REVIEW

What is the current role of partial nephrectomy for T2 tumors?

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Introduction: *To review oncological and functional outcomes for partial nephrectomy in the setting of T2 tumors.*
Materials and methods: *We performed a comprehensive literature review on partial nephrectomy for T2 tumors, focusing on major primary series reporting oncological and functional outcomes, as well as complication rates in the last 10 years.*
Results: *Recent series have reported comparable oncological outcomes between partial nephrectomy and radical nephrectomy for ≥ T2 tumors. However, most of these studies are retrospective in design with small sample sizes. With regard to functional outcomes, partial nephrectomy outperforms radical nephrectomy. However, outcomes are dependent on the amount of residual renal parenchyma left after partial nephrectomy for larger tumors. Partial nephrectomy is associated with an increased rate of complications when compared to radical nephrectomy, but in experienced hands this increase tends to remain at an acceptable level. There are few studies that have investigated the role of minimally invasive surgery (MIS) in the setting of T2 tumors. Although MIS techniques may be underutilized for management of T2 tumors, it is a feasible approach in highly selected patients.*
Conclusions: *Partial nephrectomy has emerged as an acceptable alternative for surgical management of T2 renal tumors over the last decade. Nephron-sparing surgery demonstrates similar oncological outcomes compared to radical nephrectomy and can be considered even for larger tumors in carefully selected patients whenever feasible.*

Key Words: T2 tumor, partial nephrectomy, radical nephrectomy

Introduction

Over the past two decades, partial nephrectomy (PN) has become the gold standard for the surgical management of small renal masses. PN has demonstrated similar safety, functional, and oncological outcomes compared to radical nephrectomy (RN).[1] While a large prospective randomized trial failed to show an overall survival (OS) benefit for PN compared to RN,[2] other studies have indicated that up to 26% of patients with renal cell carcinomas have pre-existing renal impairment, and patients undergoing PN are at decreased risk of developing or aggravating chronic kidney disease and cardiovascular events.[3-7] It should also be taken into consideration that the incidence of a metachronous contralateral tumor varies from 2%-6% after RN, and remains constant for more than 10 years after surgery.[8]

Although the potential benefits of PN for T1 tumors are more defined, the question of whether PN should also become a standard of care for larger tumors remains debatable.[9] There has been an increasing trend towards the use of PN for T2 tumors over the past few years,[10] given its reported equivalent outcomes compared to RN.[11] Consequently, it has been suggested that indications for PN should depend primarily on technical feasibility rather than only on tumor size.[12]

The purpose of this article is to review the literature regarding safety, oncological, and functional outcomes of PN for T2 tumors published in the last decade.

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Evidence acquisition

We performed a systematic literature review based on Pubmed, Cochrane, EMBASE and Scopus databases between 2005 and 2015 using keywords "partial nephrectomy" or " nephron-sparing surgery" in conjunction with "T2" or "> 7 cm". Only relevant articles reporting functional and oncological outcomes were included in this review and primarily articles comparing PN and RN. Articles that did not address these topics were excluded, as well as small series, abstracts, case reports, or editorials. The search was limited to the English language.

Comparing outcomes between PN and RN for T2 tumors

There are no prospective randomized studies comparing outcomes between PN and RN in the setting of T2 tumors. Most publications are retrospective in design with small sample sizes and there is considerable variability in the outcomes reported. One of the most common major limitations of retrospective studies is the inherent risk of selection bias. It is expected that surgeons opt to perform RN on patients with less favorable tumors and select patients with better performance status and with apparently less complex tumors for PN. Mir et al showed in a recent meta-analysis, that patients undergoing PN were significantly younger and had smaller masses compared to RN patients.[13] Although data should be interpreted cautiously, this is the best evidence available in the literature thus far. Table 1 summarizes major series comparing PN and RN for surgical management of T2 tumors. Tables 2 and 3 report descriptive outcomes of selected PN series.

Oncological outcomes

Most studies have reported comparable oncological outcomes for PN compared to RN for treatment of T2 tumors. However, with regard to oncological outcomes, RN still remains the procedure of choice for T2 tumors owing to the assumption that it offers better cancer control than PN.

