Peer Review File

Article information: http://dx.doi.org/10.21037/tau-20-927.

Reviewer A

I read with interest your manuscript entitled "Utilization of a three-dimensional printed kidney model for favorable TRIFECTA achievement in early experience of robot-assisted partial nephrectomy".

I think that this topic covers great interest in the era of robotics: physical and virtual 3-D models represent useful tools in order to reach TRIFECTA, even for unexperienced surgeon.

Below my comments:

Comment 1: [Cover page] 1) I would include TRIFECTA in the keywords;
Reply 1: I have added TRIFECTA to the keywords.
Change in text: Keywords: TRIFECT **(Page 4, Line number 43)**

Comment 2: [Abstract] 2) please state in the methods section the study population is a single surgeon series
Reply 2: The surgeon has performed over 50 open partial nephrectomies and 60 RAPNs, and no laparoscopic partial nephrectomies. I have added the point that there was a single surgeon in the Abstract. In the previous version of the manuscript, the number of surgeons performing open partial nephrectomy was wrong, so I changed this.
Change in text: All RAPN procedures were performed by a single surgeon. **(Page 3, Line number 29-30)**
All RAPN procedures were performed by a single surgeon with experience in more than 50 open partial nephrectomy and 60 robot-assisted radical prostatectomy procedures. **(Page7. Line number 89)**

Comment 3: [Methods] 3) please state if the population included any single kidney patient and if all the patients included had normal preoperative kidney function
Reply 3: Patients who underwent total nephrectomy were included as initial cases without any exclusions. There were two cases of unilateral kidney, which were the 18th and 30th

cases. There were a total of 12 cases of CKD, defined as an eGFR<60 mL/min/1.73 m^2, including 2 cases of unilateral kidney. I have added this to the text.

Change in text: There were 2 cases with a single kidney after nephrectomy. Chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, was seen in 24.0% of cases. **(Page 6, Line number 74-76)**

Comment 4: [Results] 4) how many retroperitoneal approaches did you perform? It would be interesting compare outcomes according to the surgical approach;

Reply 4: There were 12 cases that had a retroperitoneal approach (24%). There were no significant differences in age, sex, side, BMI, tumor size, RENAL score, surgery time, blood loss, warm ischemic time, tumor volume, or achievement of TRIFECTA between the two groups. I added the number of approaches to the text and added to the text that there were no significant differences between the two groups.

Change in text: The retroperitoneal approach was performed in 12 cases (24%). **(Page 10, Line number148-149).**

There were no significant differences in clinical characteristics or perioperative results depending on the approach (transperitoneal or retroperitoneal). **(Page12, Line number 176-178)**

Comment 5: [Results] 5) how many patients did not perform the postoperative CT due to renal dysfunction?

Reply 5: Contrast-enhanced CT could not be performed in 1 case with iodine allergy and 2 cases with renal dysfunction. Contrast-enhanced CT was performed even in the case of CKD if the patient's eGFR was >30 mL/min/1.73 m^2. In cases of renal dysfunction where contrast-enhanced CT could not be performed, a model was created using MRI without contrast media. The 3 cases in which contrast CT were not performed were evaluated by simple CT to evaluate postoperative complications.

Change in text: Postoperative contrast-enhanced CT was evaluated in 47 cases except in 1 case of iodine allergy and 2 cases of renal dysfunction. (**Page 11, Line number 159-160**)

Comment 6: [Results] 6) please explain why the renal function was evaluated only in 28 patients and subsequentially discuss it in the discussion section

Reply 6: At the time of writing the report, there were 15 cases less than 1 year after surgery and 7 cases transferred to another hospital. We received comments from the reviewer, re-aggregated post-operative renal function, collected data from other hospitals,

and updated the information. As a result, data for 46 cases, excluding 1 case transferred to the hospital, 1 case lost to follow-up, and 2 cases for which data are not available, are shown. The observation period has also been changed accordingly.

Change in text: Renal function was evaluated in 46 patients in whom renal function was confirmed at POM12.The median eGFR rates (mL/min/1.73 m^2) at the preoperative, POM3, POM6, and POM12 timepoints were 74.5, 69.5, 69.5, and 66.5, respectively. The median percent changes in eGFR at POM3, POM6, and POM12 relative to the preoperative value were -5.8%, -6.2%, and -5.9%, respectively. **(Page11, Line number 167-169)**

The mean observation period was 20.5 months (range, 3-47). (**Page 10, Line number 149**)

Comment 7: [Tables] 7) Table 3. Include as tumor characteristics the median R.E.N.A.L scores of the series for a better comparison of the surgical complexity

Reply 7: BMI, size, warm ischemic time, complications, and presence of positive margins have been added to Table 3 in addition to the RENAL score as per your comments.

