

Peer Review File

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**Reviewer A**

1) What were the surgical techniques and operations performed? How many were cervical resections, sternotomy and resection, thoracotomy and resection? How were the patients with carinal and bronchial tumors treated?

**Reply:**

We would like to thank the reviewer to point this out. In this study, tracheal resection with end-to-end anastomosis was main surgical technique in this study, which was performed for 65.2% (45/69) of patients, and remain patients were conducted with bronchus and lung resections (13/69), carinal resections (11/69). And posterolateral thoracotomy was the most surgical approach (50/69), followed by cervical incision (10/69) and median sternotomy (9/69). For patients with carinal tumors, if the tumor was small and involved the opening of main bronchus, partial carina resection and reconstruction was performed (2/5); otherwise, a total carina resection and reconstruction needed (3/5). And for patients with bronchial tumors, bronchial sleeve resection without lobectomy would be performed (9/19) when the opening of the upper lobe was not involved, while others received bronchial sleeve resection with lobectomy (10/19). To make it clear for readers, we have added corresponding information in the text.

**Changes in the text:**

It can be read as “Tracheal resection with end-to-end anastomosis was main surgical technique in this study, which was performed for 65.2% (45/69) of patients, and remain patients were conducted with bronchus and lung resections (13/69), carinal resections (11/69). And posterolateral thoracotomy was the most surgical approach (50/69), followed by cervical incision (10/69) and median sternotomy (9/69). For patients with carinal tumors, if the tumor was small and involved the opening of main bronchus, partial carina resection and reconstruction was performed (2/5); otherwise, a total carina resection and reconstruction needed (3/5). And for patients with bronchial tumors, bronchial sleeve resection without lobectomy would be performed (9/19) when the opening of the upper lobe was not involved, while others received bronchial sleeve resection with lobectomy (10/19).”

Please find changes on Page 7, Line 17-22; Page 8, Line 1-5.

2)What was the operative and 30 day mortality?

**Reply:**

We wish to thank the reviewer to point this out. In our center, a total of 72 patients with primary TBT were treated by surgery from 2004 to 2020. And the surgery was successfully performed for all patients. However, there were 3 patients died of serious complications within 30 days. Therefore, the operative and 30-day mortality were 0% and 4.17% respectively. To make it clear for readers, we have added corresponding information in the text.

**Changes in the text:**

It can be read as “A total of 72 patients with primary TBT were treated by surgery from 2004 to 2020. And the operative and 30-day mortality were 0% and

4.17% respectively. ”

Please find changes On Page 6, Line 16-18.

3)What were the post operative complications?

**Reply:**

We would like to thank the reviewer pointed this out. In our study, the incidence of postoperative complications was 44.9%. Pneumonia was the most common postoperative complications in this study, which accounted for 17.4%. And the incidence of tracheal anastomotic fistula was 10.1%, which was secondly to the pneumonia. Other complications including tracheal stenosis, recurrent laryngeal nerve palsy, chylothorax, fat liquefaction and postoperative bleeding, accounted for 7.2%, 5.8%, 1.4%, 1.4% and 1.4% respectively. And we have added related information in the text.

**Changes in the text:**

It can be read as “The incidence of postoperative complications was 44.9%. Pneumonia was the most common postoperative complications in this study, which accounted for 17.4%. And the incidence of tracheal anastomotic fistula was 10.1%, which was secondly to the pneumonia. Other complications including tracheal stenosis, recurrent laryngeal nerve palsy, chylothorax, fat liquefaction and postoperative bleeding, accounted for 7.2%, 5.8%, 1.4%, 1.4% and 1.4% respectively.”

Please find changes on Page 7, Line 10-15.

4)What were the lengths of stay?

**Reply:**

We wish to thank the reviewer to point this out. The mean length of stay was 19.4±8.6 days in our center. And we have added corresponding information in the text.

**Changes in the text:**

It can be read as “Clinical data included age, tumor size, gender, length of stay, histological type, smoking history, data of surgery, primary tumor location and symptoms.” and “The mean length of stay was 19.4±8.6 days”.

