

Peer Review File

Article Information: <https://dx.doi.org/10.21037/tau-21-384>

Reviewer A

Summary of manuscript/critical findings:

The authors describe their institutional experience of pseudoaneurysm after robotic partial nephrectomy. They described the follow-up. Overall, they found that 23% of patients experienced a pseudoaneurysm; the majority were asymptomatic.

Overall assessment:

- Originality of question: This has been described in just a couple other published series

Reply: Thank you for your comment. This is right.

- Robustness of dataset: 100 patients were included (after 6 excluded due to inability to get a CT scan)

Reply: Thank you for your comment. Yes, this is correct.

- Appropriateness of methodology: The authors' work is very interesting. Two patients were embolized preemptively for outside/social/travel concerns. This makes the final analysis more complicated.

Reply: Thank you for your comment. As you mentioned, the reader will be confused. So, we reanalyzed 98 patients after excluding 2 patients who had undergone prophylactic embolization of RAP.

- Importance of findings: The manuscript continues to further the idea of that pseudoaneurysms after partial nephrectomy are common and infrequently of clinical significance. It also demonstrates that the majority of them resolve without intervention.

Reply: Thank you for your comment. Yes, we think so.

Minor comments:

- Overall composition quality:

o The term renal artery pseudoaneurysm is often used in the literature, although I would caution the authors to use a more precise term for the location of the pseudoaneurysms which are most likely at the level of the interlobar, arcuate or even interlobular arteries.

Reply: Thank you for your comment. All of the RAPs were located on the interlobar, arcuate or interlobular arteries. To use a more precise term, we have added a new sentence in the Results section (see Page 12, line 9-10).

- Title: Appropriate

- Abstract:

o The sentence which begins “CE-CT detected 28 RAP in 23 of 100 patients by 7 days” is not well constructed. It is confusing to the reader to understand how the 2 described groups originated. The exclusion of the two patients that were preemptively embolized may need to be mentioned.

Reply: Thank you for your comment. As you mentioned, to avoid confusion, we reanalyzed 98 patients, excluding 2 patients who had undergone prophylactic embolization of RAP. The essence of the Abstract has not changed, but several details have changed.

o I would recommend describing the median tumor resection time and blood loss as opposed to indicating the odds ratio for greater or less than the median.

Reply: Thank you for your comment. We have made a new Table 2 and reconstructed the old Table 2 as the new Table 3. Factors that can be measured numerically were analyzed as continuous variables without categorization.

- Introduction:

o There is some debate about reducing cardiac events in the setting of protected renal function due to partial nephrectomy. I would describe this with caution.

Reply: Thank you for your comment. We have added a new sentence in the Introduction section (see Page 5, line 4-5)

o Many pseudoaneurysms occur at a level smaller than segmental branches of the renal artery.

Reply: The reply to this comment is similar to the reply to the previous comment.

o It is important to set up the novelty of this study relative to previous articles looking at the natural history of pseudoaneurysm after partial nephrectomy.

Reply: Thank you for your comment. The novelty of this study is that the data of 7 days, 1 month, and 3 months after RAPN are followed in all cases regardless of the presence or absence of symptoms. Asymptomatic RAPs appear immediately after RAPN and disappear. It was suggested that the relatively young age of the patients was a factor in the occurrence of RAP. We have added a new sentence in the Introduction section (see Page 6, line 4-5)

- Methods:

o Improvements should be made in the way that the cohort is described and how some

patients were excluded from final analysis. The way that the text reads now is some what confusing.

Reply: Thank you for your comment. As you mentioned, to avoid confusion, we reanalyzed 98 patients after excluding 2 patients who had undergone prophylactic embolization of RAP. Figure 1 has also changed with this new analysis (see Figure 1 and Page 26, line 10-11 in the Figure legends).

o It may be worthwhile to change the term asymptomatic renal artery pseudoaneurysm to asymptomatic renal artery pseudoaneurysm managed by surveillance, or some other more clearly defined description.

Reply: Thank you for your comment. This is very suitable. We have added ‘managed by surveillance’ in the Abstract section (see Page 3, line 10), in the Materials and Methods section (see Page 7 , line 4), and in the Results section (see Page 13, line 2)

o

- Results:

o The sentence “a major complication Clavien-Dindo grade 3 or higher was found in 4 patients with RAE” is not perfectly clear. Were the patients who underwent embolization the only patients with high-grade complication?

Reply: Thank you for your comment. RAE was the only procedure with a Clavien-Dindo complication of grade 3 or higher. We have added this sentence in the Results section (see Page 12, line 1-2)

- Discussion:

o Overall I enjoyed the discussion. It discusses many apropos and interesting topics.

