

## Peer Review File

Article information: <https://dx.doi.org/10.21037/tcr-23-1428>

### Reviewer A

The authors have reported their single centre experience in the management of bilateral Wilms tumor. Though the number has not been large but nonetheless, they have shared some important learning points. The English language is not their native language and should undergo further scientific editing to make it publishable.

One of the key points missing is in the application of radiation therapy. If this was omitted in all your patients, then this should be a worthwhile discussion points as almost all prior publications have included RT in stage III and positive margins.

**Reply 1:** In our study, only two patient received radiation due to the positive regional lymph nodes.

**Changes in the text:** Information about radiotherapy has been added to the results of the article. (see Page 8, line 161)

Besides the above, please look at the following:

Sentence 56. "Because bilateral..." delete "Because"

Sentence 88. "who didn't performed up-front" amend to "who did not receive upfront"

Sentence 89. "for 2 cycles 3 weeks" amend to "2 cycles in 3 weeks"

Sentence 89-90. "Radical surgery could be performed with single-stage or two-stage bilateral lesions operations", amend to "Radical surgery was performed as single-stage or two-stage operations"

Sentence 93. "when the collecting system is" amend to "when the collecting system was"

**Reply 2:** Modified as requested.

**Changes in the text:** The corresponding content in the article has been modified.

Sentence 116-117. The local stages of the 16 patients were listed here. However, it is common understanding that all patients will be stage V and local staging implies staging of each kidney tumor, hence you should be reporting 32 local stages instead of 16. In addition, 11 stage III was reported, which seems high, please explain if they were stage III due to the performance of biopsy.

**Reply 3:** The original intention of using local stage in the article is to reflect the initial situation of renal tumors, and whether preoperative chemotherapy can improve the survival rate. However, due to the lack of a suitable preoperative tumor staging system (2 cases who abandoned treatment without surgery were also unable to use the postoperative staging system), only the postoperative staging system could be used, resulting in confusion in understanding. Therefore,

local stage of tumor has been removed from the text and Table in the first revised edition to avoid ambiguity. The reason why there are more patients in stage III is partly due to biopsy and partly due to local lymph node metastasis.

**Changes in the text:** The local stage had been deleted in the text and table.

Sentence 120. How was GFR determination made for each kidney? Please elaborate the method of determination and explain what is normal here.

**Reply 4:** The glomerular filtration rate is determined based on the results of a radioisotope renography, so there are separate glomerular filtration rates for both kidneys. The normal value for radioisotope renography is about 80-120ml/min.

**Changes in the text:** Access and criteria for obtaining glomerular filtration rate have been added to the methods. (see Page 4, line74)

Sentence 126. Please state whether the preoperative biopsy was done by percutaneous needle biopsy or by surgical biopsy.

**Reply 5:** The method of biopsy is by open surgery.

**Changes in the text:** The route to biopsy has been updated in Methods of this article. (see Page 5, line 79)

Sentence 130. Please define what constitutes “partial response”

**Reply 6:** In this study, a partial response was defined as a reduction in tumor size between 25% and 75%.

**Changes in the text:** The evaluation criteria for chemotherapy efficacy have been added to the methods of the article. (see Page 5, line 82)

Sentences 135-136 contradicted sentence 133-134.

**Reply 7:** Line 133~134 refers to patients with multiple lesions in one kidney who are insensitive to preoperative chemotherapy. And 135~136 refers to the effect of preoperative chemotherapy when there is only one lesion in the kidney.

**Changes in the text:** No revision in the text.

Sentence 138-139. Omit “remaining”.

**Reply 8:** Modified as requested.

**Changes in the text:** The corresponding content in the article has been modified.

Sentence 145 only showed total of 26 kidneys instead of 28 kidneys. Please explain.

**Reply 9:** Because 14 patients underwent surgical treatment, and 2 of them only underwent surgery on one kidney, a total of 26 kidneys were operated on in the end.

**Changes in the text:** No revision in the text.

Sentence 162. Please define “renal insufficiency”

**Reply 10:** In this study, one patient developed hypertension and proteinuria one year after treatment, and his serum creatinine (> 132umol/L) and blood urea nitrogen (> 7.14mmol/L) increased significantly. He was diagnosed with renal insufficiency after consultation with a nephrology department.

**Changes in the text:** No revision in the text.

Sentence 171. Did the 3 patients who died, died of disease progression?

**Reply 11:** Two patients died after giving up treatment, and another patient died due to tumor recurrence.

**Changes in the text:** No revision in the text.

Sentence 173-175. You mentioned recurrence rates of 12.5% for negative margins, and 16.7% for positive margins. There was total of 17 kidneys with TE, of which 6 had positive margins. 6 had positive margins. In calculating the recurrence rates for negative margins, would you also consider those who had PN and RN as the denominator?

**Reply 12:** When calculating the tumor recurrence rate in the article, it was calculated based on the patients. There were 6 patients with positive margins and 8 patients with negative margins, so the recurrence rates were 16.7% and 12.5% respectively. If the recurrence rate is calculated according to the surgical method, RN and PN will not be included, and the recurrence rates of positive and negative margins for TE surgical method are 16.7% and 9.1% respectively.

**Changes in the text:** No revision in the text.

Sentence 238-240. Continuing preoperative chemotherapy after 12 weeks will not only fail to cause further tumor size reduction, it may induce development of anaplasia. Therefore, it is not recommended to prolong chemotherapy beyond 12 weeks.