Pleased find changes on Page 5. Line 12-13; Page 7, Line 3 and on Table 1.

5)What group of patients were treated with chemotherapy and radiation? It is unclear from the manuscript what group of patients received this treatment, why and how this decision was made? As I see from the table only a total of 26% of patients had either R1 or N1 status yet 40% received adjuvant therapy, why was this?

**Reply:**

We would like to thank the review to point this out. Due to the low incidence of primary trachea neoplasm, there is no consensus on adjuvant therapy for patients with primary tracheal neoplasm after surgery. Although some studies showed that adjuvant therapy postoperatively did not improve the overall survival for patients with primary tracheal neoplasm (Ann Thorac Surg. 109(2020):1026-1032), most studies demonstrated patients with adjuvant therapy have better overall survival than those patients without adjuvant therapy (Int J Radiat Oncol Biol Phys. 84(2012):464-470). However, the characters of patients received adjuvant therapy were not consistent in different centers. Not only patients had either R1 or N1 status received adjuvant

therapy, but also patients with the neoplasm spreading to the adjacent tissues or organs received adjuvant therapy (Asia Pac J Clin Oncol. 15(2019):244-249; Int J Radiat Oncol Biol Phys. 84(2012):464-470). In our center, other than patients with R1 or N1 status, patients with primary neoplasm that spread to adjacent organs and other structures (E2) will be taken into consideration for adjuvant therapy. And the decision of conducting adjuvant therapy for patients with E2 status was made based on the Multi-disciplinary Treatment (MDT). Therefore, in this study, a total of 40.58% (28/69) patients received adjuvant therapy. To make it clear for readers, we have added corresponding information in the text.

**Changes in the text:**

It can be read as “Adjuvant therapy was performed for patients with R1 or N1 status. And the decision of conducting adjuvant therapy for patients with E2 status was made based on the Multi-disciplinary Treatment (MDT).”

Please find changes on Page 5, Line 20-22.

**Reviewer B**

1. Most of the primary tracheobronchial tumor has been reported as malignant tumor. This study cohort showed the same tendency, but the authors included some benign cases. It had better analyzed only for the malignant cases if the authors consider the tumor extent or nodal status as a candidate for prognostic factors.

**Reply:**

We would like to thank the reviewer pointed this out, which will make the text more clarity. Indeed, it is not accurate to analyze the prognostic factor if including benign case. Therefore, we reanalyzed the data after excluding the benign cases.

Specifically, 7 benign cases were excluded, and 62 malignant cases were included in the univariate analysis and multivariate analysis. And we have modified corresponding information in the text.

**Changes in the text:**

It can be read as “For patients with malignant tumors, the estimated 5-year OS of the overall population was 77.2% and the estimated 5-year OS of SCC patients was 73.8% especially. The multivariate analysis showed that age ( $\leq 50$  years or  $> 50$  years) was independent prognostic factor for OS ( $P < 0.05$ ). Conclusions: Age is independent factor affecting the OS of primary TBT treated by surgery. Patients of TBT with younger age should be much more referred for surgery.” and “And the univariate analysis and multivariate analysis were conducted on the malignant cases.” and “Of all 69 patients, there were 62 malignant cases (SCC 16, ACC 26, mucoepidermoid carcinoma 10, carcinoids 4, adenocarcinoma 4, epithelia-myoeipithelial carcinoma 1, sarcoma 1) and 7 benign cases (inflammatory pseudotumor 3, vascular tumor 1, leiomyoma 1, schwannoma 1, plasmacytoma 1).” And “For patients with malignant tumors, the median length of follow up was 74.7 months for the overall cohort, 48.1 months for patients with ACC, 57.0 months for patients SCC and 89.7 months for patients in the other category. Estimated 1-year, 3-year, and 5-year OS of the overall population was 88.6%, 79.4%, and 77.2%, respectively, with an estimated mean survival time of 133.7 months (95% CI 115.5-151.9) (Figure 1). And all patients with benign tumors were still alive at the deadline for follow-up (range 42.67-122.90 months).” and “For patients with malignant tumors, the univariate Cox regression analysis identified that age and tumor size had significant effects on OS. Further multivariate Cox regression analysis confirmed age was the independent prognostic

factor.” and “In our study, estimated 5-year OS of the patients with malignant tumor was 77.2%”.

