneurysm formation leading to potentially life-threatening hemorrhage, and even strictures of the ureteropelvic junction. Table 1 summarizes reported overall complication rates and the incidence of urine leak and pseudoaneurysm requiring embolization for PN in the setting of cT1b or larger tumors. In a recent meta-analysis, PN was associated with a higher risk of perioperative complications as compared with RN in all studies included in the analysis (OR 1.74 95%CI 1.33–2.24) [15]. The risk is particularly high when PN is undertaken for anatomically complex tumors. Simhan et al. examined their series of open and robotic PN for anatomically complex tumors defined as those with a RENAL Nephrometry Score ≥ 7, and found that nearly 14% had major complications requiring a second procedure [17].

A subsequent multi-center study found a significantly higher rate of Clavien ≥ 3 complications for patients undergoing PN compared to RN for cT2 renal masses (17.5% vs 2.5%, respectively, $p < 0.001$) [18].

Table 1
Complication rates for patients undergoing PN for large or complex renal masses

Reference	N	T Stages Included	Overall Complications, No. (%)	Urine leak, No. (%)	Embolization of pseudoaneurysm, No. (%)
Margulis [20]	34	T2-T3b	3 (9)	2 (5.8)	1 (2.9)
Breau [21]	69	≥T2	27 (39.1)	12 (17.4)	2 (2.9)
Simhan [22]	390	T1-T3a	149 (38)	42 (10.8)	4 (1)
Becker [23]	90	T1b-T2	27 (29.6)	3 (3.3)	0 (0)
Long [24]	46	≥T2	14 (30)	6 (12.2)	0 (0)
Kopp [18]	80	≥T2	30 (37.5)	8 (10)	3 (3.8)
Tomaszewski [19]	187	T1b-T2 (subset)	47 (25.1)	17 (9.1)	1 (0.5)

These included 8 urine leaks requiring ureteral stent or percutaneous drainage, 3 pseudoaneurysms requiring embolization, and one pleural effusion requiring thoracentesis. This study also highlights that patients with highly complex tumors (RENAL score $\geq$ 10) have significantly worse OS and CSS compared to those with less complex tumors. Consideration of these perioperative risks becomes increasingly important in elderly patients and those with a higher burden of medical co-morbidities. Tomaszewski et al. showed that "high risk" patients, defined as age >75 years and Charlson Co-morbidity Index >2, had a complication rate of 22.4% compared to 14.1% for younger, healthier patients undergoing RN or PN ($P = 0.002$) [19]. No statistically significant difference in complication rates was seen between RN and PN for the overall cohort, but high-risk patients were significantly more likely to undergo RN. In the subset of patients with cT1b-T2 tumors, PN was associated with a higher incidence of post-operative complications compared to RN (25.1% vs 14.9%; $p = 0.02$).

If urologists continue to pursue complicated procedures for maximal nephron preservation, they must do so without inducing undue additional morbidity from the procedure itself, and without any compromise from an oncologic standpoint.

CONCLUSIONS

The available literature poorly addresses the optimal surgical management of localized renal tumors greater than 4 cm. This topic will likely remain controversial as urologists continue to pursue ambitious nephron-sparing approaches for larger, more complex masses, especially with technical improvements afforded by the robotic platform. However, the heterogeneity of this patient population is not consistently reflected in studies espousing nephron-sparing at all costs. We are unlikely to see an adequately powered, randomized trial materialize in the near future to provide insight on this controversy. Therefore, urologists must view the evidence with discerning eyes and fully understand the risks and benefits in specific circumstances. This is especially true in the frail or elderly patient population. Radical nephrectomy in experienced hands is a sound oncological operation with a lower risk of perioperative complications compared to partial nephrectomy. The decrease in GFR observed due solely to reduction in nephron mass from nephrectomy has not been shown to translate into a meaningful detriment to survival or quality of life. While it is tempting to accept the intuitive notion that partial nephrectomy should be superior in all cases, this intuition should not supersede the evidence that radical nephrectomy remains the gold standard for large or complex renal tumors.

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