Peer Review File

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Reviewer A

<Major Comments>

Comment 1: LL. 216-219: Please show the disease-specific survival rate.

Reply 1: Thank you for your suggestion, and we agree with it. The disease-specific survival rate was 62.5%.

Changes in the text 1: We added the disease-specific survival rate to our text as advised (see Page 9, line 210).

Comment 2: The authors should show representative CT images and MRI images in TCC cases.

Reply 2: Thank you for your suggestion, and we agree with it. We showed the representative CT images and MRI images in TCC cases as follows (Figure 1 and Figure 2):

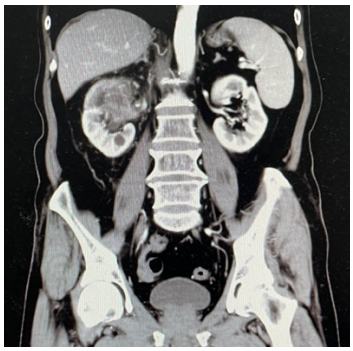

Figure 1. CT image showing the right renal pelvis urothelial carcinoma and venous tumor thrombus.

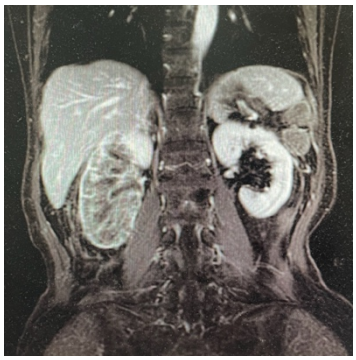

Figure 2. MRI image showing the right renal pelvis urothelial carcinoma and venous tumor thrombus.

Changes in the text 2: We added the CT and MRI images to the text. (see Figure part)

Comment 3: Patient 1 was preoperatively diagnosed as having RCC. The authors should show CT images and MRI images and discuss why preoperative diagnosis of TCC was not possible.

Reply 3: Thank you for your suggestion. The CT and MRI of Patient 1 are as follows (Figure 5). There was an irregular low-density mass in the right renal, and the reniform shape of the renal was distorted. Besides, the incidence of renal pelvis urothelial carcinoma with venous tumor thrombus was rare. Therefore, the first case in our center was considered as RCC.
In contradistinction to renal cell carcinoma, the CT features of TCC include low attenuated intraluminal filling defects in the renal pelvis, tissue necrosis and calcification. Besides, maintenance of the reniform shape of the kidney and central location of the tumor may be of help in differentiation.

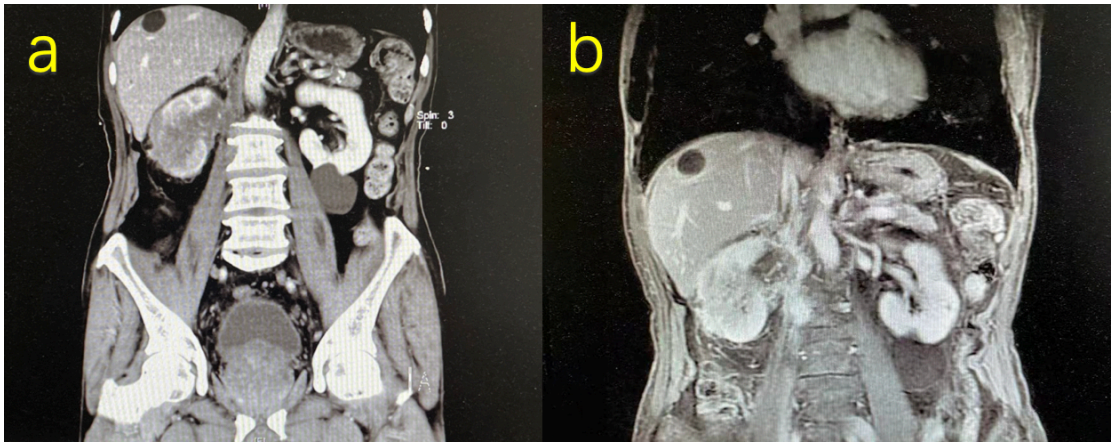

Figure 3. a) The CT image of Patient 1. b) The MRI image of Patient 1.
Changes in the text 3: We added the CT and MRI images to the text and have modified our text as advised (see Figure part and Page 10, line 227-230).