**Reply 13:** Modified as requested.

**Changes in the text:** The corresponding content in the article has been modified. (see Page 10, line 222)

Sentence 256-258. In the report from St Jude, radiation therapy was given for all patients who were found with positive margins after NSS. You have not reported if your patients received postoperative radiation if found with positive margins, as radiation may affect the final outcome.

**Reply 14:** In our study, only two patient received radiation due to the positive regional lymph nodes.

**Changes in the text:** Information about radiotherapy has been added to the results of the article. (see Page 8, line 161)

Sentence 292-293. Would you try to explain the reason for inferior outcome in your study? Or are you unable to conclude from your study? Would you like to offer an explanation as to why patients who received preoperative chemotherapy

had better survival rates?

**Reply 15:** On the one hand, the proportion of patients that were lost to follow-up and giving up treatment was relatively high in the entire study, thus affecting the calculation of survival rate; on the other hand, patients who should have received radiotherapy did not receive radiotherapy, which also affected the final survival results. Preoperative chemotherapy can reduce tumor activity and shrinks tumor size, and can also reduce the positive rate of resection margins, thereby improving overall survival.

**Changes in the text:** Corresponding explanation was added to the discussion. (see Page 11, line 271)

### **Reviewer B**

This retrospective study aims to describe one center's ten-year experience of treating bilateral Wilms tumor. The study sample is not big but it's an important subject and it's important to share experiences when it comes to unusual diagnoses. As the study lacks an unexposed cohort for comparison it can be argued that it should be classified as a case series. However, by Translational Cancer Research it would be classified as an Original article. The title is spot on, the introduction clearly defines the main aspects of the topic and explains the aim of the study and the manuscript is well disposed. However, after reading the study I was left with unanswered questions and I also want to stress that the author needs to remember that because of this being an uncommon diagnosis numbers in the study are low.

1. Results need to be rewritten and presented clearer. I'd suggest another table or that table 2 is somehow extended. At this point it's difficult to follow the text and interesting data is lost. Who had a biopsy before surgery and what did their survival look like? Did tumor stage, metachronal/synchronous tumor, liver metastases, v.cava thrombosis, lymph metastases, preop tumor rupture, cyto regime applied or reoccurrence affect the survival, event free survival or kidney function? What did the three dead die from? What about those who gave up treatment, are they followed up or lost to follow up? What about their survival?

**Reply 1:** The results have been modified as required, and Table 2 has been added to reflect treatment and prognosis information.

**Changes in the text:** Modified as requested and Table 2 was added. The original Table 2 has become Table 3.

2. There is a sentence in results, row 117 saying "0.5 and 11 for stage I, II and III respectively". Is there a figure missing in this sentence?

**Reply 2:** Because local staging of this tumor caused ambiguity and other reviewers raised similar questions, it was removed from the results.

**Changes in the text:** The local stage had been deleted in the text and table.

3. You report five-year survival, and event-free five-year survival, both in text and image and discuss it in discussion, but how many individuals were followed up for five years?

**Reply 3:** Four patients were followed for more than 5 years.

**Changes in the text:** No revision in the text.

4. Please specify what statistical tests were used.

**Reply 4:** Numerical data were expressed as mean, maximum, and minimum.

Qualitative data were expressed as frequency and percentage. Survival curves are presented according to the Kaplan-Meier method.

**Changes in the text:** The presentation of statistical methods has been improved in the article. (see Page 5, line 95)

5. Correct the few scattered grammar mistakes here and there. Look especially to the first sentence, second paragraph under Results and Treatment, row 138-139.

**Reply 5:** Corresponding grammatical errors have been corrected.

**Changes in the text:** Corresponding grammatical errors have been corrected.

6. The text describes two patients who get reoccurrence and how both had NSS, one with positive margin and one with negative. You argue that the reoccurrence rate for negative and positive margins were similar and that this indicates that residual positive margins doesn't significantly affect the outcome. However, most likely the numbers are just a coincidence or maybe due to one of the many confounders. With only two patients out of the small 16 patient sample (21 NSS) the study is most likely unable to indicate anything about the meaning of positive and negative margins.

**Reply 6:** Indeed, due to the limitation of the number of samples, more samples are needed to draw relevant conclusions about the impact of positive resection margins on survival rate in the article. In our article, cases with positive margins were microscopically positive. Therefore, what we want to illustrate from our preliminary results is that if the tumor can be gross total resection, even if the microscopic margin is positive, it may have little impact on the survival rate.

**Changes in the text:** No revision in the text.

7. Your conclusion needs to be more modest. We agree that NSS should still be recommended but the data in this study can't show that: Although NSS surgery has higher positive margins, it doesn't lead to higher tumor recurrence and it should be recommended for bilateral Wilms tumor.

**Reply 7:** Modified as requested.

**Changes in the text:** The conclusion in the article has been modified. (see Page 12, line 290)

8. There are checklists with suggested headlines on the journals website and you need to make sure the article fulfills the STROBE checklist. For example, consider

adding limitations of the study into “Discussion” and address them.

**Reply 8:** Modified as requested.

**Changes in the text:** Modified as requested. (see Page 12, line 285)

9. Well done for getting informed consent from all guardians of kids treated for bilateral Wilms during the period. Did the consent only apply to the follow-up?

**Reply 9:** Informed consent includes obtaining treatment and follow-up data for use in clinical research.

**Changes in the text:** No revision in the text.

I hope you can find time to perform the revision since I would like to see the study get published!