Editorial Commentary

Usefulness of the duration of acute kidney injury for predicting renal function recovery after partial nephrectomy

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Provenance: This is an invited article commissioned by the Section Editor Dr. Xiao Li (Department of Urology, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China).

Comment on: Bravi CA, Vertosick E, Benfante N, *et al*. Impact of Acute Kidney Injury and Its Duration on Long-term Renal Function After Partial Nephrectomy. Eur Urol 2019. [Epub ahead of print].

Submitted Jul 25, 2019. Accepted for publication Aug 08, 2019.

doi: 10.21037/atm.2019.08.38

View this article at: http://dx.doi.org/10.21037/atm.2019.08.38

Although the incidence and mortality of renal cell carcinoma (RCC) significantly varies among individual countries, according to the recent GLOBOCAN database, RCC is the sixth most frequently diagnosed cancer in men and the tenth in women worldwide (1,2). The incidence rate of RCC has been increasing in most countries, resulting in more frequent medical examinations and requiring changes to national health insurance policies (3). In addition, with improvement in the resolution of abdominal imaging, such as ultrasonography, computed tomography and magnetic resonance, small renal masses are now found incidentally (4). These small renal masses tend to be localized, with complete surgical excision being the only curative treatment.

Patients with RCC treated with radical or partial nephrectomy are at risk for deterioration in renal function after surgery resulting from acute kidney injury (AKI) sustained during the surgery itself, as well as due to renal parenchymal loss. Therefore, the recovery of renal function in patients after nephrectomy should be assessed.

To minimize the risk for adverse renal outcomes after nephrectomy for RCC, the recent guidelines from the European Association of Urology recommend partial nephrectomy for patients with T1 tumors (≤7 cm), when technically feasible, rather than radical nephrectomy (5). We previously demonstrated that postoperative residual renal function was significantly lower in patients treated with radical rather than partial nephrectomy for RCC of ≤7 cm (6). Therefore, nephron-sparing surgery preserves normal kidney function better than radical nephrectomy, thus reducing the risk of cardiovascular events and mortality (7). However, even if nephron-sparing surgery is performed to preserve renal parenchyma, it will not completely prevent the loss of renal parenchyma in the area of the renal mass and its marginal zone. In fact, in our previous findings, we reported an incidence rate of AKI, defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (8), of 24% after partial nephrectomy. Moreover, the incidence rate of new-onset chronic kidney disease (CKD) at 3 months after surgery was 6.2% after partial nephrectomy, with a ≥25% decline in the estimated glomerular filtration rate (eGFR) after 1 year identified in 8.1% of cases, although these rates were lower than those after radical nephrectomy (6). Depending on the definition of AKI used, the incidence rate of postoperative AKI after partial nephrectomy has been estimated at 9% to 41% (9). In this regard, it would be important to know whether inevitable AKI during partial nephrectomy affects long-term renal function and whether the duration of AKI should be included in the assessment of postoperative AKI in addition to the severity of renal injury.

A recent article published by Bravi *et al*. investigated the relationship between the duration of AKI and long-term recovery of renal function after partial nephrectomy (10). Their analysis was based on the data of 3,139 patients who underwent partial nephrectomy for a single cT1N0M0 renal mass between 1989 and 2018. Of this group, 388 (20%)

patients experienced AKI after partial nephrectomy. The rate of patients recovering 90% of their baseline eGFR was lower in the AKI than in the non-AKI group (30% versus 61%, respectively), with CKD upstaging required in a higher proportion of patients in the AKI than in the non-AKI group (51% versus 23%, respectively). Interestingly, patients who did not recover from the AKI for more than 3 days after surgery had worse renal function at 1 year after partial nephrectomy, including a lower proportion of patients recovering 90% of baseline eGFR or a higher proportion requiring CKD upstaging. This study emphasized that the duration, as well as the severity, of AKI affects the long-term renal function in patients after partial nephrectomy. In line with these findings, previous studies that have evaluated the association between AKI and adverse clinical outcomes after surgery showed that patients with persistent AKI had a higher risk of cardiovascular events, mortality or initiation of dialysis than those with transient AKI, despite the heterogeneity in the definition of transient AKI adopted in different studies (11-14). From this point of view, Bravi *et al*. suggested that the duration of AKI may be helpful in predicting the long-term recovery in renal function, as well as providing a clear advantage in determining the timing of treatment.

Although the duration of AKI can be applied as a prognostic factor for renal outcomes, further research is needed to determine the new definition of AKI after partial nephrectomy in patients with RCC and whether other factors would affect the long-term renal function. Previous definitions of AKI, including the Risk, Injury, Failure, Loss and End-stage Kidney (RIFLE), the Acute Kidney Injury Network (AKIN) and the KDIGO criteria, which are based on serum creatinine have limitations in the diagnosis of AKI after partial nephrectomy. Specifically, an acute increase in serum creatinine after partial nephrectomy is expected to be primarily due to the reduction in the functional parenchymal mass and ischemia during operation (9). Therefore, the incidence of postoperative AKI might be over-diagnosed, as well as the severity of AKI after nephrectomy could be higher than that of AKI after non-nephrectomy surgery (15,16). To correct this overestimation in the incidence and severity of AKI, a previous study suggested new criteria for AKI after partial nephrectomy in patients with solitary kidney, with the AKI grade based on the comparison of peak serum creatinine levels to projected postoperative serum creatinine levels, accounting for mass reduction (16). The AKI grade classified by the new proposed criteria was associated with subsequent functional recovery, even after adjustment for confounding factors, while the standard AKI criteria were not associated. Also, renal damage and recovery of renal function could be affected by parenchymal volume according to the size of renal mass, exophytic or endophytic nature, as well as type or duration of ischemia during nephrectomy (17).

Moreover, compensatory hypertrophy can occur in the remaining kidneys after a few days to months, followed by a reduction in renal parenchyma after partial nephrectomy. This adaptation mechanism may partially influence postoperative AKI and long-term renal function recovery. However, the degree of adaptation varies depending on the underlying renal disease. Moreover, kidney cancer is highly prevalent among elderly patients who are more likely to have hypertensive or diabetic nephropathy compared to that in the general population (18). Thus, pathologic evaluation of non-neoplastic kidney parenchyma should be performed after nephrectomy.

Novel urinary or serum biomarkers have been proposed for the prediction and early detection of renal injury after nephrectomy, as an alternative to AKI definitions based on serum creatinine level (9). These novel biomarkers of kidney injury would be need to account for the parenchymal loss and a real renal damage, requiring future research.

In conclusion, Bravi *et al*. provide compelling evidence that the duration of AKI is informative and simple to predict for long-term kidney function recovery after partial nephrectomy. Until a new definition of AKI after nephrectomy is provided or novel biomarkers are validated, inclusion of the duration of AKI in the assessment of renal injury might be beneficial to postoperative risk stratification. Additional studies are warranted to identify prediction models for postoperative renal function after partial nephrectomy that could inform treatment to prevent ongoing kidney injury, as well as to improve the long-term clinical outcomes.

Acknowledgments

Funding: This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2017M3A9E8023018, 2017M3A9E8023001), by a grant (BCRI18025 and BCRI19030) Chonnam National University Hospital Biomedical Research Institute.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Kim CS, Bae EH, Ma SK, Kim SW. Usefulness of the duration of acute kidney injury for predicting renal function recovery after partial nephrectomy. Ann Transl Med 2019;7(Suppl 6):S236. doi: 10.21037/atm.2019.08.38

