Peer Review File

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Reviewer A

Comments on Radiation therapy for nonmetastatic medically inoperable upper-1 tract urothelial carcinoma

Global:

Comment 1: The authors have explored an interesting topic, delivered a well written paper, however the paper explained too much on case series: this should be adapted, fe case presentation: I would delete this. Also all individual data of patients should be collected in one table with mean values, with ranges,

Also some additional adaptations should be made, especially the section on RT details should be more clear explained, See under

Reply 1: We thank for your valuable comment.

(1) We shortened the section of the case series and deleted the case presentation according to the recommendation. And we combine Tables 1 and 2 to make the expression more clearly and coherent.

(2) We are sorry about the ambiguous expression. And we have adjusted the content of radiotherapy details and explained it clear and succinct. At the same time, the limit of organs at risk was supplemented.

Changes in the text: We deleted the case presentation and added some data about the RT details and combined Tables 1 and 2 (see Page 7, line 10-16; Table 1).

Specific:

Abstract:

Comment 2: Cannot undergo this procedure for several reasons: please explain (comorbidities, etc.)

Reply 2: We thank for this comment. We have explained it clearly and rewritten the sentence according to the recommendation.

Changes in the text: We added some data about the several reasons (see Page 2, line 5).

Comment 3: Methods: is PubMed and Medline screened? Is not mentioned which search strategy is used.

Reply 3: We are sorry about the ambiguous expression. PubMed and Medline are screened and we describe the search strategy in detail. And "upper-tract urothelial carcinoma" and "radiotherapy" were used as key words in the search.

Changes in the text: We added some data about the search strategy (see Page 2, line 9).

Comment 4: Toxicity is scored according which scoring system?

Reply 4: We thank for this comment. Toxicity is scored according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0.

Changes in the text: We added some data about the scoring system (see Page 3, line 2).

Comment 5: Results: grade 3 anemia it was manageable: is a vague explanation, please be more specific.

Reply 5: We are sorry about the vague expression. We have explained it more specific according to the recommendation. It was manageable and improved with symptomatic support.

Changes in the text: We have modified our text as advised (see Page 3, line 4).

Intro:

Comment 6: concerning prevalence: higher prevalent, not only in China: also in patients with Lynch syndrome, and also in the Balkan region (Bulgaria, Greece, Romania, former Yugoslavia) in Europe: the so called ''Balkan endemic nephropathy'': an indolent inflammatory process of the renal interstitium is associated with the development of urothelial tumors of the renal pelvis and ureter (see Rouprêt M, et al Eur Urol. 2017) Add this.

Reply 6: We thank for your valuable comment. As you mentioned, in the Balkan region, Balkan endemic nephropathy is associated with the development of urothelial tumors of the renal pelvis

and ureter. We have reedited the sentence according to the recommendation.

Changes in the text: We added some data about the Balkan endemic nephropathy (see Page 4, line 4, 5).

Comment 7: Other treatments: Add intracavitary administration of pyelocalyceal mitomycin as an alternative treatment to nephroureterectomy: mitomycin is admixed with a reverse thermogelation hydrogel. Initial complete response rate of 59 % (Kleinmann N, et al Lancet Oncol. 2020;21(6):776)

Reply 7: We thank for your valuable comment. As you mentioned, we also think that this treatment is an important option for patients.

Changes in the text: We added some data about treatment of pyelocalyceal mitomycin (see Page 4, line 12-15).

Methods:

Comment 8: PET-CT: is this performed for all patients? To confirm no evidence of malignancy in the bladder / urethra: is this correct? Moreoever to confirm cN0M0 status? You cannot see this well on PET-CT?

Reply 8: We thank for your valuable comment.

(1) 5 of 8 patients performed the PET-CT and all patients underwent complete CT scans, as a basis for diagnosis. We have reedited the sentence to make it clearer.

