Partial nephrectomy is not the proven standard for Stage T1b renal cell carcinoma

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Renal cell carcinoma (RCC) has historically been managed by radical nephrectomy (RN). Over time, nephron-sparing strategies have been popularized and encouraged for patients at risk of renal insufficiency (poor baseline renal function, bilateral tumours, tumour in a solitary kidney or a history of nephron-threatening conditions, such as hypertension or diabetes). Only in the past 10 years has elective partial nephrectomy (PN) for tumours <4 cm (T1a) become an acceptable treatment option with well-documented data to support cancer control.[1]

Based on concerns of diminished long-term renal function, but equivalent cancer control, many members of the urologic community have recently been actively promoting elective PN for T1a and larger tumours. A commonly cited study by Go and colleagues demonstrated a relationship between poor renal function and subsequent cardiovascular disease, hospitalization and worsened overall survival (OS).[2] This study included all causes of chronic renal insufficiency. In retrospective analyses of patients undergoing surgery for RCC, those being treated by PN had an improved OS versus those treated by RN, and it has been postulated that the loss of renal function was relevant to OS in these patients.[3] There appeared to be mounting proof that PN was superior to RN, albeit with low-level evidence. Consequently, more surgeons begun to embrace elective PN for T1a tumours, but at a slower than expected rate.[4] Encouraged by this data and perhaps also reflective of an increased comfort with PN, surgeons expanded the indications for "elective" PN.[5] ***Herein lies the problem: the expanding indications are without substantive supportive evidence.*** Although technically feasible, for elective PN in T1b RCC to be acceptable there must be: (1) equal or improved cancer control; (2) equivalent or diminished morbidity; and (3) improved long-term renal function benefitting overall survival

1. Cancer control

Regarding cancer control, Leibovich and colleagues initially demonstrated equivalent 5-year cancer-specific survival (CSS), with a slightly higher, albeit insignificant, recurrence rate for PN versus RN (6% vs. 2%) in patients with T1b tumours.[5] Thereafter, in a summary of the experience at Mayo and Memorial Sloan Kettering, Thompson and colleagues compared PN to RN for T1b tumours.[6] The PN group was more likely to have a solitary kidney and suffer from chronic kidney disease. With a median follow-up of 4.8 years, there was no significant difference in CSS or OS. Badalato and colleagues used administrative data to identify patients undergoing PN and RN for T1b tumours between 1998 and 2007.[7] Propensity score-matching was used to adjust for potential baseline differences and no difference in CSS or OS was found. Even when stratified by tumour size and age, a survival difference could not be confirmed. Similarly, Zini and colleagues reviewed 7 institutional databases (n = 451) of patients undergoing PN or RN for T1a-b RCC.[8] They found that nephrectomy type did not affect mortality.

Peycelon and colleagues published their experience with PN in tumours >4 cm with most patients having T1b disease.[9] The multifocal rate was 15% and the positive surgical margin (PSM) rate was 13%. They concluded that although PN for T1b tumours appeared to be effective, "the oncological safety for tumours >7 is less obvious."[9] Although PSMs are felt to have little impact on CSS, the literature is largely based on tumours <4 cm, of which most are low grade with a known favourable natural history. With increasing size, tumours >4 cm are more likely to be higher grade and locally invasive. The long-term biologic potential of PSMs in this setting is unknown and potentially significant.

2. Complications and morbidity

PN for larger tumours will likely introduce significant morbidity. For T1a tumours, the morbidity of RN and PN is generally equivalent; the only difference is the type of complication experienced.[10] Based on the European Organization for Research and Treatment of Cancer (EORTC) randomized clinical trial, the rate of severe hemorrhage was slightly higher after PN then RN (3.1% vs. 1.2%). Ten patients (4.4%), all treated with PN, developed urinary fistulae. Re-operation for complications was necessary in 4.4% of PN and 2.4% of

RN patients. From other series, transfusion rates upwards of 27.9% have been reported for PN in T1b tumours.[9] Although techniques may have improved, one must also keep in mind that these are published data, and thus biased towards better results and not reflective of real world practices. Based on administrative data the PSM rates in Ontario for all tumours is 12%, much higher than the published rates from centres of excellence (Finelli et al, unpublished). Published studies likely underestimate the expected complication rates of performing PN, particularly in the setting of T1b tumours.

