

Peer Review File

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Review Comments

Reviewer A

Comment 1: The authors reported only four cases of RCC with IVC with TT but during the dissection, it seems that none of them had lumbar veins to be clamped or ligated. Can the authors confirm this?

Two patients had pre-surgical treatment and the TT decrease from level II to level I. Can the authors clarify if they did two level I and 2 level II or 4 cases of level I.

The use of the robot as a tool for the surgical treatment of RCC with IVC TT has been described at length. Could the authors describe what is different about their four cases?

Reply 1: Thank you for your valuable comments. As you have pointed out, it is very important to pay attention to the lumbar veins that drain into the IVC while performing RARN with IVCTT. In the present study, the lumbar veins draining into the IVC were dissected in all four cases. The following statement has been added to the Surgery subsection of the **Results section** (page 7, lines 122–123): “*The lumbar veins draining into the IVC were dissected to avoid backflow in all four cases.*”

We performed RARN with IVC TT at level I in all cases. To avoid misunderstanding, we have modified the **Table**. In particular, new columns of “*IVC thrombus level at diagnosis*” and “*IVC thrombus level at operation*” were added. The **Methods** and **Results** sections and **Table** have also been modified accordingly.

In the present study, we performed RARN with IVC TT level I in all cases. As you pointed out, there were almost no differences among the four cases in terms of operative procedures and perioperative outcomes. Although no novel findings in terms of treatments for RARN with IVCTT at level I have been suggested, we focused on the safety and feasibility of RARN with IVCTT at level I because they have not yet been established owing to a lack of related studies in the literature, especially in Japan. Although the sample size was relatively small, we believe that demonstrating the safety and feasibility of RARN with IVCTT is valuable, especially for the Japanese population.

Reviewer B

This case series reported the initial treatment results of RARN with IVCTT. They demonstrated the feasibility of RARN with IVCTT

However, several issues need to be addressed before publish. The meaning of this paper should be educational. This is because the author's institution is a leading position in robotic surgery in Japan.

Therefore, I think that the author should add some TIPS of the surgery, not just a description of the commonplace surgical procedures, etc. as described in the textbooks.

Comment 1: How were the indications chosen?

Reply 1: Thank you for your valuable comments. Surgical and focal treatments for patients with metastatic renal cell carcinoma (mRCC) generally have minimal evidence; however, several recent investigators have advocated relative indications for presurgical treatments. Among these, two more articles have been cited to discuss the indications for presurgical treatments. The following sentences and two new articles have been added to the section of Discussion (page 11, lines 189–196) and References.

Changes in the text: Discussion, Page 11, Lines 189–196

Dason et al. have reported that significant extrarenal disease, excessive surgical morbidity, poor performance status unrelated to IVC thrombus, and patient preference were relative indications for presurgical treatments(2). Other studies have shown that immediate cytoreductive nephrectomy (CN) for metastatic renal cell carcinoma (mRCC) is currently considered only for a limited number of patients, while deferred CN could be applied in a larger patient population that has favorably responded to systemic therapy(15).

New two references

2. Dason S, Mohebbi J, Blute ML, Salari K. Surgical Management of Renal Cell Carcinoma with Inferior Vena Cava Tumor Thrombus. Urol Clin North Am. 2023 May;50(2):261-284. Epub 2023/03/23. doi:10.1016/j.ucl.2023.01.007. Cited in: Pubmed; PMID 36948671.

15. Naito S, Kato T, Tsuchiya N. Surgical and focal treatment for metastatic renal cell carcinoma: A literature review. Int J Urol. 2022 Jun;29(6):494-501. Epub 2022/03/28. doi:10.1111/iju.14841. Cited in: Pubmed; PMID 35340081.

Comment 2: In the case of Level 2, how did you manage the intraoperative lumbar vein? Did you ligate all of them?

Reply 2: Thank you for your comments. As you have pointed out, it is very important to pay attention to the lumbar veins that drain into the IVC when performing RARN with IVCTT. In the present study, when performing RARN with IVCTT, the thrombus classification was level I in all four cases. Therefore, the lumbar veins draining into the IVC were dissected in all four cases. The following statement has been added to the Surgery subsection of the Results section (page 7, lines 122–123): “*The lumbar veins draining into the IVC were dissected to avoid the backflow in all four cases.*”. Moreover, to avoid any misunderstanding regarding the thrombus level, we have modified the Table. In particular, new columns for “*IVC thrombus level at diagnosis*” and “*IVC thrombus level at operation*” were added. The Methods and Results sections and Table have been modified accordingly.

Comment 3: What to do if there is backflow from lumbar vein?

Reply 3: Thank you for your comments. All lumbar veins should be clamped and divided, or controlled using bipolar cautery if they are small, to avoid backflow during IVC clamping. As you pointed out, the number of lumbar veins that should be attended to increases as the thrombus classification level increases. However, if there is some backflow from the lumbar vein during IVC clamping, immediate IVC reconstruction is required. As described above, the following statement has been added to the Surgery subsection of the Results section (page 7, lines 122–123): “*The lumbar veins that drain into the IVC were dissected to avoid backflow in all four cases.*”

Comment 4: Did thrombus choose floating type as an indication for surgery?