(2) And CT was used to confirm no evidence of malignancy in the bladder / urethra, which is very important because it help us to make sure that the tumor was located only in the upper urinary tract. The PET-CT was used to determine whether there were metastases in other parts of the body. Therefore, CT and PET-CT can help us to make TNM staging diagnosis.

Changes in the text: We have modified our text as advised (see Page 6, line 3-6).

Comment 9: A bit further PET/CT is performed if indicated…? An CT of chest abd, pelvis…? Please be consequent.

Reply 9: We are sorry about the vague expression. As was stated in the previous question, CT and PET-CT can help us to make TNM staging diagnosis. And all patients performed the CT,

some of patients perfected PET/CT. We have reedited the sentence.

Changes in the text: We have modified our text as advised (see Page 6, line 12).

Comment 10: The ethical standards are according Peking University First Hospital? International, these standards are not known. Are these according Helsinki principles? Please explain…The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving humans.

Reply 10: We thank for your valuable comment. Yes, all procedures performed in studies involving human participants were in accordance the ethical standards of the Helsinki principles.

Changes in the text: We have modified our text as advised (see Page 6, line 16).

Comment 11: Treatment: 2 strategies:

P-SABR is a bit complicated explained, moreover a dose is prescribed to the GTV with no CTV: please explain why? Moreover, no PTV margin for the boost plan? Is this a simultaneous integrated boost (SIB)? This is very ambitious and not correct according RT principles.

The CRT are delivered with a SIB? If so, mention this…

Reply 11: Thank you for raising this important issue. We are sorry about the vague expression.

(1) P-SABR regimen is a little more complicated. The focus of the p-SABR regimen is sequential dose administration, with SABR as the first stage of radiotherapy followed by the second stage of conventionally fractionated radiotherapy, rather than a SIB.

(2) And the definitions and margins of CTV and PTV were added. The limit of organs at risk was supplemented.

Changes in the text: We added some data about radiotherapy technique (see Page 7, line 10-16; Page 8, line 5,11).

Comment 12: FU extending to 6-12 months in case of prolonged stability? What does that mean, be specific, after 2 years?

Reply 12: We are sorry about the ambiguous expression. Yes, the patients were followed up with intervals extending to 6–12 months after 2 years.

Changes in the text: We have modified our text as advised (see Page 8, line 16).

Comment 13: Review literature: What is the search strategy?

Reply 13: We are sorry about the ambiguous expression. PubMed and Medline are screened and we describe the search strategy in detail. And "upper-tract urothelial carcinoma" and "radiotherapy" were used as key words in the search.

Changes in the text: We added some data about the search strategy (see Page 9, line 5,7).

Results:

Comment 14: Are still alive: without disease progression? if so, add this.

Reply 14: We thank for this comment. Yes, the remaining 6 patients were still alive without disease progression.

Changes in the text: We added some data about the survival (see Page 9, line 15; Table 2).

Comment 15: grade 3 anemia it was manageable: is a vague explanation, please be more specific.

Reply 15: We are sorry about the vague expression. We have explained it more specific according to the recommendation. It was manageable and improved with symptomatic support.

Changes in the text: We have modified our text as advised (see Page 10, line 8).

Comment 16: Are the renal functions measured? Is not mentioned in M-M + are the ureterostenosis controlled? Also not mentioned.

Reply 16: We thank for this comment. Ureteral stricture due to tumor mass could also be relieved under tumor control. At the last follow-up, there was no significant long-term impairment of renal function, and no ureterostenosis occurred.

Changes in the text: We added some data about this (see Page 10, line 4).

Comment 17: Part of the case presentation: I would delete this: is too much a part as a case report….

Reply 17: We thank for your valuable comment. We shortened the section of the case series and deleted the case presentation according to the recommendation.

Changes in the text: We have deleted the case presentation.

Discussion:

Comment 18: page 12 r 5-8: However, the durations of ….and to estimate adverse events more accurately.

This is limitation and should be mentioned in limitation section, delete here.