Laparoscopic surgery is significantly less morbid than open renal surgery and specifically, laparoscopic radical nephrectomy (LRN) has been shown to be less morbid than open PN.[11] Open renal surgery, particularly through the commonly used flank incision, is a source of flank bulge and chronic pain in a significant proportion of patients.[12] In Ontario, open PN is associated with a rib resection rate of 15% (Finelli et al, unpublished). This figure would likely increase with larger tumours being managed by PN. In a controversial, but thought provoking, study, Matin and colleauges compared LRN to open PN for tumours <4 cm.[11] The mean age, American Society of Anesthesiologists (ASA) and tumour size were higher in the LRN group. However, the median analgesic requirement and length of stay (1 vs. 5 days) were significantly less for the LRN group ($p < 0.001$). This is only one example of several studies that demonstrated the diminished morbidity of laparoscopic nephrectomy versus open PN or RN.

If one specifically looks at laparoscopic partial nephrectomy (LPN), the rates are relatively low and concentrated at high volume centres.[13] The uptake of LRN has been much more rapid and performed by a wide range of surgeons.[13] Given the complexity of LPN, a broader indication for elective PN will result in more open renal surgeries and PN-related complications, both of which would result in significantly more morbidity than one would see with LRN.

3. Long-term renal function benefit and overall survival

The benefit of long-term renal function is intuitively appealing, but solely founded on administrative data and retrospective and/or single centre series.[14,15] There has been suggestion that OS is improved for patients having undergone PN versus RN.[16] Patients undergoing RN are more likely to be older and carry more comorbidities and, although the benefit of PN persisted in most analyses when using propensity score-matching, it became much less significant than on initial analyses.[16] In a recent review of advanced PN, Touijiere and colleagues concluded that although there is preliminary evidence to support PN for larger tumours, "the potential for selection bias and residual confounding factors may contribute to the observed difference (benefit)."[17] To my knowledge, there has never been a study to demonstrate diminished dialysis or renal replacement rates in patients treated by elective PN versus RN. Obviously, PN is beneficial to renal function, but it is yet to be determined that the loss of nephron mass with surgery for RCC is independently a significant detriment to survival.

Lastly, one must follow the evidence. Surgeons have been criticized for not conducting randomized clinical trials to address important issues.[18] In this particular instance, we have Level 1 evidence that PN is not superior to RN for tumours <5 cm. [19] It continues to astound me that when Level 1 evidence exists we look for flaws in study design to refute the findings that do not support our convictions. Although a critique of this study is beyond the scope of this debate, the results clearly showed that PN was not superior to RN for OS. If anything, RN may have been associated with better survival outcomes. Therefore in the absence of Level 1 evidence for elective PN in T1b tumours, one must be cautious in recommending PN. Although there may be real benefits to elective PN for T1b tumours, the current data do yet support it, as a standard and, thus, it would be prudent to proceed with caution.

