The Management of a Clinical T1b Renal Tumor in the Presence of a Normal Contralateral Kidney

NEPHRON SPARING SURGERY

When a patient is seated in front of you with a 6 cm contrast enhancing renal mass and a normal contralateral kidney and asks, "Doc, what should I do? Should I get the whole kidney taken out or just the tumor?" most urologists have a preferred answer. In fact, when presented with identical patient scenarios, including computerized tomography images and a 3-dimensional rendering of the tumor within the kidney, 81% of high volume, academic surgeons recommend a partial nephrectomy (PN) compared to only 30% of surgeons working in different settings.[1] It appears that many patients ultimately undergo a radical (RN) or PN based more on surgeon practice patterns than patient preference or tumor characteristics. However, what if the patient asks, "Doc, what is the *right* thing to do?" In this case review of the literature will help our patients get the answers they deserve. We review the data suggesting that PN is often the best choice.

For patients with clinical stage T1b tumors, there is little debate that PN yields cancer control outcomes equivalent to those provided by RN. This conclusion is supported by multiple studies comparing cancer specific survival between these 2 treatments, including a phase 3 trial[2] and a meta-analysis that pooled data from multiple studies comprising cases with a diverse range of clinical stages (T1a to T3a).[3]

If we can confidently counsel patients about equivalent cancer control, then the next question is whether there are substantive differences in short-term convalescence and/or complications after PN vs RN. Clearly, there are certain (significant) complications, including postoperative bleeding and urine leak, which are more common with PN. However, while this finding leads many to argue that the overall morbidity and complication risk is greater with PN,[2] recent data suggest that these differences may actually be small and dependent largely on factors such as tumor complexity and surgeon experience.[4,5]

While issues around short-term morbidity can be debated, the reality is that a recommendation for elective PN in this group of patients only makes sense if there is a long-term benefit to preserving uninvolved nephrons in the tumor bearing kidney. Criteria with respect to clinical measures of renal function have been met. Multiple studies have consistently identified higher postoperative glomerular filtration rates and, as a consequence, a lower incidence of new onset chronic kidney disease (CKD) among patients with clinical stage T1b tumors treated with PN rather than RN.[2,3,6] Moreover, this better preservation of kidney function is evident even when ischemia time exceeds 20 to 30 minutes.[7]

Even more importantly, data suggest that preservation of renal function may translate into better long-term outcomes for patients undergoing nephron sparing surgery. For instance, among medical patients, chronic kidney disease is associated with a graded risk of adverse cardiovascular events and death from any cause, namely, as kidney function worsens, the risk of these unfavorable outcomes increases in synchronicity.[8] However, the unanswered question is whether surgically induced CKD caused by the performance of RN rather than PN has a natural history analogous to that observed with medical CKD. In other words, does better preservation of kidney function via nephron sparing surgery translate into better long-term survival via avoidance of CKD related morbidity and mortality?

A definitive answer to this question is not yet available as many of the studies examining long-term survival after PN vs RN provide limited or no data on postoperative kidney function. Nonetheless, captivating data from several observational studies (comprising thousands of patients) indicate that treatment with PN is associated with better long-term survival. In the absence of randomization this survival advantage can be easily dismissed as due to selection bias and/or residual confounding. While this is certainly plausible, at least 2 studies used advanced econometric techniques designed to address such concerns, and both still identified a long-term survival benefit with PN.

Weight et al performed a single institution retrospective cohort study of more than 1,000 patients

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treated with PN or RN for a suspected clinical stage T1b kidney cancer.[9] The 2 important strengths of this study were 1) the investigators implemented a propensity score analysis to better balance measured confounding variables (eg age, comorbidities, tumor size, preoperative renal function) between the treatment groups and 2) availability of granular clinical data allowed specific examination of the relationship between postoperative renal function and long-term survival. The pivotal finding was that postoperative renal function was strongly associated with overall and cardiovascular specific survival. Moreover, postoperative renal function appeared to explain the better survival outcomes for patients treated with PN vs RN. While certainly not definitive, these data begin to clarify a link among nephron sparing surgery, preservation of renal function and longer life.

Although it did not include patients with tumors larger than 4 cm, a second relevant study was a population based analysis for which data from SEER (Surveillance, Epidemiology and End Results) were linked with Medicare claims to compare cancer specific and overall survival among patients treated with PN or RN for clinical stage T1a kidney cancer.[10] This study included more than 7,000 patients and comprised an instrumental variable analysis, an approach widely used by economists and other social scientists, to address the issue of residual bias and/or unmeasured confounding (ie unmeasured differences between patients in the PN and RN cohorts). The principal finding was that patients treated with PN had a significantly lower risk of death from any cause. There was no difference in cancer specific mortality between the treatment groups. Although this study did not include patients with clinical stage T1b tumors, its findings, based on methods that can account for unmeasured confounding, motivate continued examination of this question.