Reply 18: We thank for your valuable comment. We reedited and adjusted the logical structure of the paragraph according to your suggestion.

Changes in the text: We have deleted the case presentation and have modified our text as advised (see Page 14, line 14).

Comment 19: Page 14: r11: IG: can help reduce errors, and also reduce margins… Now in this study there is no clear margin concept described: this should be added.

Reply 19: We thank for your valuable comment. We added the definitions and margins of CTV and PTV.

Changes in the text: We added some data about clear margin concept (see Page 7, line 11).

Comment 20: Limitation section should be before Future perspectives.

Reply 20: We thank for this comment. We adjusted the logical structure of the paragraph according to the recommendation.

Changes in the text: We have modified our text as advised (see Page 14, line 14).

Comment 21: Add in limitation: the margin concept, without CTV, and minimal PTV?

Reply 21: We thank for your valuable comment. We added the definitions and margins of CTV and PTV.

Changes in the text: We added some data about clear margin concept (see Page 7, line 11,12; Page 8, line 1).

Comment 22: Conclusion:

Add that future research has to be established to confirm these results.

Reply 22: We thank for your valuable comment. We added that future research should be conducted to confirm these results according to the recommendation.

Changes in the text: We added some data about conclusion (see Page 15, line 3).

Reviewer B

The authors attempt to report clinical outcomes of 8 patients with upper urinary tract urothelial carcinoma treated with definitive radiotherapy and to show the usefulness of radiotherapy for the diseases. There were no local relapses in the study and 6 patients are still alive at the last follow-up.

Comment 1: However, four of the six patients have been followed up for 1 year or less, and the data seem to be unclear especially because of wide variety of treatment methods regarding the irradiation dose and field. Although they mentioned them as limitations of their study, they have to describe the reasons why they used different irradiation doses and PTV in more detail. The lack of data about PTV in conventional radiotherapy for patients with extended fields should be also improved. For renal pelvis cancer, they used the high-dose stereotactic radiotherapy, and atrophic change of the irradiated kidney in a case presentation was observed 3 months after treatment (Figure 4). I suppose that his renal function may be worsened, because his ipsilateral aging kidney (84 years old) does not seem to be normal. Late complications may be underestimate in the present study because of the short-term follow-up results.

In addition, there are some grammatical errors in the manuscript, and the style of references are unsuitable for the journal guideline. Please recheck them before resubmission, carefully.

Reply 1: Thank you for raising this important issue.

(1) We have adjusted the content of radiotherapy details and explained it clear and succinct. When the tumor was located in the renal pelvis and upper ureter, most patients were treated with p-SABR regimen because it's farther from the intestine. However, when the tumor was located in the middle and lower ureter, the CRT protocol was chosen and the field of CTV extended, including the adjacent ureteral passage region and the lymphatic drainage region.

(2) At the last follow-up, although atrophic changes in the irradiated kidney occurred, the patient's renal function was maintained. We agree with your comment that late complications may be underestimate in the present study because of the short-term follow-up results. We have acknowledged the small sample size and short observation of our study in Discussion section. We are looking forward to study with larger cohort in the future.

(3) We have reviewed and corrected the grammatical errors and the style of references.

Changes in the text: We added some data in Radiotherapy technique section (see Page 7, line 9-16).

Specific comments

Comment 2: P7. (Methods) Please add information regarding clinical target volume in the present study. Furthermore, PTV in the CRT method should be also mentioned. In addition, dose constrains of the organs at risk should be shown here.

Reply 2: We thank for your valuable comment. We added the definitions and margins of CTV and PTV. At the same time, the limit of organs at risk was supplemented.

Changes in the text: We added some data in Radiotherapy technique section (see Page 7, line 9-16; Page 8, line1, 11-13).

Comment 3: P7 (Methods) Were all patients treated with radiotherapy alone?

Reply 3: We thank for this comment. Yes, all patients were treated with radiotherapy alone.