Reply: Thank you for your kind comment.

o I would not say that pseudoaneurysm is the most undesirable complication after treatment.

Reply: Thank you for your constructive comment. We have changed this text as advised (see Page 14, line 9).

o I would recommend including the data which assesses nephrometry score is in a table, possibly a supplemental table.

Reply: Thank you for your constructive comment. The analysis is destabilized by categorization in a small number of cases. Therefore, nephrometry score was also analyzed as a continuous variable: on univariate analysis, the higher the score, the more likely it was a factor of RAP (see Table 3).

o The sentence which ends, “suggesting that vascular injury due to needle movement may be a trigger,” does not necessarily follow logically in that sentence.

Reply: Thank you for your comment. We have deleted this sentence.

- Conclusion:

- Tables and Figures:

o The pictures in figure 2 is very nicely done

Reply: Thank you for your kind comment.

Reviewer B

This is an interesting study examining the incidence and natural history of asymptomatic renal artery pseudoaneurysm after robotic assisted partial nephrectomy, providing evidence that this entity may be safely observed among patients with no clinical signs/symptoms. The authors also conclude that younger age may be an independent factor associated with the development of renal pseudoaneurysm after partial nephrectomy.

-With 2 primary surgeons, there may be subtle variations in technique that may affect the post-operative incidence of renal pseudoaneurysm. Do these surgeons differ in terms of surgical approach?

Reply: Thank you for your comment. There was no significant difference in the chi-square test between surgeons (A vs. B) or in approach (Transperitoneal vs. retroperitoneal) ($p=0.1248$). We have added a new sentence in the Result section (see Page 11, line 10-12).

-Did any of the "asymptomatic" patients have any signs of potential pseudoaneurysm, such as gross hematuria? This is a critical point, as diagnosis and intervention clinically often depends on these factors. If truly asymptomatic, this fact should also be reflected in the title of the manuscript.

Reply: Thank you for this fine advice. No patients had symptoms such as gross hematuria. We have added a new sentence in the Results section (see Page 11, line 15-16). In addition, a majority of patients in this study had no symptoms, and only 2 patients had symptomatic RAP. As you suggested, we think it is preferable that this fact be reflected in the title of the manuscript, and have accordingly added "asymptomatic" to it.

-Sentence 1 in paragraph 2 of the results section is unclear. Are the 25 pseudoaneurysms diagnosed in 98 patients all diagnosed beyond 7 days of surgery, or on day 7 itself?

Reply: Thank you for your comment. The answer is on day 7 itself. As this is difficult to understand, we have rewritten the above contents in the Abstract (see Page 3, line 5-14) and in the Results section (see Page 12, line 4).

-What Clavien > grade 3 complications occurred?

Reply: Thank you for your comment. Only selective renal arterial embolization (RAE) occurred. We have added a new sentence in the Results section (see Page 12, line 1-2).

-Would suggest reporting IQR for medians, rather than range

Reply: Thank you for your constructive comment. We have reflected your advice in the text and Tables.

-Table 1: renal artery clamp (total vs selective) is reported twice

Reply: Thank you for your comment. We have deleted it.

-There are very few patients with high nephrometry scores, which precludes a meaningful analysis of this subgroup. It would have been interesting to assess rates and clinical course of pseudoaneurysm in this particular group, given the association with higher rates of renal pseudoaneurysm.

Reply: Thank you for your comment. As you mentioned, we decided that it would be difficult to categorize by nephrometry score, because very few patients had a high nephrometry score. Accordingly, we re-analyzed this as a continuous variable. The results showed that the higher the nephrometry score in the univariate analysis, the more likely it was to become an RAP-causing factor (see Table 2 and Table 3).

-For the univariate/multivariate analysis - would analyze age as a continuous variable rather than categorical variables. The division of patients into each age category is not consistent (ie, different year intervals for each group), which may bias the analysis.

Reply: Thank you for this constructive comment. Considering your point, we re-analyzed age as a continuous variable. As shown in Table 3, younger people tended to be at risk of developing RAP ($p=0.06$) in both univariate ($p=0.0617$) and multivariate A ($p=0.0643$) logistic analyses. Younger people tended to be at risk of developing RAP. Therefore, when divided into two groups by the median, younger people were at significantly greater risk of developing RAP. When the ages were categorized into 3 groups to clarify the results, the youngest group had a significantly higher risk of developing RAP. As you note, the possibility of bias in the method of categorizing age cannot be denied. For example, even if the age intervals were divided by 10, 15 and 20 years so that they would match, it would be difficult to improve these biases and linearity could not be shown. We therefore considered it acceptable to divide the study into three groups so that the number of cases in each was the

same, although the age intervals do not match. We added some sentences in the Results (see Page 13 line 5- Page 14 line 2).

