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Letter to the Editor

Reply to Steven C. Campbell, Chalairat Suk-Ouichai, and Yun-Lin Ye's Words of Wisdom 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. Antonelli A, Minervini A, Sandri M, et al. Eur Urol 2018;74:661–7 and 2019;75:198

We appreciate the Words of Wisdom commentary by Campbell and colleagues [1]. Several of the criticisms they raise—including those regarding the rate of missing estimated glomerular filtration rate (eGFR) readings and the lack of data on nephrometry—are entirely reasonable and can be attributed to the retrospective design of our study [2]. However, some of their comments deserve a more in-depth discussion, as addressed below.

The authors noted that our study did not account for the selection bias related to the indication for partial (PN) versus radical nephrectomy (RN). We carefully bore this issue in mind and, being conscious of the underlying bias, avoided any direct comparison of cancer-specific mortality (CSM) between RN and PN. Our analysis indeed explored the relationship between eGFR and CSM regardless of surgical approach. To this end, we applied a multivariable competitive-risk model adjusted for several confounders, and also included PN versus RN as a covariate to consider the unreported features that are hidden in surgical selection. In addition, the analyses were repeated separately in the PN and RN subcohorts, which confirmed that there was only a linear inverse relationship between eGFR and CSM below the value of 65 ml/min (hazard ratio 1.35, 95% confidence interval [CI] 1.02–1.92 for PN; $p = 0.038$; 1.23, 95% CI 1.03–1.47 for RN; $p = 0.026$) [2]. Definitely, our conclusion that "PN should be preferred whenever feasible" relies only on a rule of thumb on the basis that if PN provides a greater chance of sparing renal function above certain limits, then following our hypothesis it should also protect against CSM.

Campbell et al also stated that the results from the EORTC-30904 randomized trial should refute our hypothesis. First, it should be noted that EORTC-30904 [3], which was conducted before the dissemination of elective PN, received multiple criticisms and prematurely closed because failed to reach the planned accrual (only 541 instead of 1300 patients were enrolled) over a long period of time (11 yr). There is no doubt that contemporary practice has been largely influenced by the huge number of retrospective studies, both historical and contemporary, that univocally showed an advantage in favor of PN rather than this single trial intended to provide a high level of evidence. With regard to the specific point raised by Campbell et al, we would reply that the follow-up time of 9.3 yr reported as significantly longer than ours actually refers to the follow-up duration for oncological outcomes in the EORTC trial [3]. Conversely, the follow-up time for functional outcomes was substantially shorter (6.7 yr [4]), making the gap in relation to our follow-up time (5.1 yr) less significant. Finally, we would argue against any attempt to translate our results to the EORTC trial, since oncological and functional outcomes were not referred to corresponding time points in the latter.

The basis for our project was results from longitudinal population-based nephrology studies published in the literature that first evidenced the existence of an association between eGFR and CSM in several oncological settings among hundreds of thousands of individuals. In addition, the well-known proinflammatory and immunosuppressive effects due to the reduction in renal function after RN [5,6] provide a biological explanation for our hypothesis. Furthermore, it is noteworthy that a threshold was observed for the relationship between eGFR and CSM, below which the two variables were inversely linearly related, as this trend resembles what occurs for all the detrimental effects due to the onset of chronic kidney disease.

Nevertheless, we fully agree with Campbell and colleagues that the role of renal function in cancer is multifaceted and no direct causal associations should be supported by retrospectively designed studies such as ours. Although a randomized trial among patients with organ-confined renal masses is unlikely, future studies to confirm or refute our results are eagerly advocated.

Conflicts of interest: The authors have nothing to disclose.

DOI of original article: https://doi.org/10.1016/j.eururo.2018.10.038.
https://doi.org/10.1016/j.eururo.2019.01.028

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January 17, 2019