Changes in the text: We added some data (see Page 9, line 13).

Comment 4: P7 (Methods) Please explain the intervals between SABR and CRT in three patients.

Reply 4: We thank for this comment. The p-SABR regimen is sequential dose administration and there was no interval between SABR and CRT component.

Changes in the text: We have modified our text (see Page 8, line 4).

Comment 5: P7 (Methods) I cannot understand "The PTV margin was approximately 50-60 Gy"

Reply 5: We are sorry about the ambiguous expression. The PTV dose was approximately 50–60 Gy in 25 fractions.

Changes in the text: We have modified our text (see Page 8, line 8).

Comment 6: P7 (Methods) Describe the details of follow-up examination.

Reply 6: We thank for this comment. During the follow-up period, physical examination, CT and

blood routine and renal function examination were needed.

Changes in the text: We added some data in follow-up section (see Page 8, line 16).

Comment 7: P7 Please explain the dose delivery techniques to accurately treat moving tumors with radiotherapy in the present study.

Reply 7: We thank for this comment. It was the limit in our study lack of technical control of radiotherapy dose for tumors greatly affected by movement. We have acknowledged the 4D breath-gating techniques may be needed in Discussion section.

Changes in the text: (see Page 14, line 11).

Reviewer C

The authors presenting manuscript describing the use of definitive radiotherapy for patients with UTUC who were not willing or able to proceed with surgical resection. These data are relatively novel in that surgery has been the standard of care for many years. I find the manuscript interesting and helpful for providing some data for this occasionally encountered clinical scenario.

Major Issues

Comment 1: With a median follow-up of only 13.5 months, it is difficult to draw many conclusions about the effectiveness of this treatment. Furthermore, it makes it challenging to report to year estimated LRFS and DSS since many patients did not even reach the 2 years mark follow-up. Consider reporting more crude outcomes instead of actuarial outcomes.

Reply 1: Thank you for raising this important issue. We agree with this comment. We have focused on descriptive data and crude outcomes to highlight the local control of the tumor.

Changes in the text: We have deleted year estimated LRFS and DSS the modified our text as advise (see Page 9, line 15).

Comment 2: Details regarding radiation planning need to be much more clear. Was motion management used? One patient is listed is having lymph node involvement, or only the positive lymph nodes treated or were elective nodes also treated? How were the patients immobilized? Were there any dose constraints that were used?

Reply 2: We thank for your valuable comment.

(1) We have added more details in Radiotherapy technique section, including the concept of CTV, PTV and limitation of OARs. And the choice of radiotherapy regimen is also explained in detail.

(2) Motion management was not used. It was the limit in our study. And we have acknowledged the 4D breath-gating techniques may be needed in Discussion section.

(3) In the patient with the N2+, the positive lymph nodes were identified as part of GTV and elective nodes regions were included in CTV.

(4) All patients were immobilized with the thermoplastic film.

Changes in the text: We have modified our text and added some data (see Page 7, line 6,10; Page 8, line 11).

Comment 3: Did any patients receive systemic therapy, such as chemotherapy or immunotherapy?

Reply 3: We thank for this comment. All patients were treated with radiotherapy alone, without any systemic therapy.

Changes in the text: We added some data (see Page 9, line 13).

Comment 4: More details regarding changes in renal function would be helpful. That is, could you report estimated GFR before and after radiation for all patients?

Reply 4: Thank you for raising this important issue. We have added the estimated GFR before and after radiation for all patients. And there was no significant long-term impairment of renal function, although the follow-up time was not long enough.

Changes in the text: We added some data (see Figure 2).

Comment 5: In the discussion, I would tone down statements about this study showing much evidence that radiation is beneficial for survival. While the results are promising, there isn't much of a comparison group of untreated or surgical patients. I would focus on local control.

Reply 5: Thank you for raising this important issue. We agree with this comment. And we have reedited and refocused to focus on the local control of the tumor in the discussion section.