Standing in contrast to the findings from these large observational studies are the results from a single phase 3 randomized, controlled trial involving only 541 patients, which compared long-term survival after partial vs radical nephrectomy. There was no survival benefit with PN and in the intention-to-treat analysis patients treated with RN actually had better outcomes.[2] While this finding must be acknowledged as potentially practice-changing, it is also true that the EORTC (European Organisation for Research and Treatment of Cancer) trial had several significant shortcomings with respect to its design and implementation. Therefore, we believe that this single negative study, comprised largely of patients with T1a tumors, should not be considered definitive proof that we should abandon elective PN for clinical stage T1b tumors.

Ultimately, our field would benefit greatly from a randomized controlled trial that specifically compares a variety of relevant outcomes after PN vs RN for clinical stage T1b tumors. These outcomes would include, among others, postoperative complications, longitudinal renal function, health related quality of life, and cancer specific and overall survival. The findings of such a study would be bolstered significantly if its design and analysis explicitly account for additional factors that influence these outcomes, including surgeon volume and tumor complexity. In the end it may well be that certain patients with clinical stage T1b tumors are best treated with PN, while others should undergo total kidney removal. This decision may appropriately be influenced by the characteristics (eg comorbidity, tumor location) and preferences of the patient, and experience of the surgeon. The availability of such data would represent a major advance toward individualizing surgical treatment for patients with kidney cancer. Until more data are available, however, elective PN should remain an acceptable treatment option for patients with T1b tumors.

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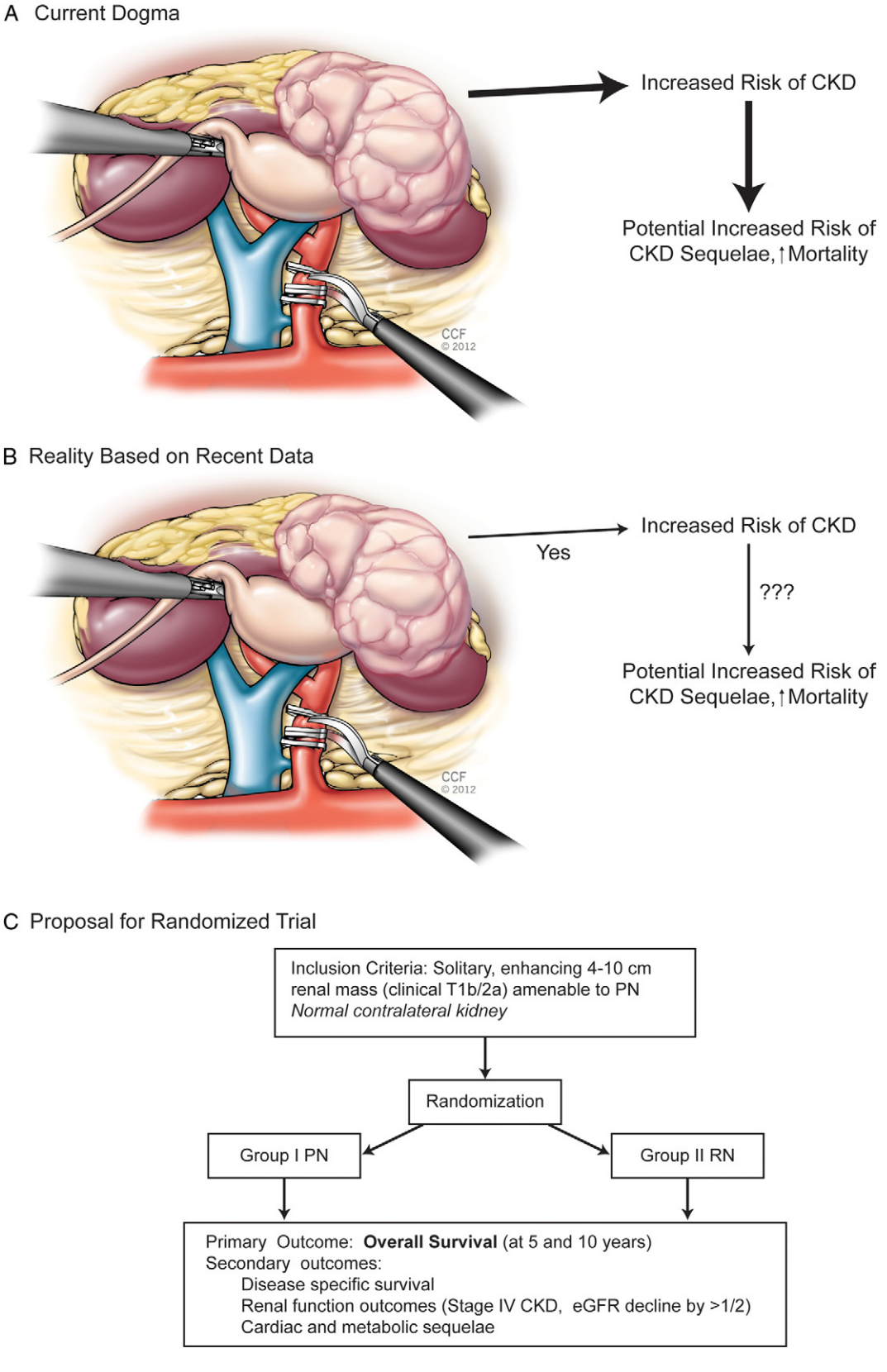
RADICAL NEPHRECTOMY

Persuasive dogma in our field mandates that partial nephrectomy should be performed when feasible, even in the presence of a normal contralateral kidney. Radical nephrectomy is associated with an increased risk of chronic kidney disease, and current belief suggests that this leads to morbid cardiovascular events and increased mortality rates (part *A* of figure). While avoiding RN is advisable for small renal masses,[11] what about larger tumors, specifically the clinical T1b (4 to 7 cm) renal mass?