Margulis et al[14] retrospectively analyzed outcomes of a large group of patients who underwent PN or RN

TABLE 1. **Major series comparing partial nephrectomy (PN) and radical nephrectomy (RN) for T2 tumors**

		Margulis et al[14]	Jeidres et al[21]	Breau et al[18]	Kopp et al[19]
# of patients	RN	567	45	207	122
	PN	34	17	69	80
Tumor size, cm	RN	9.3†	8.8	8.5	10.2
	PN	5.2†	8.9	7.5	8.8
Estimated blood loss, mL	RN	994.9	n/a	200	225†
	PN	975	n/a	400	325†
Perioperative* complications (%)	RN	2.9†	n/a	31	24.6†
	PN	9†	n/a	39.5	37.5†
Overall survivor (%)	RN	n/a	n/a	n/a	80
	PN	n/a	83.8	70	83.3
Cancer specific survival (%)	RN	74	87.2†	75	82.5
	PN	78	67†	83	86.7
Recurrence free survival (%)	RN	62†	n/a	n/a	69.8
	PN	82†	n/a	n/a	79.9
Disease progression (%)	RN	43.4	n/a	36	23.7
	PN	62.1	n/a	28	10
Follow up, months	RN	43.4	46.8	38.4	47.4
	PN	62.1	32.4	38.4	35.1

†$p < 0.05$
*Margulis et al reported only procedure-related complications
n/a = not available
Disease progression = metastatic disease or local recurrence

TABLE 2. **Clinical characteristics and functional outcomes of partial nephrectomy (PN) for T2 tumors**

	Peycelon et al[22]	Karellas et al[32]	Becker et al[17]	Long et al[27]	Esen et al[40]	Brandao et al[26]
# of patients	16	34	91	46	17	29
Tumor size, cm	8.38	7.5	9.2	8.7	8.2	8.0
Length of stay, days	16	4	12	n/a	n/a	4
Change in renal function (%)	+6.8%^{creatinine}	-15%^{eGFR}	-12%^{eGFR}	n/a	-13.8%^{eGFR}	-15.8%^{eGFR}
Estimated blood loss, mL	559	500	n/a	225	267.6	250
Perioperative transfusion, number of patients (%)	n/a	n/a	16 (17.7)	4 (8.6)	2 (11.7)	8 (27.5)
Perioperative complications (%)	18.8%	32.3%	29.6%	34.7%	35.7%	45%
Approach	16 OPN	32 OPN 7 LAP	90 OPN 1 LAP	n/a	13 OPN 4 ROB	29 ROB

Creatinine in mg/dL; eGFR in mL/min/1.73^2
n/a = not available; OPN = open; LAP = laparoscopic; ROB = robotic-assisted

for pT2 or pT3 renal cell carcinoma (RCC). In this cohort of 601 patients, 567 (94%) underwent RN and 34 (6%) underwent PN, with a mean follow up of 43.4 and 62.1 months, respectively. There was a significantly higher 5 year recurrence-free survival (RFS) for PN versus RN (82% versus 62%, $p < 0.012$), but cancer specific survival (CSS) was equivalent for both procedures. Patients treated with PN had smaller tumors, but a higher incidence of pT3a disease compared to those that underwent RN. On multivariate analysis, adjusted for tumor stage, grade, and histological subtype, the type of surgery was not an independent predictor of recurrence or cancer specific mortality (CSM). Despite the difference in pathological stage, both groups showed equivalent oncological outcomes. Similarly, Weight et al[15] compared oncological outcomes between PN and RN for a median follow up of 53 months, and demonstrated that there was no difference in CSS or OS even after adjusting for upstaging of pathological specimens. Additionally, the authors demonstrated that grade, age, and Charlson score were predictors of OS, not the stage or the type of surgery performed.

These findings are consistent with a recent analysis from the SEER database showing that tumor size did not necessarily correlate with tumor grade, and approximately 75% of tumors > 7 cm and 65% of tumors > 10 cm were low grade lesions.[16] These data provide support for the idea that PN is a feasible alternative for management of larger tumors from an oncological standpoint. Becker et al[17] investigated oncological outcomes in 91 patients undergoing PN for tumors > 7 cm. Their findings showed similar oncological outcomes (5 year rates for OS, CSS, and RFS of 88%, 97%, and 91%, respectively) compared to

TABLE 3. **Oncological outcomes of partial nephrectomy (PN) for T2 tumors**

	Peycelon et al[22]	Karellas et al[32]	Becker et al[17]	Long et al[27]	Esen et al[40]	Brandao et al[26]
# of patients	16	34	91	46	17	29
Overall survivor (%)	n/a	78	88	94.5	n/a	92.9
Cancer specific survival (%)	56.2	89	97	94.5	n/a	n/a
Recurrence free survival (%)	n/a	71	91	88	n/a	n/a
Disease progression (%)	37.5	n/a	n/a	10.9	5.8	14.2
Follow up, months	70	n/a	28	13.1	35.2	17.3

n/a = not available
Disease progression = Mets or local recurrence

historical RN series. Similarly, Breau et al[18] reported comparable oncological results for both procedures.