Changes in the text: We have modified our text as advised (see Page 11).

Comment 6: The discussion is a bit too long. The topics covered are reasonable, but should be shortened to improve readability.

Reply 6: Thank you for your value comment. And we have reedited and shorten the length to improve readability and keep the focus on the point in the discussion section.

Changes in the text: We have modified our text as advised (see Page 11-14).

Comment 7: I would remove figure 5 and consider replacing it with a Table. It seems inappropriate to present a K-M curve as an aggregate of separate studies.

Reply 7: Thank you for your value comment. We agree with this comment. We have removed figure 5 and replacing it with a Table 4.

Changes in the text: We have modified our text as advised (see Table 4).

Minor Issues

Comment 8: Please fix this sentence on Page 4, Line 2. It currently states "Radiotherapy may offer a therapeutic alternative in such UTUC cases". Please clarify which cases, I assume you mean those in patients not fit for surgery.

Reply 8: We thank for this comment. We have rewritten the sentence according to the recommendation.

Changes in the text: We have modified our text as advised (see Page 5, line 6).

Comment 9: Page 5, Line 4-change "organ" to "organs"

Reply 9: We thank for this comment. We have rewritten the sentence according to the recommendation.

Changes in the text: We have modified our text as advised (see Page 5, line 9).

Comment 10: Please clarify if this was a prospective or retrospective study.

Reply 10: We thank for this comment. This was a retrospective study.

Changes in the text: We added some data (see Page 6, line 3).

Comment 11: Page 7, Line 9-10 says " The PTV margin was approximately 50-60 Gy" I assume this means the PTV dose was 50-60 Gy, please clarify.

Reply 11: Thank you for your value comment. We agree this comment. The PTV dose was 50-60 Gy. And we have reedited the sentence.

Changes in the text: We have modified our text as advised (see Page 8, line 8).

Comment 12: For the case report patient, you describe the SABR boost (3 fractions) and

subsequent CRT (22 fractions), while indicating the PTV dosing in 25 fractions. This is a bit confusing and does not really make sense radiobiologically. I would consider simply not reporting the PTV dosing.

Reply 12: Thank you for your value comment. We agree this comment. In order to highlight the key points and improve the readability of the full text, we shortened the section of the case series and deleted the case presentation.

Changes in the text: We have deleted the case presentation.

Comment 13: Page 11, Line 10 add the word "cancer" prior to "specific survival..."

Reply 13: We thank for this comment. We have rewritten the sentence according to the recommendation.

Changes in the text: We have modified our text as advised (see Page 11, line 7).

Comment 14: The authors note that the 2 patients who progressed had high T-stage/N+ disease. I would make this more clear that one patient was T4 and the other was N2+ (both in the text and the abstract).

Reply 14: Thank you for your value comment. We agree this comment. We have rewritten the sentences according to the recommendation.

Changes in the text: We have modified our text as advised (see Page 2, line 15; Page 9, line 16).

Comment 15: Page 13, Line 14 indicates that extended fields were used in 3 patients, but there is really no description of this in the methods. Please clarify

Reply 15: Thank you for your value comment. We are sorry about the ambiguous expression. For patients, the extended field of CTV included the adjacent ureteral passage region and the lymphatic drainage region.

Changes in the text: We added some data (see Page 8, line 1).

Comment 16: The potential role of chemotherapy needs to be mentioned in the discussion, given the recent POUT results (Birtle, et al Lancet 2020)

Reply 16: Thank you for raising this important issue. We agree with this comment. And we added the results clinical significance of the POUT study in the discussion section.

Changes in the text: We added some data about POUT study (see Page 14, line 3).

Comment 17: I recommend combining Tables 1 and 2.

Reply 17: Thank you for your value comment. We agree with this comment. And we have combined Tables 1 and 2.

Changes in the text: We have modified our text as advised (see Table 1).