Re: Below Safety Limits, Every Unit of Glomerular Filtration Rate Counts: Assessing the Relationship between Renal Function and Cancer-specific Mortality in Renal Cell Carcinoma

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Eur Urol 2018;74:661–7

Experts' summary:

This retrospective analysis evaluates the relationship between estimated glomerular filtration rate (eGFR) and cancer-specific mortality (CSM) for patients with *c*T1–2 renal cell carcinoma (RCC) managed with partial nephrectomy (PN) or radical nephrectomy (RN). The study population is robust (n = 3457) and the median functional follow-up was 61 months, although only 66% of patients had both preoperative and postoperative eGFR values and 61% of the total population had only one or two such measurements. Median follow-up for survival outcomes was <5 years, with only 128 patients (3.7%) deceased due to RCC. The main finding was that reduced eGFR below a critical level (the knot) correlated with greater CSM on multivariable analysis. For instance, for postoperative eGFR <60 ml/min/1.73 m^2, defined 1 year after surgery, the data suggested that each additional 10-unit reduction in eGFR correlated with a 1.44-fold increase in the risk of CSM. Hence the title, "Every unit of GFR counts . . . " The authors conclude that "whenever feasible, nephron-sparing approaches should be preferred."

Experts' comments:

This is an interesting paper that will further enrich the ongoing debate about the relative merits of PN and RN [1]. PN has been associated with better overall survival in several retrospective series, presumably because of lower incidence of chronic kidney disease (CKD) and thus a lower risk of morbid cardiovascular events. However, these series also showed a correlation between PN and reduced CSM, which was paradoxical, suggesting selection bias [1]. An important study by Shuch et al. [2], who compared outcomes between PN/RN cohorts and control subjects without cancer matched for age and comorbidity, also suggests strong selection bias. The PN cohort had better overall survival when compared to matched controls, despite having cancer, suggesting that PN patients had better general health even though they appeared similar on paper.

Furthermore, if reduced renal function is having deleterious oncologic effects, how can one explain the oncologic findings from EORTC-30904? This is the only randomized trial of PN versus RN and, as expected, PN provided better functional outcomes (mean eGFR 67 ml/min/1.73 m^2 at 1 year for PN compared to 52 ml/min/1.73 m^2 for RN) [3]. Clearly, the RN patients had crossed the "knot" and should have experienced greater CSM, particularly given that the follow-up in this study (9.3 yr) was nearly twice as long as in the Antonelli study. However, in EORTC-30904 there were eight RCC-related deaths in the PN cohort versus only four in the RN group, and tumor progression was observed in 12 PN patients compared to nine RN patients [4].

While Antonelli and colleagues accounted for tumor grade/stage, they were not able to control for tumor volume and complexity. Larger and more centrally located tumors have often replaced more of the normal parenchyma, leading to reduced renal function. Such tumors are also more likely to be managed with RN, and if PN is performed, it is typically associated with greater loss of function. Such tumors also tend to be more aggressive, which could confound the analysis [1]. The authors also did not control for performance-status, which is another potentially important confounder. Patients with low performance status often have preexisting CKD and are more often managed with RN, leading to a further reduction in renal function. Such patients may also be predisposed to worse oncologic outcomes, independent of renal functional status.

The relationships between renal function, overall survival, and oncologic outcomes can be very complex for any cancer, and this is particularly true for RCC [5]. A randomized trial of PN versus RN, ideally for tumors with greater oncologic potential, will be required to address the ongoing controversies about this fundamentally important issue [1].

Conflicts of interest: The authors have nothing to disclose.

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https://doi.org/10.1016/j.eururo.2018.10.038