Reply 4: Thank you for your comments. Regarding the discussion of the floating-type thrombus, we would like to focus on the use of an IVC filter. So far, several investigators have advocated indications for the use of IVC filters. Some investigators showed that preoperative filter placement could complicate proximal surgical control and tumor thrombus removal, whereas others showed that preoperative placement involved the incorporation of the tumor into the filter. In addition, a Cochrane Database review, which was completed in 2010, stated that no recommendations could be made regarding the use of IVC filters.

Considering these findings, IVC filters were not used in any of the cases. Moreover, we believe that the types of thrombus observed in the cases in this study are not likely to affect the indications for RARN with IVCTT.

The sentence, “*IVC filters were not placed in any case.*” has been added to the Surgery subsection of the Results section (page 7, lines 110–111). Furthermore, the following sentence has been added to the Discussion section (page 10, line 174): “*In all cases, an IVC filter was not used for presurgical treatment.*”

Moreover, regarding research concerning IVC filter use, the following sentences and four new articles have been added to the Discussion (page 10, lines 174–180; page 11, line 181) and References:

In all cases, an IVC filter was not used for presurgical treatment. So far, several investigators have advocated indications for the use of IVC filters. Some investigators have shown that preoperative filter placement could complicate proximal surgical control and tumor thrombus removal(11), whereas others have shown that preoperative placement involves incorporation of the tumor into the filter(12, 13). A Cochrane Database review was completed in 2010, which stated that no recommendation could be made regarding the use of IVC filters (14).

New four references

11. Zisman A, Wieder JA, Pantuck AJ, Chao DH, Dorey F, Said JW, Gitlitz BJ, deKernion JB, Figlin RA, Belldegrun AS. Renal cell carcinoma with tumor thrombus extension: biology, role of nephrectomy and response to immunotherapy. J Urol. 2003 Mar;169(3):909-16. Epub 2003/02/11.

doi:10.1097/01.ju.0000045706.35470.1e. Cited in: Pubmed; PMID 12576811.

12. Gershman B, Leibovich BC. Assessing the Evidence for the Surgical Management of Renal Cell Carcinoma with Venous Tumor Thrombus: Room to Grow. *Eur Urol.* 2016 Aug;70(2):281-2. Epub 2016/01/13. doi:10.1016/j.eururo.2015.12.033. Cited in: Pubmed; PMID 26755340.

13. Woodruff DY, Van Veldhuizen P, Muehlebach G, Johnson P, Williamson T, Holzbeierlein JM. The perioperative management of an inferior vena caval tumor thrombus in patients with renal cell carcinoma. *Urol Oncol.* 2013 Jul;31(5):517-21. Epub 2011/04/26. doi:10.1016/j.urolonc.2011.03.006. Cited in: Pubmed; PMID 21514183.

14. Young T, Sriram KB. Vena caval filters for the prevention of pulmonary embolism. *Cochrane Database Syst Rev.* 2020 Oct 8;10(10):CD006212. Epub 2020/10/08. doi:10.1002/14651858.CD006212.pub5. Cited in: Pubmed; PMID 33027844.

Comment 5: (Method) The concept of the surgical method should be described in the METHOD section of the abstract. For example, "En-bloc" or "IVC-first,Kidney-last "[*]. There are various reports on RN with IVCTT for laparoscopic or robot-assisted surgery. With the abstract described, I could not understand the surgical concept at a glance.

[*] Int J Urol. 2019 Mar;26(3):363-368. doi: 10.1111/iju.13873. Epub 2018 Dec 3. PMID: 30508876.

Reply 5: Thank you for this valuable suggestion. In the present study, the kidney-last robotic technique was developed to minimize the risk of tumor embolism and major hemorrhage.

We have added the following sentence to the **methods** section of **Abstract** (page 2, lines 31–33):
“To reduce the risk of tumor embolism and major hemorrhage, an “IVC-first, kidney-last” robotic technique was developed.”

Comment 6: I think it would be better to discuss the impact of presurgical medication on surgery, with reference to previous reports. For example, adhesion, etc.

Reply 6: Thank you for this valuable suggestion. From a surgical perspective, ICI-based combination therapy results in a severe desmoplastic reaction, which increases perinephric adhesions and inflammation, as well as surgical complexity. The following sentences and a new article have been added to the **Discussion** (page 12, lines 202–205) and **References**.

However, from a surgical perspective, ICI-based combination therapy results in a severe desmoplastic reaction, which increases perinephric adhesions and inflammation, thus increasing surgical complexity (21).

New reference

21. Isali I, Braun A, Bukavina L, Psutka SP. Role of cytoreductive surgery in the era of immunotherapy. *Curr Opin Urol.* 2022 Nov 1;32(6):618-626. Epub 2022/09/10.

doi:10.1097/MOU.0000000000001037. Cited in: Pubmed; PMID 36081404.