Change in text: Table

Comment 8: [References] 8) Please try your best to citate:

The role of vascular clamping during robot-assisted partial nephrectomy for localized renal cancer: rationale and design of the CLOCK randomized phase III study.

Cindolo L1, Antonelli A2, Sandri M3, Annino F4, Celia A5, De Concilio B5, Giommoni V4, Nucciotti R6, Sessa F7, Porreca A8, Veccia A2, Schips L9, Minervini A7; AGILE Group (Italian Group For Advanced Laparo-Endoscopic Surgery).

Minerva Urol Nefrol. 2019 Jun;71(3):249-257. doi: 10.23736/S0393-2249.18.03134-X. Epub 2018 Sep 24.

Improved prediction of nephron-sparing surgery versus radical nephrectomy by the optimized R.E.N.A.L. Score in patients undergoing surgery for renal masses.

Sterzik A1, Solyanik O1, Eichelberg C2, Jost M2, Graser A1, Lausenmeyer EM2, Otto W2, Waidelich R3, Stief CG3, Burger M2, May M4, Brookman-May SD3.

Minerva Urol Nefrol. 2019 Sep 5. doi: 10.23736/S0393-2249.19.03610-5. [Epub ahead of print]

3D mixed reality holograms for preoperative surgical planning of nephron-sparing surgery: evaluation of surgeons' perception.

Checcucci E1, Amparore D2, Pecoraro A2, Peretti D2, Aimar R2, De Cillis S2, Piramide F2, Volpi G2, Piazzolla P3, Manfrin D2, Manfredi M2, Fiori C2, Porpiglia

Minerva Urol Nefrol. 2019 Oct 10. doi: 10.23736/S0393-2249.19.03485-4. [Epub ahead of print]
Which patients with clinical localized renal mass would achieve the trifecta after partial nephrectomy? The impact of surgical technique.
Bianchi L1,2, Schiavina R3,4, Borghesi M3,4, Chessa F3,4, Casablanca C3, Angiolini A3, Ercolino A3, Pultrone CV3,4, Mineo Bianchi F3, Barbaresi U3, Piazza P3, Manferrari F3,4, Bertaccini A3,4, Fiorentino M5, Ferro M6, Porreca A7, Marcelli E4,8, Brunocilla E3,4.

Reply: Thank you for instructing me which papers to cite. Unfortunately, there was no MINERVA UROLOGICA E NEFROLOGICA journal in Japanese universities. In addition, the office of MINERVA UROLOGICA E NEFROLOGICA was closed until August 30th, so I could not purchase online subscriptions. I contacted the author at the e-mail address given in the paper and waited for a few days, but I could not contact anyone except Dr Bianchi. Therefore, unfortunately, I could not read the papers you instructed at the time of writing this letter.

I thank the referees for their careful reading of our manuscript and for your helpful suggestions. Also, thank you for suggesting additional references. I am confident that your advice will lead to a better paper.

Reviewer B

The authors present their work using 3D printed models rendered from patients DICOM images utilized as a preoperative planning tool to improve TRIFECTA outcomes (identified as no preoperative complications, negative surgical margins, WIT < 25min) during robot-assisted partial nephrectomy in 50 patients with a majority (>92%) of cases low or intermediate risk by a single surgeon. TRIFECTA was achieved in 86% of cases. The authors present this as a retrospective review of outcomes without any comparative control group.

Comments 1: [Introduction] The authors report that some studies have reported the development and use of 3D printed models for RAPN (1-5), ….. few reports have discussed the effects of their use on patient outcomes. Please refer to the review article

published in this Journal as a significant number of publications have not only mentioned but demonstrated improved patient outcomes.

Ghazi AE; Teplitz BA. Role of 3D printing in surgical education for robotic urology procedures.Translational andrology and urology..2020;9(2):931-94

Reply 1: As pointed out by the reviewer, recent reviews of 3D models are summarized in the review reported by TAU, and I have quoted them in the paper. Similar to our report, there was also a report suggesting 3D models as a preoperative surgical course, reducing the operation time and blood loss. It seems that many of the previous reports do not have many cases due to the high cost of model making. I think our report stands out by the low production cost of US $10 on average, and the number of models that we have created and the number of models that have been used for actual surgery in many cases is 50.