The study by Kopp et al[19] analyzed one of the largest contemporary North American cohorts comparing oncological outcomes between PN and RN for large kidney tumors. Survival outcomes were evaluated controlling for R.E.N.A.L nephrometry score.[20] Among 122 and 80 cases of RN and PN, respectively, there were no differenced in 5 year RFS, CSS, and OS for PN when compared to RN (69.8% RN versus 79.9% PN, p = 0.115; 82.5% RN versus 86.7% PN, p = 0.407; 80% RN versus 83.3% PN, p = 0.291, respectively). On the other hand, when patients with a R.E.N.A.L. score above or below 10 were compared, there was an improvement in OS, CSS, and RFS (p < 0.001) among those with a score < 10. On multivariate analysis, the type of procedure was not associated with disease progression, CSM, or all-cause mortality, but R.E.N.A.L score > 10 was associated with disease progression (HR 5.31, p = 0.006). These data suggest that oncological outcomes may be more related to tumor complexity rather than the type of surgical procedure that was performed.

Jeldres et al[21] analyzed three separate variables (tumor size > 7 cm, high Fuhrman Grade, and pT3 stage) and compared their effects on oncological outcomes in a matched cohort of 45 and 17 patients undergoing RN and PN, respectively. When comparing tumors > 7 cm, they found that PN was associated with a 5.3-fold higher rate of CSM compared to RN (p = 0.025). A major limitation of this study was the small sample size in the PN group, which may have impacted survival outcomes of the study. Similarly, Peycelon et al[22] reported that PN was less feasible than RN for tumors > 7 cm in terms of oncological outcomes. In an attempt to address the limitations of previous studies,[21] Hansen et al[23] investigated a much larger cohort of patients from the SEER database, and found that PN and RN had comparable rates of CSM after propensity-based matched analysis adjusting for tumor size, stage, and grade. According to the authors, the decision to perform PN should depend more on technical ability and not necessarily on tumor grade or stage.

It is known that PN is associated with an increased risk of positive surgical margins for larger and more complex tumors, which can be minimized by a RN approach since the whole kidney is being removed. While previous studies failed to show any association between positive surgical margins and risk of recurrence,[24] a recent publication showed an increased risk of recurrence for PN, particularly in patients with adverse pathology findings (pT2-3a or Fuhrman III/IV).[25] However, the impact of recurrence on OS or CSS is still not clear to determine the true clinical relevance of a positive surgical margin.

Although recent studies have reported equivalent oncological outcomes for PN and RN,[10,17,19,23,26-28] these numbers might be overestimated due to potential selection bias. Curiously, some studies have reported superior oncological outcomes for PN compared to RN, which may easily be explained by selection bias.[13] In addition, there was great variation in the cut off size of tumors selected for PN in these studies. Randomized controlled trials are needed in order to better characterize and compare oncological outcomes between PN and RN in the setting of T2 tumors.

Functional outcomes

Preservation of renal parenchyma and decreasing the potential risk of developing chronic kidney disease (CKD) are the major reasons for performing PN. Van Poppel et al[29] published renal function outcomes from EORTC 30904, where RN and PN for tumors < 5 cm were compared after a median follow up of 6.7 years. PN was associated with a significant reduction in the incidence of stage A (estimated glomerular function – eGFR < 60 mL/min/1.73 m^2, 64.7% PN versus 85.7% RN, p < 0.001) and stage B (eGFR < 45 mL/min/1.73 m^2, 27% PN versus 49%, p < 0.001) renal dysfunction. Several other studies demonstrated benefits of PN for preservation of renal function for tumors < 7cm.[3-7,30] Lane et al[31] have suggested that the percentage of spared parenchyma may be the most important factor for preservation of renal function. Consequently, as tumor size increases, the percentage of parenchyma remaining after PN may not confer optimal renal functional outcomes. On the other hand, PN in larger tumors has been historically used for imperative settings (i.e., solitary kidney), and therefore may be extrapolated to the elective setting.