Please find changes on Page3, Line 10-15; Page 5, Line 6-7; Page 6, Line 19-22; Page 9, Line 5-10; Page 9, Line 21-22; Page 10, Line 1; Page 10, Line 18; Table 3; Table 4; Figure 1; Figure 2.

2. In the result section, the sentence was unclear “Tumors in SCC patients tended to be larger and more extensive than tumors in other histology ( $P < 0.05$ ).” What was longer for SCC?

**Reply:**

We would like to thank the reviewer pointed this out. We have modified the sentence, which can be read as “the average tumor size of patients in SCC group was larger than that of patients in others group (2.6cm vs 2.0cm)( $P < 0.05$ ). And the percentage of the tumor spreading adjacent structures in SCC group was higher than that in others group (50.0% vs 11.1%) ( $P < 0.05$ ).” To make it clear for the readers, we changed it in the text.

**Changes in the text:**

It can be read as “The average tumor size of patients in SCC group was larger than that of patients in others group (2.6cm vs 2.0cm) ( $P < 0.05$ ). And the percentage of the tumor spreading adjacent structures in SCC group was higher than that in others group (50.0% vs 11.1%) ( $P < 0.05$ ).”

Please find changes on Page 8, Line 21-22; Page 9, Line 1.

3. Why did the authors decide the size cut-off as 2cm?

**Reply:**

We would like to thank the reviewer pointed this out. However, there is currently no recognized staging system for primary tracheobronchial tumors, and the most widely used staging standard was proposed by Bhattacharyya. And T1 was defined as primary tumor confined to trachea and tumor size <2 cm; T2 was defined as primary tumor confined to trachea and tumor size >2 cm. The staging system demonstrated a relatively good distinction in survival for patients of different T-stages. (Otolaryngol Head Neck Surg. 131(2004):639-642). And Benjamin et al also used 2cm as size cut-off, in which the T stage was defined as follows: T1 (tumor diameter ≤2cm, confined to trachea), T2 (tumor diameter >2 cm, confined to trachea), or T3 (arising from but extending outside of trachea)(J Am Coll Surg. 202(2006):237-246). Therefore, in this study, we defined the cut-off of tumor size as 2cm. To make it clear for the readers, we have added corresponding information in the text.

**Changes in the text:**

It can be read as “Based on previous studies, 2cm of tumor size was used as cut-off for analyzing (1).”

Please find changes on Page 5, Line 14-15.

4. Please explain the suspected reason for no survival difference between R0 and R1 disease.

**Reply:**

We would like to thank the reviewer pointed this out. Currently, the effect of complete resection on survival remains controversial in primary tracheabronchial neoplasm. Several studies showed that the overall survival between patients with



complete resection and incomplete resection was not significant ( Ann Thorac Surg. 96(2013):1998-2004; Thorac Cardiovasc Surg. 112(1996):1522-1531). And our result also demonstrated that there was no survival difference between R0 and R1 disease. The reason maybe that patients with R1 disease were mainly ACC (8/10), which was a kind of low-grade malignant tumor. To make it clear for readers, we have added corresponding information in the Section of discussion.

**Changes in the text:**

It can be read as “Thirdly, the effect of complete resection on survival remains controversial in primary tracheobronchial neoplasm. Usually, R0 resected is required, and many studies have also proved that R0 resection has a better prognosis than R1(6). However, several studies indicated that the overall survival between patients with having complete resection and incomplete resection was not significant (25,26). Yang et al pointed that patients with ACC which was a kind of low-grade malignant tumor can receive R1 during surgery, because tension-free anastomosis is more important for patients than R0 resection for ACC (25). And our result also demonstrated that there was no survival difference between R0 and R1 disease. The reason maybe that patients with R1 disease were mainly ACC (8/10). In our ACC group, positive margin was encountered in 30.8% of patients, which was similar to previous studies (25,27)”.