Comment 4: Please show some intraoperative photographs.
Reply 4: We appreciate your suggestion, and agree with it. The Figure 3 shows the intraoperative photographs.

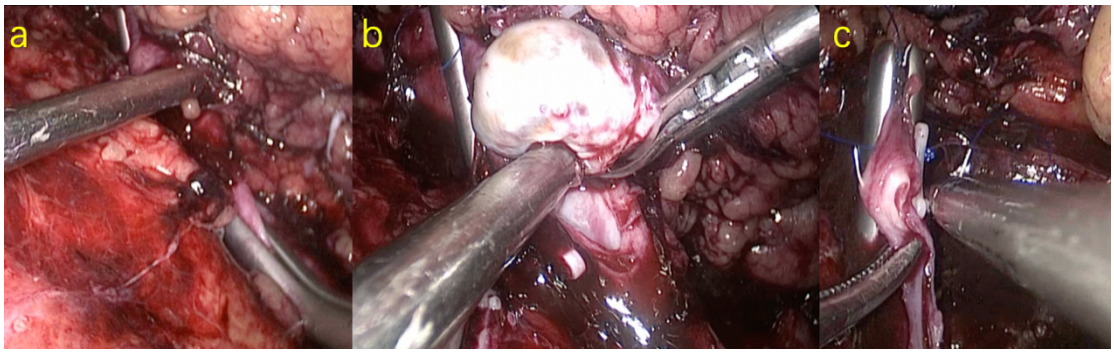

Figure 3. a) The inferior vena cava (IVC) was clamped using a Satinsky clamp. b) The IVC was incised, and the tumor thrombus was exposed. C) The incision on the IVC then was sutured continuously.
Changes in the text 4: We added the intraoperative photographs to the text (see Figure part).

Comment 5: Please show macroscopic images and photomicrographs of the resected specimens.

Reply 5: We are appreciated for your suggestion, and agree with it. The Figure 4 shows the macroscopic image and photomicrographs of the resected specimens.

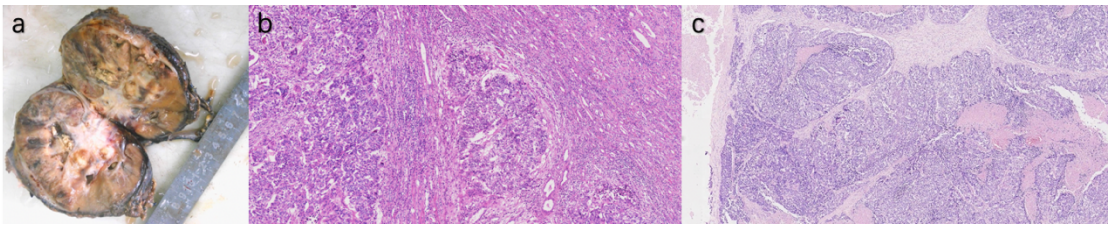

Figure 4. a) The macroscopic image of specimen. B) The pathological specimen shows urothelial carcinoma in the renal mass tumor (H&E; original magnification, x100). C) The pathological specimen shows urothelial carcinoma in tumor thrombus (H&E; original magnification, x50).
Changes in the text 5: We added the macroscopic images and photomicrographs of the resected specimens to the text (see Figure part).

Comment 6: Please describe about the chemotherapy and immunotherapy in more detail (name of the drug, doses, duration…).
Reply 6: Thank you for your advice, and we agree with it. However, it is to be regretted that the adjuvant therapy is not detailed. Because some patients live in other cities, and they received adjuvant therapy in their local hospital. Thus, we tried our best to improve the follow-up. As for the adjuvant therapy, what we know are shown as below. Patient 1 and Patient 8 did not receive adjuvant therapy. Patient 2 had chemotherapy with gemcitabine and cis-platinum in another hospital. Patient 3 had three cycles chemotherapy with gemcitabine (1.6 g) and nedaplatin (60 mg), and received radiotherapy for recurrence. Patient 4 had chemotherapy and immunotherapy in other hospital, but there was no detail recorded. Patient 5 had 3 cycles chemotherapy with gemcitabine and cis-platinum in another hospital. Patient 6 had 5 cycles chemotherapy with gemcitabine and cis-platinum in another hospital. Patient 7 was considered as RCC in another hospital and received targeted therapy before surgery. Then, she underwent surgery in our center, and pathological result showed UC. She did not receive adjuvant therapy after surgery.
Changes in the text 6: We have modified our text as advised (see Page 8, line 198-207).