It has been hypothesized that most renal functional outcomes are driven by preoperative eGFR instead of the type of surgery or ischemia time. Ching et al[33] investigated 5 and 10 year renal functional outcomes in 282 patients with a solitary kidney treated with PN and showed that preoperative eGFR was a significant predictor of renal function after PN. Recently, Lane et al[34,35] suggested that pre-existing (preoperative) CKD should be considered as a potential prognostic factor and investigated postoperative GFR between patients with and without preexisting CKD. Among 4,299 patients who underwent surgery for renal cancer, patients with prior CKD had significantly higher risk of progressive decline in renal function compared to patients that had no prior CKD with a median follow up of 9.4 years. These data suggest that preoperative renal impairment rather than surgically-induced

CKD is the main predictor of postoperative renal functional outcomes. Additionally, it was shown that a postoperative GFR of < 45 mL/min/1.73 m^2 is associated with an increased risk of mortality. Based on these findings, it is reasonable to consider RN for patients with complex large renal masses and a normal functioning contralateral kidney, since the contralateral kidney can compensate for the loss of one kidney. However, when there is pre-existing CKD or potential risk factors for CKD such as diabetes and hypertension, efforts should be made to pursue PN despite tumor size, due to a higher probability of de novo CKD in these patients postoperatively.

Prospective data to elucidate mechanisms responsible for development of de novo CKD are needed. Few studies have retrospectively compared rates of de-novo CKD between PN and RN in large tumors. Breau et al[18] showed a statistically significant increase in median creatinine levels with RN compared to PN (33% versus 9.5%, p < 0.001). Karellas et al[32] also found a significant change in eGFR after PN for tumors ≥ 7 cm (65 versus 55 mL/min/1.73 m^2 p = 0.003). Among 34 patients undergoing PN, only one (3%) required hemodialysis after surgery. However, there would have been a more drastic decrease in eGFR and a requirement for hemodialysis in all patients with a solitary kidney if they were to undergo RN. Due to the retrospective nature of both studies, limited data on patient comorbidities was available and it is not known whether patients at increased risk of CKD (who may benefit most from nephron-sparing surgery) are receiving PN.

Along with oncological outcomes, Kopp et al[36] compared renal functional outcomes between PN and RN for T2 tumors applying R.E.N.A.L score to control for tumor complexity. In a cohort with relatively similar comorbidities, there was a significant decrease in eGFR for patients undergoing RN versus PN (–19.7 versus – 11.9 p = 0.006) and a significant increase in creatinine levels, although not clinically relevant (0.3 versus 0.2 p = 0.003). De novo CKD was 40.2% for RN versus 16.3% for PN (p < 0.001). However, patients undergoing PN had significantly smaller masses compared to the RN group, which contributes to potential selection bias.

It is worth mentioning that tumor characteristics such as location, complexity, and depth may play a role in eGFR changes. When stratifying for R.E.N.A.L score ≥ 10, Kopp et al[36] found no significant difference in the type of surgery, suggesting that PN does not provide any benefit in terms of renal functional outcomes compared to RN due to less preservable parenchyma in more complex tumors. Therefore, R.E.N.A.L score may be used as an indicator of preservable parenchyma when choosing PN for patients with larger tumors. This result was endorsed by Brandao et al[26] who reported a similar decline in eGFR between robotic-assisted partial nephrectomy (RAPN) for tumors ≥ 7 cm and ≤ 4 cm (15.8% versus 12.2% p = 0.98). This can be explained by the fact that more than 60% of the T2 tumors were less complex, and only a small volume of renal parenchyma was actually removed.

There are clear benefits in renal functional outcomes for small masses with PN, yet there is still controversy whether PN may attenuate renal impairment for larger and complex tumors, since benefits may be mitigated by the fact that lesser parenchyma can be preserved.