Please find changes on Page 12, Line 3-13.

5. Were there any differences in treatment strategies for  $\geq 50$  and  $<50$  patients?

**Reply:**

We would like to thank the reviewer pointed this out. In this study, the treatment

strategies for patients between  $\geq 50$  group and  $< 50$  group were not different. Specifically, for both of patients with  $\geq 50$  and  $< 50$ , tracheal resection was the main surgical technique. And Chi-square test showed that there were no differences in types of resection for primary tracheobronchial tumors between  $\geq 50$  and  $< 50$  patients ( $P > 0.05$ ). Although adjuvant therapy postoperatively was more common in patients  $\geq 50$ , the difference was not significant between  $\geq 50$  and  $< 50$  patients ( $P > 0.05$ ). Briefly, patients were treated with adjuvant therapy postoperatively in  $\geq 50$  and  $< 50$  group was 48.4% (13/31) and 34.2% (13/38) respectively. To make it clear for the readers, we have added corresponding information in the text.

**Changes in the text:**

It can be read as “Furtherly, the treatment strategies for patients between  $\geq 50$  group and  $< 50$  group were not different. Specifically, for both of patients with  $\geq 50$  and  $< 50$ , tracheal resection was the main surgical technique. And Chi-square test showed that there were no differences in types of resection for primary tracheobronchial tumors between  $\geq 50$  and  $< 50$  patients ( $P > 0.05$ ). Although adjuvant therapy postoperatively was more common in patients  $\geq 50$ , the difference was not significant between  $\geq 50$  and  $< 50$  patients ( $P > 0.05$ ). Briefly, patients were treated with adjuvant therapy postoperatively in  $\geq 50$  and  $< 50$  group was 48.4% (13/31) and 34.2% (13/38) respectively.”

Please find changes on Page 8, Line 13-20.

6. This article was reported from the surgical department. It will help readers to show the reconstruction method of the airway following the size of the tumor.

**Reply:**

We would like to thank the reviewer pointed this out. In our center, end-to-end anastomosis is conducted when the tumor size is less than 2cm. If resection length is between 2-4cm, it's necessary to release the tissues around the trachea, and for patients with cervical tumors, a heavy "guardian" suture is placed to prevent excessive extension of the neck in the immediate postoperative period. If the tumor size is more than 4cm which means length of resection is more than 5cm usually, the hilum release will be performed for reducing anastomotic tension. In order to make it more clear for readers, we have added corresponding information in the text.

**Changes in the text:**

It can be read as "end-to-end anastomosis is conducted when the tumor size is less than 2cm. If resection length is between 2-4cm, it's necessary to release the tissues around the trachea, and for patients with cervical tumors, a heavy "guardian" suture is placed to prevent excessive extension of the neck in the immediate postoperative period. If the tumor size is more than 4cm which means length of resection is more than 5cm usually, the hilum release will be performed for reducing anastomotic tension."

Please find changes on Page 10, Line 3-8.

**Reviewer C**

Dear Authors

Thanks a lot for this very interesting work with a good experience.

However a major comments in this work: authors split this population in 3 groups ( SCC, ACC and others ) and report in results and discussion : "With regards to oncologic outcomes we showed that OS was 6 no statistically significant among ACC,

SCC and other pathological types while many previous studies showed strong difference, especially for SCC(5,6,12,13,17).”

It could be explain that the third populations is far to be homogeneous (mucoepidermoid carcinoma 10, carcinoids 4, adenocarcinoma 4,flammatory pseudotumor 3, sarcoma 1, vascular tumor 1, leiomyoma 1, schwannoma 1, epithelia-myoeipithelial carcinoma 1, plasmocytoma 1) : a survival of adenocarcinoma or sarcoma or even mucopeidemoid carcinoma could not be compare to vascular tumor or leiomyoma....Maybe muco-epidermoide could go with ACC? And adenocarcimoa withSCC ?

