

## Answering reviewers

### Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** The authors reported the rare case of urinary tract lymphoepithelioma-like carcinoma, mixed type. With its rarity, there is no consensus on standard surgical procedures and adjuvant treatment. Here are some questions for the authors. Could the authors provide more details about the margin status from other literature you mentioned in Table 1. ? If all of them were free margin, what is the benefit of extensive surgery to bladder cuff? Your palliative RT was for the enlarged lymph node, without tissue diagnosis of disease. Could you provide the rationale for this treatment to emphasize your suggestion about adjuvant RT in your guideline? The manuscript was systematically well written, with some language issues needed correction.

### Answering:

**1. Question:** Could the authors provide more details about the margin status from other literature you mentioned in Table 1.?

1        **Answering:**

2        Our discussion is constituted majorly by the following literatures, which provide  
3        long-term surveillances:

4        A.    Lopez-Beltran A et al.<sup>(3)</sup>: The margin status was not mentioned, and the  
5        corresponding author didn't answer the mail regarding it.

6        B.    Haga K et al. <sup>(4)</sup>: The margin status was not mentioned, and the  
7        corresponding author didn't answer the mail regarding it.

8        C.    Valverde Martínez S et al. <sup>(8)</sup>: Pure type LELC with pT4R0pN1cM0 was  
9        mentioned.

10       D.    Terai A et al.<sup>(10)</sup>: Intraoperative frozen section analysis showed the ureteral  
11       stump to be free of carcinoma.

12       E.    Tamas EF et al. <sup>(11)</sup>: This was a pT3 tumor and the margin status was not  
13       mentioned in the text. After writing to the corresponding author, Jonathan I  
14       Epstein M.D., they could not provide the margin status.

Che Hsueh Yang <b101098093@tmu.edu.tw>

Dear Jonathan I Epstein, M.D.,

I am Bill Yang, a urological trainee from Taiwan, and this time write this mail for the question regarding the article titled of "Lymphoepithelioma-like carcinoma of the urinary tract: a clinicopathological study of 30 pure and mixed cases" ( Mod Pathol. 2007 Aug;20(8):828-34.; DOI: 10.1038/modpathol.3800823). In this article, you reported 1 pT3 LELC at renal pelvis without recurrence during the follow-up. However, the status of the surgical margin of it is not mentioned neither at context nor at table. May I ask the surgical margin status of that pT3 renal pelvis LELC ? Thank you very much for spending time reading this mail, and hope you all keep safe and well in this pandemic viral infection.

Best regards,  
Bill Yang

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Jonathan Epstein <jepstein@jhmi.edu>

I am sorry but was too long ago and don't have the information.

1    **2. Question:** If all of them were free margin, what is the benefit of extensive  
2    surgery to bladder cuff?

3    **Answering:**

4    In the introduction section, we mentioned that although LELC is named after  
5    lymphoepithelioma at nasopharynx, LELC behaves totally differently to it,  
6    which immunochemically is proved by negative hybridization of EBV <sup>(7, 11)</sup>.  
7    Instead, they <sup>(7, 11)</sup> found abnormal expression of p53 in LELC, which can  
8    enhance urothelial carcinoma (UC) proliferation and progression. Also, positive  
9    GATA3, CK7, CK20, CK 5/6 and p40 <sup>(3)</sup> stains make it similar to UC. The  
10    current immunochemical evidences suggested it to be a variant of high grade UC.  
11    Although there is no consensus for urinary tract LELC, based on histological and  
12    immunochemical features, we favor the treatment of high grade UC at upper  
13    urinary tract to this cancer. According to National Comprehensive Cancer  
14    Network (NCCN) guideline, nephroureterectomy with bladder cuff resection and  
15    regional lymphadenectomy can provide better progression-free survival to UC at  
16    upper urinary tract and renal pelvic, especially high grade ones.

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18    In this case, initial biopsy from ureteroscopy was high grade urothelial  
19    carcinoma, and the peripelvic fat and renal parenchyma were involved (T3 stage),

1 judged from preoperative computed tomography and then proved by  
2 postoperative pathological examination. Thus, for a case of T3 high grade UC at  
3 renal pelvis, nephroureterectomy with bladder cuff resection was the optimal  
4 choice with a little prolonged operation time than no cuff resection. In a  
5 population-based study by Lughezzani et al. (Should Bladder Cuff Excision  
6 Remain the Standard of Care at Nephroureterectomy in Patients With Urothelial  
7 Carcinoma of the Renal Pelvis? A Population-Based Study. Eur Urol. 2010;  
8 57(6):956-62. PMID: 20018438 DOI: 10.1016/j.eururo.2009.12.001),  
9 nephroureterectomy without bladder cuff resection in T3 would increase 1.25  
10 folds of cancer-specific mortality.

11  
12 In the current largest case series from Lopez-Beltran A et al.<sup>(3)</sup>,  
13 nephroureterectomy without bladder cuff excision was applied to two patients of  
14 pT3 LELC at ureter as well. However, no available information could be  
15 provided about their margin status and only 29-month and 39-month follow-ups  
16 were mentioned, respectively. As of others <sup>(4, 10)</sup> listed in Table 1 with  
17 nephroureterectomy, one <sup>(4)</sup> didn't have margin status documented, and the other  
18 <sup>(10)</sup> had an obviously favorable T stage (T2) in terms of overall survival. Thus,  
19 these two reports <sup>(4, 10)</sup> had limited roles on this topic.

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2       In conclusions, from this case and evidence of immunochemical stains, operation  
3       to bladder cuff can provide a progression-free survival to 8 years, and, according  
4       to NCCN guideline of high grade UC at upper urinary tract, the stump will be  
5       vulnerable to recurrence if the operation is not extended to bladder cuff.

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7 **3. Question:** Your palliative RT was for the enlarged lymph node, without tissue  
8       diagnosis of disease. Could you provide the rationale for this treatment to  
9       emphasize your suggestion about adjuvant RT in your guideline?

10       **Answering:** There was no positive lymph node by the specimen, but the new  
11       lymph node-like tissue obviously formed compared to the preoperative images at  
12       the area of left renal hilum. In the postoperative computed tomography, we  
13       observed the clips, used for vascular control, seated just in front of the left renal  
14       hilum and away from the lymph node-like tissue. Besides, there were no any  
15       lymph nodes in specimen. This could be many reasons, and we were afraid of  
16       inadequate dissection.

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18       Besides, the LELC in this case was mixed with UC. Based on the NCCN  
19       guideline, this kind of mixed histology had more aggressive nature than pure UC.

1        Having these disadvantages and T3 tumor itself, this patient has a high risk of  
2        progression and she'd be better treated as recurrence. In light of this, we  
3        administered adjuvant chemotherapy first, but it was suspended for patient's  
4        intolerance to adverse effects. Active surveillance was an option after stopping  
5        adjuvant chemotherapy, but the patient still worried about the cancer recurrence.  
6        At that time, the alternative choice was radiation therapy (RT) that also has an  
7        effective response to UC. Some reports supported the use of adjuvant RT for  
8        reducing local recurrence, distant metastasis, and cancer specific death in  
9        peripelvic fat/renal parenchyma-invasive urothelial carcinoma. Thus, we  
10       believed that, even without pathological proof of this lymph node, adjuvant  
11       radiation therapy would still be a choice to help lower the rate of local recurrence  
12       and it truly worked on this patient.

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