Comment 7: Table 1: More detailed pathological findings such as tumor grade, vascular invasion, and tumor infiltration should be shown.
Reply 7: Thank you for your advice, and we agree with it. More detailed pathological findings are shown as follows:
Patient 1: High-grade urothelial carcinoma, with involvement of the renal parenchyma, perinephric fat, proximal ureter, and hilar lymph node. Vascular invasion and nerve invasion were observed. The tumor thrombus consisted of UC, which had histologically invaded the walls of the IVC.
Patient 2: High-grade urothelial carcinoma, with involvement of the renal

parenchyma, renal sinus, proximal ureter. Hilar lymph node, postcaval lymph node, and para-aortic lymph node were involved by tumor. No vascular invasion was observed.
Patient 3: High-grade urothelial carcinoma, with involvement of the renal parenchyma and renal sinus. Vascular invasion and nerve invasion were observed. No lymph node was involved. There were tumor thrombus and bland thrombus in the IVC, and UC invaded the walls of the IVC.
Patient 4: High-grade urothelial carcinoma with massive necrosis, and the renal parenchyma, renal sinus, and peripelvic fat were involved. Vascular invasion was observed. The tumor thrombus was in renal vein, with bland thrombus. Para-aortic lymph node was involved by tumor.
Patient 5: High-grade urothelial carcinoma, with sarcomatoid differentiation, undifferentiated carcinoma, and massive necrosis. Renal parenchyma and peripelvic fat were involved. There was tumor thrombus in the renal vein and IVC. Retroperitoneal lymph node was involved by tumor.
Patient 6: High-grade urothelial carcinoma, with involvement of the renal parenchyma and renal sinus. Vascular invasion and nerve invasion were observed. Hilar lymph node was involved by tumor.
Patient 7: High-grade urothelial carcinoma with massive necrosis, and the renal parenchyma, renal sinus and peripelvic fat were involved. There was tumor thrombus in the renal vein and IVC. Hilar lymph node was not involved by tumor.
Patient 8: High-grade urothelial carcinoma with massive necrosis, and the renal parenchyma, renal sinus and peripelvic fat were involved. No vascular invasion was observed. Hilar lymph node and vena cava lymph node were involved by tumor.
Changes in the text 7: We added the content to the Table 1 (see MR-Table 1.).

Comment 8: Table 1: It is strange that the authors did not perform cytological examination of urine in some of the cases even though TCC was suspected. Please explain.
Reply 8: Thank you for your question. The positive rate of urine cytology is low for upper tract urothelial carcinoma, so not all the suspected patients were performed this examination. Studies have shown that urine cytology, although a useful test, is positive in only 59% of the patients with upper tract urothelial carcinoma [1]. However, we believe that we will perform urine cytology for all the suspected urothelial carcinoma patients in the future.
[1] Sarnacki CT, McCormack LJ, Kiser WS, Hazard JB, McLaughlin TC and Belovich DM: Urinary cytology and the clinical diagnosis of urinary tract malignancy: a clinicopathologic study of 1,400 patients. J Urol, 106: 761, 1971.
Changes in the text 8: This comment doesn't require to modify text.

Comment 9: Table 1: Time to recurrence and time to metastasis should be shown.
Reply 9: Thank for your suggestion, and we agree with it. We will add the time to

recurrence and time to metastasis to the Table 1.
Changes in the text 9: We added the time to recurrence and time to metastasis to the Table 1. (see MR-Table 1.).

Comment 10: Patient 1 developed neither recurrence nor metastasis, but died. Why?
Reply 10: Thank you for your question. We are sorry for wrong information. We again followed-up the family of Patient 1 and looked up his medical record. We found that Patient I had local recurrence 6 months after surgery. His condition was poor, and died of cancerous cachexia.
Changes in the text 10: We have modified our Table (see MR-Table 1.).