Change in text: Some studies have reported the development and use of three-dimensional (3D) printed models for RAPN (1-6). Although these models are useful for patient education, preoperative planning, and training, limited reports have discussed the effects of their use on clinical outcomes. In a report using 3D-printed soft-tissue physical models as preoperative simulation in 7 cases, it was also reported that bleeding was reduced (7). **(Page 5, Line number 53-57)**

Comment 2: [Methods] Please provide details on the success of the imaging segmentation of the arterial and venous branches, was the software able to reach tertiary branches? How was this measured for accuracy?

Reply 2: Here is a quote from a previous report at TAU (Yamazaki M, Takayama T, Fujisaki A, Kamimura T, Mashiko T, Fujimura T. Robot-assisted partial nephrectomy of initial cases using a 3D square-block type kidney model. Translational Andrology and Urology. 2020;9(2):494-500.)

First, patient contrast-enhanced computed tomography (CT) images of were obtained and the CT protocol involved the SOMATOM Definition FLASH CT (Siemens Healthineers, Munich, Germany; slice thickness, 0.75 mm). A contrast medium (350 mg iohexol) was injected at 540 mL/kg over a time period of 25 seconds.

Secondly, the acquired digital images were visualized in three dimensions using Ziostation2 (Ziosoft, Tokyo, Japan) and SYNAPSE Vincent (Fuji Film, Tokyo, Japan). All 3D images depicting the kidney outline, the urinary tract, the blood vessels, and the tumor were saved separately as Digital Imaging and Communication in Medicine data. Consequently, they were converted to Standard Triangulated Language files using

Osirix (Pixmeo SARL, Geneva, Switzerland) and then synthesized using a Meshmixer (Autodesk, California, USA). A Meshmixer was also used to reproduce the outline of the kidney in a grid.

All the arteries and veins taken by CT under the above conditions are reflected in the model. The arteriovenous arterioles up to the third branch are reflected, and the fourth branch is reflected depending on the blood vessel. The thick blood vessels that needed to be clipped at least during the resection were reflected in the model.
Although the accuracy could not be measured, there was at least no difference between the image constructed by CT and the model, and there was no difference with the model in securing the arteriovenous arterioles during the operation.
Change in text: According to a previous article (8), each final printed model was actual size and has a square-block structure so that the inside could be seen (see Figure 1 for representative images). In the model, arteriovenous arterioles could be reproduced up to the tertiary branches and the branching of the quadratic branches. **(Page 7, Line number 87-88)**

Comment 3: [Surgical technique] The authors provide very little information on how the model was effective in planning for the procedure. The only subjective data was a non-validated survey (with limited details on number of questions or type of questions) at the end of the case. No comparison to perceptions in surgeons after viewing the CT scan was provided or details on surgeons viewing the Ct scan (time, frequency). Most if not all publications would at least provide a survey from the surgeons before and after viewing the model to assess this. The methodology presented here is not only subjective but is a combination of the surgeon viewing the CT, the model and performing the procedure with an inability to distinguish between them (even if the surgeon is specifically asked the value of the 3d model its not easy to distinguish that at the end of the case unless you have their baseline assessment).
Reply 3: As the reviewer pointed out, it was very difficult to show the usefulness and effect of the model, and it was not possible to point out the usefulness with the limited questionnaire method. In order to describe the usefulness of this model in our single-arm treatment results, we compared TRIFECTA with previous reports. In other words, the achievement rate of TRIFECTA is naturally low in the early stage of RAPN, but the usefulness of this model was shown by the good achievement rate of TRIFECTA by using the model.
We are currently recording a video of the surgeon during surgery to quantify how much

the surgeon looks at the model during surgery. Although the data are limited, the models with higher RENAL scores are referred to during surgery. In particular, we often refer to models when securing blood vessels. At the time of resection, we have observed the model for complete endophytic mass over time, but no conclusion has been reached yet. We are planning to write a paper with these results in the near future. We are also submitting a paper comparing CT and 3D models on the accuracy of RENAL scoring for resident education.

Change in text: None

Comment 4: [RESULTS] Unfortunately despite the impressive outcomes these are expected in the patient populations with renal masses presented in this manuscript with 92% of the patients with a nephrometry score <9, average tumor size 2.5cm and average BMI 24.5.

Reply 4: The reviewer commented that the average tumor size was small, the difficulty was low, and that the BMI was low in many cases. Certainly, it may have been the case that the degree of difficulty was not high. Our report showed results for RAPN in all 50 cases of T1a RCC diagnosed since the introduction of RAPN. There were no exclusion criteria for difficulty (T1b is excluded as it is not suitable as an initial case). There was no bias in case selection. Therefore, the tumor size may be small and the difficulty level (score >9) in the nephrometry score may be low (because of lack of T1b).

