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**Authors' reply to the reviewer's comment**

**#Reviewer 1**

Kondo et al. reviewed the current status of lymph node dissection (LND) in upper tract urothelial carcinoma (UTUC) patients underwent radical nephroureterectomy (RNU). They have a lot of experience in this field and in fact they up-dated their surgical outcome in the review paper. The review article is written in a clear manner. Other minor comments are listed below.

**Comment 1 from Reviewer 1**

1) The authors described that LND could have therapeutic benefit in UTUC patients underwent RNU. On the contrary, especially in renal pelvic cancer, LND could reduce local recurrence and might improve cancer specific survival. The reviewer recommends to overview the therapeutic benefit of LND especially in ureteral tumor.

**<Author's reply>**

We thank the reviewer for the valuable input and excellent suggestions. To comply with the reviewer's suggestion, we have added some sentences that give a perspective on the role of lymphadenectomy in ureteral cancer in page 15, line 2, as follows:

Again, our prospective study failed to show the survival benefit of lymphadenectomy in ureteral cancer. However, our recent retrospective study shows that lymphadenectomy is also likely to improve survival in patients with upper/middle ureteral cancer, but not in those with lower ureteral cancer (prepared for submission). The template of lymphadenectomy for upper/middle ureteral cancer is similar to that for renal pelvic

cancer. I believe that the benefit of lymphadenectomy will be confirmed in upper/middle ureteral cancer in the future. The reason why patients with lower ureteral cancer did not benefit from lymphadenectomy needs to be determined. Some possible explanations include an inadequate template and the higher malignant potential of lower ureteral cancer.

### **Comment 2 from Reviewer 1**

2) The difference of mode and complication of LND between transperitoneally and intraperitoneally need to be discussed in detail.

#### **<Authors' reply>**

We thank the reviewer for highlighting an important issue. We understand that the reviewer's comment is regarding the differences between the transperitoneal and “retroperitoneal” approach. In this study, lymphadenectomy was performed with the retroperitoneal approach in all patients. Hence, we cannot comment on the surgical complications arising in cases of transperitoneal lymphadenectomy. However, a randomized trial that included kidney cancer patients showed that there was no increase in the rate of complications when open lymphadenectomy with the transperitoneal approach was performed. To comply with the reviewer's comment, we have added some sentences on the surgical approach in page 21, line 17, as follows:

We performed lymphadenectomy in an open procedure with a retroperitoneal approach in all patients. Thus, we cannot comment on transperitoneal lymphadenectomy for UTUC. However, in the above randomized phase 3 trial for kidney cancer, all surgeries were done with a transperitoneal open procedure.<sup>[61]</sup> Thus, we believe that lymphadenectomy does not increase the risk of complications, irrespective of the approach used.

### **Comment 3 from Reviewer 1**

3) The reviewer agrees with the survival benefit of LND in patients with advanced UTUC. On the other hand, urothelial cancer has chemo-sensitive, then survival improvement in advanced UTUC is due to not only template LND but also adjuvant chemotherapy. The authors need to discuss this point.

#### **<Authors' reply>**

We thank the reviewer for this important suggestion. We should discuss the possibility that adjuvant chemotherapy may act synergistically with lymphadenectomy. Collective results support that the therapeutic effect of lymphadenectomy is independent, but not synergistic with adjuvant chemotherapy. To comply with the reviewer's suggestion, we have revised the subheading 6.3 from “*Association with neoadjuvant chemotherapy*” to “*Association with neoadjuvant or adjuvant chemotherapy*” and have discussed the role of adjuvant chemotherapy in page 19, line 13 as follows:

Adjuvant chemotherapy might enhance the therapeutic benefit of lymphadenectomy. Several studies examined the effect of adjuvant chemotherapy, but most failed to show an improvement in patient survival.<sup>[51, 52, 54-56]</sup> We examined the role of adjuvant chemotherapy in a retrospective study. Lymphadenectomy was a significant independent factor reducing the risk of cancer mortality, but adjuvant chemotherapy was not a significant factor, even in the univariate analysis (hazard ratio: 1.89; 95% confidence interval: 0.677–5.43; p=0.222).<sup>[35]</sup> Our prospective study also showed that adjuvant chemotherapy does not influence either cancer-specific or disease-free survival on univariate analysis in patients with renal pelvic cancer.<sup>[23]</sup> Thus, these results suggest that the therapeutic benefit of lymphadenectomy is independent, but not synergistic with adjuvant chemotherapy.

#### **Comment 4 from Reviewer 1**

4) The authors introduced that three guidelines are currently available for UTUC. As now another guideline from Japanese Urological Association (Evidenced-based clinical practice guideline for upper tract urothelial carcinoma (summary--Japanese Urological Association, 2014 edition)., Oya M, Kikuchi E; Committee for Establishment of Clinical Practice Guideline for Management of Upper Tract Urothelial Carcinoma; Japanese Urological Association. Int J Urol. 2015 Jan;22(1):3-13.) is also available, the reviewer could refer the guideline.

#### **<Authors' reply>**

We thank the reviewer for the important suggestion. In the revised manuscript, we have referred to the guideline from the Japanese Urological Association in page 22, line 11 as follows:

The guideline of the Japanese Urological Association also supports the staging benefit, and recommends lymphadenectomy to improve survival in patients with advanced disease with suspected muscle invasion as a grade C recommendation.<sup>[65]</sup>