Comment 11: Table 2: Insufficient. More information about clinical stage, pathological findings, the method of surgery, adjuvant therapy, and prognosis is needed. Only showing the number of patients gives no relevant information to our readers.
Reply 11: Thank you for your suggestion, and we agree with it. And, we had added the mentioned information to the Table 2.
Changes in the text 11: We have modified our Table 2 as advised (see MR-Table 2.).

Comment 12: LL. 240-242: This can't be drawn from their study. In general, lymph node metastasis is not specific to TCC and its presence is not useful to distinguish TCC from RCC.
Reply 12: Thank you for your suggestion, and we agree with it. There was no study that showed lymph node metastasis is specific to TCC. Thus, we deleted the corresponding content.
Changes in the text 12: We have modified our text as advised (see Page 10, line 238).

Comment 13: LL. 247-250: Needs citation.
Reply 13: Thanks for your suggestion. And we added the citation to this part.
Changes in the text 13: We have modified our text as advised (see Page 10, line 243-246).

Comment 14: Please discuss the complication rate in the authors' series by citing literature.
Reply 14: Thank you for your suggestion, and we agree with it. There were three patient who had post-operative complications, and the complication rate is 37.5% in our study. Because the number of renal pelvis UC and venous TT reported is limited, the complications reported was also limited. Concepcion RS et al reported a UC patient with TT complicated by restrictive pulmonary insufficiency, resultant renal vein thrombosis and renal failure. And this patient died 31 days after surgery [12]. Cerwinka WH et al reported two patients

complicated by pulmonary embolism [22]. There was no complication rate of renal pelvis UC and venous TT reported. However, previous studies showed that radical nephrectomy with thrombectomy was related to major perioperative morbidity (range 50-78%) and mortality (range 2.7-8.3%) [35-37]. Compared with this, we believe that our complication rate is acceptable.

35. Haddad AQ, Leibovich BC, Abel EJ, et al. Preoperative multivariable prognostic models for prediction of survival and major complications following surgical resection of renal cell carcinoma with suprahepatic caval tumor thrombus. Urol Oncol 2015; 33:388. e1–9.

36. Ebbing J, Wiebach T, Kempkensteffen C, et al. Evaluation of perioperative complications in open and laparoscopic surgery for renal cell cancer with tumor thrombus involvement using the Clavien-Dindo classification. Eur J Surg Oncol 2015;41: 941–52.

37. Toren P, Abouassaly R, Timilshina N, et al. Results of a national population-based study of outcomes of surgery for renal tumors associated with inferior vena cava thrombus. Urology 2013;82: 572–7.

Changes in the text 14: We have modified our text as advised (see Page 11, line 260-269 and References part).

Comment 15: The prognosis of patients in the authors' series is poor. Is surgery really necessary for TCC patients with tumor thrombus? Please discuss.

Reply 15: Thank you for your question, and we think that it is very important. The surgery is necessary for RCC patients with venous TT. Radical nephrectomy with thrombectomy could remove the tumor completely, and achieve the therapeutic purpose. Besides, cytoreductive surgery is still beneficial for metastatic RCC patients with TT. However, the exact role of surgery in the management of renal pelvis UC patients with venous TT is not defined, because of the limited available literature. In our opinion, for non-metastatic renal pelvis UC patients with venous TT, surgery could reduce tumor loading, and might be helpful to improve the survival. But, more cases are still needed to verify this.

Changes in the text 15: We have modified our text as advised (see Page 10, line 246-250).

Reviewer B

Comment 1: The authors may want to provide the number of cases of 1) renal pelvic or upper tract UC treated surgically and 2) renal pelvic UC with venous TT treated non-surgically during the study period at the authors' institution. These figures may help the readers understand the rarity of the disease condition.

Reply 1: Thank you for your suggestion, and we agree with it. From March 2016 to January 2019, 247 patients were pathologically diagnosed with upper tract urothelial carcinoma and underwent underwent surgery at our institution. And there were only eight renal pelvis urothelial carcinoma with venous tumor thrombus during the study period at our institution. All the renal pelvis urothelial carcinoma with venous tumor thrombus underwent surgery.