Complications

One of the main criticisms of PN for larger tumors is the increased potential risk of perioperative complications. Three studies retrospectively compared the rate of complications between PN and RN and found a higher incidence of overall complications associated with PN, Table 1. In imperative settings, it may be acceptable to have a higher rate of major complications after PN to prevent anephria, but in elective surgeries major complications should be comparable to RN for T2 tumors. Nonetheless, challenging PN for complex kidney masses can be time consuming even in experienced hands and it has been shown that increased operative time (OT) is associated with higher complication rates.[37] Margulis et al[14] reported similar OT for PN and RN (186.8 min versus 185.9 min, p = 0.946), but a significantly higher procedure-related complication rate for PN (2.9% for RN versus 9% PN p = 0.001), which included prolonged urinary fistula in two (6%) patients. Kopp et al[19] showed a significant increase in OT for PN compared to RN (221 min versus 153 min, p = 0.001), but similar risk of overall complications, even though the incidence of high grade complications was markedly increased for PN compared to RN (17.5% versus 2.5%, p < 0.001). PN was also associated with significantly higher estimated blood loss compared to RN (median 325 mL versus 225 mL p = 0.05), but similar transfusion rate. Transfusion was associated with a 3.5-fold risk of all-cause mortality regardless of the type of surgery, which is in agreement with a recently published study.[38]

Breau et al[18] examined complication rates as a secondary outcome in a matched cohort of 69 and 207 patients undergoing PN and RN, respectively. Indications for PN were elective in 29 (42%) patients, of which 12 (41%) were pT2 and 14 (59%) were pT3. Similar complication rates for both approaches were reported. However, as many as 12 (17.5%) patients

undergoing PN developed a urine leak. Becker et al[17] also assessed complication rates associated with PN for tumors > 7 cm and stratified them using Clavien-Dindo score (CDS).[39] An overall complication rate of 29.6% was observed, yet the majority (89.1%) of these were minor complications (CDS grades 1 or 2).

PN for larger tumors is presumed to be associated with a higher risk of urine leak, but interestingly Karellas et al[32] reported just four (11%) patients with this type of complication. Three patients (75%) had tumors ≤ 7.3 cm, while the other patient (25%) had a larger tumor (19 cm), supporting the fact that tumor size is not the only predictor of urinary leak. Nevertheless, urine leak remains one of the most common procedure-related complications associated with PN, with rates ranging from 3% to as high as 19%.[17,22,27,32,40]

Minimally invasive surgery (MIS) has emerged as a gold standard for PN in cT1a tumors,[1] but the role of MIS for larger kidney tumors remains controversial due to concerns over potentially higher complication rates. A contemporary French study[28] investigated trends in utilization of PN and RN in a prospective population-based cohort. Among 667 RN procedures, 47.8% had a laparoscopic approach while out of 576 PN procedures, 36.7% of cases had an MIS approach (21% laparoscopic; 15.7% robotic-assisted). As expected, in the setting of T2 tumors, MIS was underutilized, with the majority of patients undergoing open surgery (92% for PN versus 71% for RN, $p < 0.001$). At the time of writing this review, Brandao et al[26] reported the only series comparing complication rates of RAPN in tumors ≥ 7 cm and compared it to a control group of tumors ≤ 4 cm, where MIS/RAPN was used as the gold standard approach. The overall complication rate (37.9% versus 15.8%, $p = 0.005$) and OT (200 min versus 180 min, $p = 0.005$) were higher in patients with tumors ≥ 7 cm. However, major complications were comparable between both groups. Several limitations of this study need to be addressed, especially the small sample size in the group of patients with larger tumors and a discrepancy in the distribution between groups without any matching or controlling for bias. Apparently, MIS for PN in T2 tumors is feasible, yet it should be considered only in highly selected cases.

Taken together, PN is associated with increased rates of overall and major complications compared to RN, but still within an acceptable range in experienced hands. Patients should be fully informed of the potential risks and benefits of undergoing PN as part of a shared decision-making process. In addition, surgeons should weigh the potentially increased risk of morbidity related to PN, especially for more complex tumors.

Conclusion

With technical improvements and increasing experience seen over the past decade, PN has emerged as an alternative option for the management of T2 tumors. Most studies support the use of PN, reporting similar oncological outcomes, improved renal function, and acceptable complication rates compared to RN at experienced centers. Although no randomized controlled trial comparing PN to RN in the setting of T2 tumors currently exists, PN should be considered as a surgical option whenever feasible. Further prospective studies are needed to investigate the true benefit of PN for management of larger kidney tumors. □

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