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References

1. Hafez KS, Fergany AF, Novick AC. Nephron sparing surgery for localized renal cell carcinoma: impact of tumor size on patient survival tumor recurrence and TNM staging. *J Urol* 1999;162:1930-3. http://dx.doi.org/10.1016/S0022-5347(05)68071-8
2. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-305. http://dx.doi.org/10.1056/NEJMoa041031
3. Huang WC, Elkin EB, Levey AS, et al. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors—is there a difference in mortality and cardiovascular outcomes? *J Urol* 2009;181:55-61. http://dx.doi.org/10.1016/j.juro.2008.09.017Miller DC, Hollingsworth JM, Hafez KS, et al. Partial nephrectomy for small renal masses: an emerging quality of care concern? *J Urol* 2006;175(3Pt1):853-7. http://dx.doi.org/10.1016/S0022-5347(05)00422-2
4. Leibovich, BC, Blute ML, Cheville JC, et al. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. *J Urol* 2004;171:1066-70. http://dx.doi.org/10.1097/01.ju.0000113274.40885.db
5. Thompson RH, Siddiqui S, Lohse CM, et al. Partial versus radical nephrectomy for 4 to 7 cm renal cortical tumors. *J Urol* 2009;182:2601-6. http://dx.doi.org/10.1016/j.juro.2009.08.087
6. Badalato GM, Kates M, Wisnivesky JP, et al. Survival after partial and radical nephrectomy for the treatment of stage T1bNOMO renal cell carcinoma (RCC) in the USA: a propensity scoring approach. *BJU Int* 2011; http://dx.doi.org/10.1111/j.1464-410X.2011.10597.x. Epub 2011 Sept 20.
7. Zini L, Patard JJ, Capitanio U, et al. Cancer-specific and non-cancer-related mortality rates in European patients with T1a and T1b renal cell carcinoma. *BJU Int* 2009;103:894-8. http://dx.doi.org/10.1111/j.1464-410X.2008.08252.x
8. Peycelon M, Hupertan V, Comperat E, et al. Long-term outcomes after nephron sparing surger for renal cell carcinoma larger than 4 cm. *J Urol* 2009;181:35-41. http://dx.doi.org/10.1016/j.juro.2008.09.025
9. Van Poppel H, Da Pozzo L, Albrecht W, et al. A prospective randomized EORTC intergroup phase 3 study comparing the complications of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol* 2007;51:1606-15. http://dx.doi.org/10.1016/j.eururo.2006.11.013

10. Matin SF, Gill IS, Worley S, et al. Outcome of laparoscopic radical and open partial nephrectomy for the sporadic 4cm o less renal tumor with a normal contralateral kidney. *J Urol* 2002;168(4Pt1):1356-9. http://dx.doi.org/10.1016/S0022-5347(05)64448-5
11. Chatterjee S, Nam R, Fleshner N, et al. Permanent flank bulge is a consequence of flank incision for radical nephrectomy in one half of patients. *Urol Oncol* 2004;22:36-9. http://dx.doi.org/10.1016/S1078-1439(03)00099-1
12. Abouassaly R, Alibhai SM, Tomlinson GA, et al. Unintended consequences of laparoscopic surgery on partial nephrectomy for kidney cancer. *J Urol* 2010;183:467-72. http://dx.doi.org/10.1016/j.juro.2009.10.002
13. McKiernan J, Simmons R, Katz J, et al. Natural history of chronic renal insufficiency after partial and radical nephrectomy. *Urology* 2002;59:816-20. http://dx.doi.org/10.1016/S0090-4295(02)01501-7
14. Huang WC, Levey AS, Serio AM, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol* 2006;7:735-40. http://dx.doi.org/10.1016/S1470-2045(06)70803-8
15. Weight CJ, Lieser G, Larson BT et al. Partial nephrectomy is associated with improved overall survival compared to radical nephrectomy in patients with unanticipated benign renal tumours. *Eur Urol* 2010;58:293-8. http://dx.doi.org/10.1016/j.eururo.2010.04.033
16. Touijer K, Jacqmin D, Kavoussi LR, et al. The expanding role of partial nephrectomy: a critical analysis of indications, results, and complications. *Eur Urol* 2010;57:214-22. http://dx.doi.org/10.1016/j.eururo.2009.10.019
17. Horton R. Surgical research or comic opera: questions, but few answers. *Lancet* 1996;347:984. http://dx.doi.org/10.1016/S0140-6736(96)90137-3
18. Van Poppel H, Da Pozza L, Albrecht W, et al. A prospective, randomized EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol* 2011;59:543-52. http://dx.doi.org/10.1016/j.eururo.2010.12.013

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