A more fundamental question must be answered first. How strong is the evidence that supports the above paradigm? In reality it is based on a series of retrospective studies that are likely contaminated by selection bias. Despite intensive efforts to control for recognizable and unrecognizable confounders through multivariate and other sophisticated analyses, there is no way to eliminate them. A recent meta-analysis of the literature provides the most damning evidence.[4] Kim et al evaluated 35 retrospective studies of PN vs RN comprising more 4,000 patients and based on the pooled analysis reported that PN resulted in 61% risk reduction for develop-



Conceptual issues related to radical nephrectomy in setting of normal contralateral kidney. *A*, current dogma presumes strong correlation between CKD related to surgery and adverse outcomes. *B*, recent data have called into question such relationships, suggesting potential difference between CKD due to medical causes vs that due to surgery. *C*, randomized trial will be required to define merits and limitations of each approach.

ment of severe CKD ($p < 0.001$) and a 19% risk reduction in all cause mortality ($p < 0.001$). However, this meta-analysis also revealed a 29% risk reduction in cancer specific mortality in favor of PN ($p = 0.002$) which is difficult to explain. It is intuitive that PN is not a stronger oncologic intervention than RN. The only reasonable way to explain this result is selection bias, and the underlying selection bias is likely contributing to the other results in favor of PN. How can we reconcile this?

The best way to eliminate selection bias, of course, is to perform a randomized clinical trial, which brings us to EORTC 30904.[2] In this important trial of patients with small (less than 5.0 cm), solitary, clinically localized renal masses and a normal contralateral kidney 268 were randomized to undergo PN and 273 were randomized to undergo RN. As expected the trial showed an advantage for RN in terms of lower morbidity, while PN provided better renal functional outcomes. Based on the current paradigm, we would have anticipated better overall survival in the PN group, primarily driven by a reduced incidence of cardiovascular deaths. However, the 10-year overall survival was actually better for RN than PN (81% vs 76%, respectively, $p = 0.03$) and cardiovascular deaths were less common in the RN group (20 vs 25). This trial has some flaws and most thought leaders in the field, including the authors, do not want to interpret it literally. However, the important concept that we should take away from EORTC 30904 is that it suggests that the functional advantage of PN in the setting of a normal contralateral kidney may not be as great as previously believed.

Stated another way, there may be a difference between CKD due to medical causes (CKD-M) vs that due to surgery (CKD-S). Patients with CKD-M due to hypertension, diabetes or other renal impediments continue to have these comorbidities and renal function will progressively decline, eventually placing them at risk for adverse events.[8] However, patients with CKD only after surgery typically do not require further surgery and might stabilize with time. We tested this hypothesis in a series of more than 4,000 patients undergoing either PN or RN, including 1,182 with CKD-M and 927 with CKD-S. We found that patients with CKD-M experienced a mean annual renal function decline of 4.7% compared to only 0.7% for the CKD-S group.[12] Furthermore, survival of patients with CKD-S was similar to patients with no CKD, and substantially better than patients with CKD-M.

Further studies are required but our data suggest that patients with CKD-S are much more stable and may not suffer from the increased mortality rates that plague patients with CKD-M. A more comprehensive analysis of renal function outcomes from EORTC 30904 is now in progress, with preliminary results demonstrating stable renal function in the PN and RN groups out 10 to 15 years. Taken together, these studies suggest that the renal function advantage of PN in the setting of a normal contralateral kidney may not be as beneficial as previously thought (part *B* of figure).

Where does this leave us in 2013? Clearly there is still an essential role for PN in patients who do not have a contralateral kidney or when preservation of renal function is at a premium. In addition, most small renal tumors (T1a, less than 4.0 cm) have limited oncologic potential and RN represents therapeutic overkill in this setting. The main point of contention relates to patients with clinical T1b/T2a tumors and a normal contralateral kidney. These tumors have increased oncologic potential and in many cases have already replaced a considerable proportion of the nephron mass, leaving less to be saved with PN. These patients should be considered for RN to reduce the potential morbidity of the procedure and provide optimal oncologic outcomes. The favorable long-term outcome for patients undergoing donor nephrectomy also supports selective use of RN as long as it is applied intelligently. In the end, a randomized clinical trial of PN vs RN will be required in this population to provide high level evidence and guide patient counseling (part *C* of figure). Such a trial will also provide a wealth of information about renal function after surgery which will help us reassess current dogma and place this field on more solid ground heading into the future.

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