-I disagree with the authors' comments in the Discussion section regarding routine post-operative imaging to detect renal artery pseudoaneurysm. Given the overall low reported incidence and the authors' own findings that most asymptomatic pseudoaneurysms will resolve without intervention, this approach would lead to significant over-imaging and diagnosis of a finding that would otherwise minimally change clinical care in the absence of other signs/symptoms. While the authors are not advocating for routine post-operative CT for all patients, this point should be made more clear in the Discussion section.

Reply: Thank you for your comment. As you mentioned, routine CT may have been over-imaging retrospectively, as it was found that most of the RAP disappeared within 3 months. This observational study of RAPN was started in a single university hospital in a situation where the natural history of RAP was unclear, and also where we wanted to understand possible complications other than RAP. Therefore, we planned to carefully follow the progress of all patients continuously from the first case, and take CTs routinely. Patients who understood the above underwent RAPN. We have added some sentences as one of the limitations in the Discussion section (see Page 19, line 3-8).

-The discussion would be further strengthened by including a discussion regarding the relevance of diagnosing asymptomatic pseudoaneurysm after robotic partial nephrectomy and the clinical scenario in which the findings of this paper might be applied, as one would not expect patients to undergo routine early post-operative imaging in the absence of clinical signs or symptoms.

Reply: Thank you for this constructive advice. We have used your comment in the Discussion section (see Page 18, line 8 and Page 18, line 13-14).

Reviewer C

The authors have an interesting study for 100 patients to document the incidence of both clinical and subclinical RAP after robotic assisted partial nephrectomy (23% at 7 days, 4 patients required selective embolization - 2 symptomatic before the 7 day CT scan, 2 prophylactic. The others resolved by 1 month). In addition, they looked at the risk factors associated with RAP and the natural history of incidental RAP.

The paper's main shortcomings is the number of patients - it is a small series of 100 patients by 2 main console surgeons. However, it is a unique series of consecutive patients with no patient opting out to participate in a 7day protocol CT scan. The second shortcoming is that for a symptomatic RAP, the percentage of symptomatic / clinically significant RAP that required treatment is on the high side (4%) and hence may reflect the incidence of RAP specific to their RAPN technique.

The paper can be improved if it addresses the following:

1. Please provide information on what proportion of cases were total or segmental arterial cases done (this should be a factor for prediction of RAP). Please confirm that the surgical technique is enucleation for the cases (vs. resection / enucleo-resection). Please provide more details on the the outer cortical closure /renorrhaphy technique. Is the suture continuous with Hem o lok clips placed at entry / exit points or only 2 clips at the end. The tumor excision and renorrhaphy technique have obvious implications on post op bleeding and obviously RAP. Attention should therefore be given to providing a detailed description of the technique.

Reply: Thank you for your constructive comment. First, we showed the proportion of total and segmental arterial cases in Table 1, and have added a new Table 2 considering your comment 3. Results showed no significant correlation of RAP occurrence by total clamp or segmental clamp. Second, regarding surgical technique, we have added new sentences in Surgical technique of the Materials and Methods section (see Page 8, line 9 – Page 9, line 1).

2. The usefulness of this paper is that subclinical RAP occurs frequently and detectable at 7 days which resolve after 30 days. I therefore feel the statistical analysis for risk factor of subclinical RAP not useful and redundant. These would not be picked up had the CT scans not be done and therefore not clinically important. I therefore feel there is limited contribution from doing the univariable and multivariable analysis in table 2; unless there is a clinical consequence.

Reply: Thank you for your constructive comment. As you mentioned, we have newly added Table 2 according to your comment 3. As shown in Table 2, five factors were found related to the presence or absence of RAP. As shown in Table 3, in a logistic regression analysis that examined the factors of RAP development using these five factors, we confirmed that all five factors may be factors in univariate analysis, and age was significant in multivariate analysis, as in the first report.

3. The number of patients with clinical significant RAP is too small to do any meaningful analysis, It is therefore better to first focus on characterizing the clinical consequence of the subclinical RAP group (those not embolized) before any need to assess for risk factors. Please compare in addition to the oncological outcomes, the clinical (LOS, operative time, blood loss) and functional outcomes (renal function decline 7days, 30days) of the patients with and without subclinical RAP (removing those 2 that were embolized before 7days). I think if there are no clinical consequences, identifying risk factors may not be consequential either.

Reply: Thank you for your constructive comment. As you mentioned, this study had a small number of cases, which was described in the limitation of the Discussion section (see Page 19, line 3-8). We did in fact obtain meaningful data. We have added a new Table 2 (see Page

13, line 1-4). This Table 2 also contributed significantly to the logistic analysis shown in the newly added Table 3 (see Page 13, line 5 – Page 13, line 2).