



# Renal cell carcinoma: the oncological outcome is not the only endpoint

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The primary focus for patients diagnosed with cancer is the prognosis in terms of survival. Equally, surgeons are generally concerned about the treatment approach of the tumor, the recurrence-free survival and cancer-specific survival. However, there is a balance between surgical cure of the renal mass and renal functional preservation.

Renal cell carcinoma (RCC) is the eighth most common malignancy diagnosed in the United States. Every year, approximately 140,000 people die worldwide due to RCC (1). The downward stage migration of RCC that occurred concomitant to increased incidental findings on imaging studies led to an increase in the number of patients eligible for surgical management. The surgical removal of the tumor represents the treatment of choice in localized disease with excellent cancer specific survival.

However, given the central role of kidneys in filtration, one should consider the functional outcome to be as important as the oncological one in most cases.

Specifically, a reduction of the eGFR after surgery may negatively impact overall survival, despite providing a virtually free cancer-specific survival. Hence, this points to the first point in the article: prognosis is based on both cancer risk and overall survival from kidney failure.

In accordance with the Hippocrates' Oath (*Primum non nocere*) a treatment that potentially harms has to be avoided. In the treatment of kidney cancer, over time, the attention has been shifted towards a conservative approach. Partial nephrectomy (PN) is now regarded as the gold standard in the case of a small renal mass. In fact PN allows for the safe preservation of healthy parenchyma

with an equally low cancer recurrence risk compared to radical nephrectomy.

Specifically, high priority should be given to patients that are at a high risk of renal function deterioration in the short and long-term. In fact, the abrupt cessation of renal function, e.g., acute kidney injury (AKI) and the long-term decline of eGFR, namely chronic kidney disease, should be taken into account especially when counseling patients regarding surgery. Those conditions are intimately related, and one represents a risk factor for the other (2). Unfortunately, not enough attention has been given to patients at high-risk of AKI after PN and generally AKI is regarded as a self-limited condition and many times as a collateral finding rather than a side effect of the surgery itself. In fact, AKI after PN can be attributed to (I) the surgically-induced ischemia that is a modifiable factor required to carry out a successful procedure; (II) the manipulation of the organ; and (III) the volume of excised functional renal parenchyma.

Conversely, more attention has been given to AKI from recent medical literature (as opposed to surgical). As an example, Kellum *et al.* proposed the term "kidney attack" (3) to impart increased urgency following the acute cessation of renal function, commonly referred to as AKI.

However, this condition, that represents a common occurrence in hospitals worldwide in both medical and surgical settings (4), still remains an under-investigated issue (2,3). We acknowledge the difficulty of designing randomized control trials in this regard, given the heterogeneity of the conditions leading to AKI and its

abrupt onset.

Concerning nephron sparing surgery, AKI remains a well-known postoperative risk factor. Aspects related to the tumor itself might promote this condition by means of functional parenchymal invasion and/or compression. Furthermore, the surgically induced ischemia that is often required does not help the case. Our group has recently demonstrated that the occurrence of postoperative AKI plays a pivotal role in the deterioration of renal function and efforts should be made in identifying patients at high-risk of developing AKI (5). The study analyzed a cohort of patients who underwent robot-assisted PN for clinically localized kidney cancer. When predicting eGFR reduction between 3 and 15 months (endpoint chosen in order to account for eGFR fluctuations occurring during the first 3 months after surgery) it became evident that AKI played a significant role in augmenting the risk of facing a reduction in eGFR magnitude greater than one forth from the baseline (a commonly accepted definition of AKI, in clinical practice).

Unfortunately, AKI has long been considered a self-limiting condition. However, the latest evidence points to what now seems to be pretty clear: AKI increases the risk of renal function deterioration in the long-term and can consequently result in a decreased quality of life when renal replacement therapy becomes necessary. Moreover, it augments the risk of overall mortality. Unfortunately, not much can be done from a surgical standpoint when treating patients with RCC when renal clamping is necessary.

We therefore believe that concerning surgical management of RCC, risk assessment for the development of significant eGFR reduction is warranted. During patient counseling, the surgeon should mention that adjuvant treatments that might be required (including VEGF and mTOR inhibitors) list nephrotoxicity among their side effects (6). The option for active surveillance can be considered for small renal masses in patients at high risk of AKI (especially those with pre-existing CKD). Active surveillance is now emerging as a safe and effective strategy for the management of small renal masses (4 cm or less). Therefore, a surgeon has to balance the risks and benefit of surgical intervention, especially in elderly patients (7,8). Trials aimed at optimizing renal functional recovery after surgically-induced AKI should be implemented. Potentially, the use of crystalloids in patients undergoing RAPN and have a high risk of developing AKI could be explored in

an effort to evaluate for an eventual benefit in this patient population (9).

Finally, while we conduct studies that will help elucidating how to prevent and/or treat AKI in a way that can result in reducing the risk of deteriorating renal function, doctors should consider this important factor in treatment decision making and weigh the alternative option of active surveillance in those at high risk of renal failure.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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