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Platinum Opinion

A Return to the Days of Radical Nephrectomy as the "Gold Standard" for Localized Renal Cell Carcinoma? Not So Fast

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We have read with great interest the recently published findings of Gershman et al. [1]. The authors examined a large single-institutional dataset of radical (RN) and partial (PN) nephrectomies for T1 renal cell carcinoma (RCC), conducting propensity score analyses, and noted that PN was associated with improved functional outcomes compared with RN (a decline in estimated glomerular filtration rate [eGFR] of <45 ml/min/1.73 m^2, hazard ratio [HR] 2.7–2.99, $p < 0.001$), with no differences between RN and PN with respect to metastases (HR 0.91–1.67, $p = 0.07$–0.9) and cancer-specific mortality (HR 1.0–1.08, $p = 0.3$–0.9). Furthermore, no difference was noted in favor of PN for all-cause mortality (ACM; HR 1.14–1.15, $p = 0.2$–0.3), except for inverse probability weights (HR 1.18; $p = 0.03$), and RN was associated with a significantly reduced rate of local recurrence (HR 0.19–0.27, $p < 0.001$). The manuscript is a significant contribution to an increasing burden of evidence suggested by European Organisation for Research and Treatment of Cancer (EORTC) 30904 first and then by subsequent investigations, which suggest that at best the survival impact of functional preservation without pre-existing chronic kidney disease (CKD) is small [2,3] and limited by age and comorbid status [4].

Despite these findings, one must be careful not to overstate that PN has limited benefit in cT1 RCC, or that surgically induced CKD (CKD-S) is a benign entity without long-term impact. In an analysis of 4299 patients undergoing surgery for RCC, Lane et al. [3] noted that ACM was higher for CKD-S than for no CKD (HR 1.19, $p = 0.03$) and postoperative baseline eGFR <45 ml/min/1.73 m^2 was a significant predictor of adverse outcomes. In a recently published analysis of 212016 patients with RN and PN for T1–T2 RCC utilizing the US National Cancer Database, Ristau et al. [4] demonstrated an overall survival benefit due to nephron preservation in propensity score-adjusted models for patients with T1a tumors (HR 0.73, 95% confidence interval [CI] 0.70–0.75), which was smaller in larger (T1b–T2) RCC (HR 0.88, 95% CI 0.83–0.94, $p = 0.01$) tumors. Furthermore, the overall survival benefit favored PN over RN in T1a tumors for nearly all patient age groups at all time points from diagnosis, which for T1b/T2 tumors was attenuated by age, with no survival benefit being seen in favor of PN over RN in patients $\geq$75 yr of age (HR 0.89, 95% CI 0.76–1.06) [4].

Herein lay two major limitations of Gershman et al.'s [1] analyses. First of all, the authors analyzed a heterogeneous cohort of T1 RCC, and did not examine whether there were differences in survival for RN versus PN between T1a and T1b disease, which have been demonstrated in larger data sets [4,5]. Furthermore, the average age in the reweighted pseudocohort analyses of Gershman et al. [1] was 66 yr for PN and 65 yr for RN, significantly older than the median age range of diagnosis of RCC in the USA and worldwide (57–61 yr), which may also account for the attenuation in survival benefit for PN.

Taken together, these findings suggest that globally the effects of CKD-S are incremental, and driven by age and how competing risks of mortality and renal function play out over time [3,4]. As such, even a robust single-institutional dataset is unlikely to detect such an effect, and Gershman et al.'s [1] use of an underpowered sample size to detect an effect of CKD-S on overall survival by nephron preservation, and a cohort that was heterogeneous (where a potential benefit to T1a tumors was not identified) and at an age where survival advantage was more likely to be time limited likely explained the lack of other-cause mortality survival difference.

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The paradigm in almost every other cancer type is organ preservation, especially if there are no adverse oncological concerns. At this point, including the results of Gershman et al. [1], EORTC 30904 [2], and a number of well-conducted meta-analyses, PN has oncologically equivalent outcomes to RN in cT1–cT2 disease and provides a functional benefit [5]. Furthermore, contemporary reports suggest that the perioperative risks of low- and even moderate-complexity PN, even in the setting of larger tumors, are similar to those of RN [6].

Regarding patient well-being, the benefits in favor of PN are significant over RN [7]. When patients hear that they have CKD, there is a burden of anxiety regardless of whether the etiology is surgical or medical [7]. Emerging data suggest a burden of metabolic sequelae of CKD-S, which is similar to medical CKD that is rarely reflected in most literature focusing upon changes in eGFR and CKD classes [8,9].

As such, the decision regarding PN versus RN should be based on an individualized competing cause of mortality assessment. The findings of Gershman et al. [1] should not be overinterpreted as being an endorsement to preferentially perform RN for T1 RCC. They do not change the compelling evidence in favor of PN for cT1 masses as a reference standard of care and should not change the paradigm shift in favor of consideration of PN in most cT1 and cT2 masses [10].

Ultimately, Gershman et al.'s [1] findings nonetheless point to the growing controversy over increasing utilization of PN for larger (cT1b/cT2) and/or complex masses. The potential for an increased risk of local recurrence without an ultimate impact on cancer-specific mortality in a cohort of mostly cT1a masses would likely be magnified in larger tumors (cT1b/cT2) and would support a proposal for a randomized clinical trial to examine the impact of local control on oncological efficacy in larger renal masses. Such a clinical trial would do much to answer lingering questions about the impact of upstaging, margin status, and local control on the natural history and oncological outcomes in larger masses, and settle the role of nephron-sparing surgery in elective circumstances for larger masses. Nonetheless, the paper by Gershman et al. [1] adds to the collective data favoring PN to optimize functional preservation while maintaining oncological equipoise in the management of most pT1 renal cancers.

Conflicts of interest: The authors have nothing to disclose.

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