Changes in the text 1: We have modified our text as advised (see Page 6, line 141-144).

Comment 2: The authors should clarify whether curative operation had been done or not. The authors mentioned that they performed operation for curative or cytoreductive purpose. The authors may want to provide whether they had attempted curative or cytoreductive operation.
Reply 2: Thank you for your suggestion, and we agree with it. We are sorry for the incorrect information. The eight patients in our center underwent operation for curative purpose. The eight patients had no metastasis before surgery.
Changes in the text 2: We have modified our text as advised (see Page 7, line 156).

Comment 3: The authors should discuss neoadjuvant chemotherapy (NAC) in cases of renal pelvic UC with venous TT. Because of disappointing survival outcomes, NAC may be considered for such cases.
Reply 3: Thank you for your suggestion, and we agree with it.
At that time, no clear evidence to supporting neoadjuvant chemotherapy for upper tract urothelial carcinoma. And the patients in our series, with good performance status, refused to receive neoadjuvant chemotherapy. Thus, no patients in this series received neoadjuvant chemotherapy. There were just some studies showed that neoadjuvant chemotherapy may help for bladder UC. We speculated that it might have improve survival for upper tract UC. Compared with adjuvant chemotherapy, the neoadjuvant therapy may reach a better outcome, because some patients might not be tolerance to chemotherapy after nephrectomy. However, if neoadjuvant chemotherapy is considered, the diagnosis should be assured by pathological examination. Besides, the patient's preference and performance status should be taken into consideration when choosing neoadjuvant therapy.
Changes in the text 3: We have modified our text as advised (see the Page 12, line 279-288).

Comment 4: The authors showed the number of cases in the literature in Table 2. The most important is 1) what treatment was given (including surgical treatment and NAC or adj chemo) and 2) pathology and prognosis. Please revise the table by updating these information. The authors may want to discuss whether TT compromises prognosis by itself or via accompanying unfavorable pathology.
Reply 4: Thank you for your suggestion, and we agree with it. We have revised the Table 2 as suggested. In this series, all the patient had late stages (T3~4) and high grades, which may be relevant to the poor prognosis. Thus, their prognosis is poor. As for TT, it has an influence on the prognosis of renal cell carcinoma. For renal pelvis UC, it is difficult to analysis the influence of TT on patient, because of the limited sample size of renal pelvis UC and TT. On the whole, we

believe that both TT and unfavorable pathology had a bad influence on prognosis.
Changes in the text 4: We have modified Table 2 and our text as advised (see the MR-Table 2 and Page 11, line 275-278).

Reviewer C
Comment 1: Minor comments would be to change TCC. Please use urothelial carcinoma (UC) instead.
Reply 1: Thank you for your suggestion, and we agree with it. We have used urothelial carcinoma (UC) to replace transitional cell carcinoma (TCC).
Changes in the text 1: We have modified our text as advised (see the whole text).

Comment 2: Please expand more on the limitations of the study such as short follow up. Also, why were these patients offered neoadjuvant cisplatin-based chemotherapy?
Reply 2: Thank you for your suggestion, and we agree with it. We expand more content on the limitations. The content is as follows: We admit that the current study has some limitations. First, its retrospective nature is a shortcoming, and may cause some bias. Second, the sample size of this study is small, due to the low incidence of renal pelvis UC with venous TT. Thus, a multi-center study with large sample size is needed. Third, the follow-up time is short. Fourth, all the patients in this study did not receive neoadjuvant cisplatin-bases chemotherapy. Thus, we cannot evaluate the therapeutic effect of neoadjuvant chemotherapy.
No clear evidence exists either to support or oppose the use of neoadjuvant chemotherapy at that time. And some patients' performance status was poor and some patients in our study refused to receive neoadjuvant chemotherapy. Thus, these patients were not offered neoadjuvant cisplatin-based chemotherapy in our study.
Changes in the text 2: We have modified our text as advised (see Page 12, line 289-294 and Page 12, line 279-283).

Comment 3: English language review is advised
Reply 3: We are very appreciated with this important suggestion and agree with it. And this manuscript has been revised by English-native speaker.
Changes in the text 3: We have modified our text as advised (See the whole text).