In a 2011 study published in BJUI (Surgical outcomes of robot-assisted partial nephrectomy. Benway BM, Bhayani SB. BJU Int. 2011 Sep;108(6 Pt 2):955-61), a summary of initial cases was described. Although the TRIFECTA achievement rate is unknown, the tumor size is similar to ours, but complication rates, conversion to open surgery, and PSM are generally worse than ours. We did not cite these reports in this paper because we compared them with other reports using TRIFECTA as an index to make up for the shortcomings of being a single-arm study. In low-volume facilities like ours, poorer perioperative outcomes and oncologic outcomes are expected due to inexperience when introducing RAPN. It is considered that simulation by the model was useful for improving the perioperative results and the oncological outcomes.

Change in text: None

Comment 5: [RESULTS] Had the authors underwent a sub analysis with a break down their results based on nephrometry score (low, intermediate and high) these outcomes may have been more pronounced (compare difference in outcomes based on RENAL scores) but still do not allow us to evaluate if the 3D model actually helped reach these outcomes

unless there was a control group (ie a group without 3D model).

Reply 5: As the reviewer commented, the limitation of this study is that there are no cases without a model. It is generally known that the higher the RENAL score, the higher the difficulty of surgery. The reason for the favorable results obtained for tumors with a high RENAL score and high difficulty is as follows.

1) Case of complete endophytic renal tumor (avoiding PSM, prolonged warm ischemic time); - By looking at various angles with the same actual-sized model, I was able to imagine the excision line even with the endophytic renal tumor. It was especially useful to visualize the distance and angle at which the excision should be started.

2) Cases close to the urinary tract (avoiding urinary fistula); - Since it is possible to simulate in advance where the urinary tract will open during tumor resection, even if the urinary tract is opened, it can be closed with reliable needle movement.

3) Tumor in the hilum of the kidney (avoiding vascular damage, conversion to open surgery, extended surgery time); - The model clearly shows the main blood vessels to be secured and the location of the tumor. Blood vessels that feed the tumor can be processed in advance. By observing from various angles with the model, damage to major blood vessels can be avoided. In renorrhaphy, the direction of needle movement was determined with the blood vessel at the bottom of the tumor in mind, which helped avoid pseudoaneurysm after surgery.

Change in text: None

Comment 6: [Discussion] Unfortunately the impact the 3D models had on the learning curve is difficult to justify in this study design the learning curve. From my understanding the model here is a hard model that is directly 3D printed and thus is merely a visual aid that can look and manipulate but not cut dissect and provide hemostasis. Therefore the justification that looking at the model and manually (not robotically) removing the tumor to see the relationship to the surrounding structures will not improve their technical ability to perform the procedure (ie throw a suture to control the bleeding) but only Improve their understanding (know where a potential bleeding vessel would be). I would say this learning curve is a natural progression of a "good" surgeon.

Reply 6: As the reviewer commented, it may be difficult to justify whether the learning curve based on the 3D model has improved simply by obtaining efficient visual information.

In particular, it is difficult to justify the learning curve because there is no comparison group without the 3D model.

Compared to a previous review of early cases (Surgical outcomes of robot-assisted partial

nephrectomy. Benway BM, Bhayani SB. BJU Int. 2011 Sep;108(6 Pt 2):955-61), we can say that the WIT is short, there are few complications, and there were no instances of PSM. We had a single surgeon with experience in 60 cases of robot-assisted radical prostatectomy, 50 cases of open surgery, and no experience in laparoscopic partial nephrectomy. In other words, he is not a skilled surgeon but a general-level surgeon, and the result is better than the previous reports. I am convinced that the visual effects of the model helped improve the surgical outcome.
Change in text: None

Comment 7: [Conclusion] Unfortunately despite a good sample size and the enormous amount of effort put into fabricating the 3D printed models for all these patients, the study design is inadequate (lack of equal RENAL score groups, only a single surgeon, no control group) to truly evaluate the effectiveness of the 3D printed models in improving trifecta outcomes in RAPN.
Reply 7: We completely agree with the reviewer. It may have been a little better if there was a control group or if an additional surgeon performed surgeries. However, as mentioned above, by using the model from the first case of RAPN, similar or better results have been obtained compared to past reports. Although technologies such as virtual reality are currently in development, such a model that can be easily and inexpensively created is also sufficiently useful in terms of its practical utility. This model is especially useful in cases where there is a risk of increased complications, such as when RAPN is introduced in a low-volume hospital like ours or when a new operator is introduced.
Change in text: None

We wish to express our appreciation to the reviewers for their insightful comments on our paper. The comments have helped us significantly improve the paper.