In order to clarify this classification Authors could be help by their pathologist or oncologist and use de WHO tumor classification, and then compare the survival of groups based on the aggressiveness of the tumor.

**Reply:**

We would like to thank the reviewer to point this out. With the help of pathologist in our center, we reclassified the pathologic types based on the WHO tumor classification. And 7 cases were classified as benign trachea neoplasm, including flammatory pseudotumor (3), vascular tumor (1), leiomyoma (1), plasmocytoma (1), schwannoma (1). Therefore, we reanalyzed the data after exlucding the benign cases. Specifically, 7 benign cases were excluded, and 62 malignant cases were included in the univariate analysis and multivariate analysis. Because SCC and ACC were the most common pathologic types, which account for more than 2/3 of the primary tracheobronchial neoplasm (Lung Cancer. 132(2019):87-93). Therefore, it is important to clarify the prognostic factor for patients with SCC or ACC. And most studies split population into SCC, ACC and others malignant (Ann Surg Oncol.

14(2007):968-976; Ann Thorac Surg. 110(2020):1012-1022). Based on these studies, we also divided the population into 3 groups (SCC, ACC and others) for analyzing. And we have modified corresponding information in the text.

**Changes in the text:**

It can be read as “For patients with malignant tumors, the estimated 5-year OS of the overall population was 77.2% and the estimated 5-year OS of SCC patients was 73.8% especially. The multivariate analysis showed that age ( $\leq 50$  years or  $> 50$  years) was independent prognostic factor for OS ( $P < 0.05$ ). Conclusions: Age is independent factor affecting the OS of primary TBT treated by surgery. Patients of TBT with younger age should be much more referred for surgery.” and “And the univariate analysis and multivariate analysis were conducted on the malignant cases.” and “Of all 69 patients, there were 62 malignant cases (SCC 16, ACC 26, mucoepidermoid carcinoma 10, carcinoids 4, adenocarcinoma 4, epithelia-myoeipithelial carcinoma 1, sarcoma 1) and 7 benign cases (inflammatory pseudotumor 3, vascular tumor 1, leiomyoma 1, schwannoma 1, plasmacytoma 1).” And “For patients with malignant tumors, the median length of follow up was 74.7 months for the overall cohort, 48.1 months for patients with ACC, 57.0 months for patients SCC and 89.7 months for patients in the other category. Estimated 1-year, 3-year, and 5-year OS of the overall population was 88.6%, 79.4%, and 77.2%, respectively, with an estimated mean survival time of 133.7 months (95% CI 115.5-151.9) (Figure 1). And all patients with benign tumors were still alive at the deadline for follow-up (range 42.67-122.90 months).” and “For patients with malignant tumors, the univariate Cox regression analysis identified that age and tumor size had significant effects on OS. Further multivariate Cox regression analysis confirmed age was the independent prognostic

factor.” and “In our study, estimated 5-year OS of the patients with malignant tumor was 77.2%”.

Please find changes on Page3, Line 10-15; Page 5, Line 6-7; Page 6, Line 19-22; Page 9, Line 5-10; Page 9, Line 21-22; Page 10, Line 1; Page 10, Line 18; Table 3; Table 4; Figure 1; Figure 2.

#### **Reviewer D**

1. Page 4 line 10-13: The authors are summarizing prognosticators of the literature but are not writing if these prognosticators were associated with prolonged or decreased overall survival.

#### **Reply:**

We would like to thank the reviewer pointed this out. We have modified our text and added some information to make it clearer on manuscript, which can be read as “Previous studies have reported that age(young), lymph node involvement(N0), small tumor size, margin status (Negative), histology (ACC) and the use of radiotherapy were associated with an improved survival of tracheobronchial patients (9-13)” .

#### **Changes in the text:**

It can be read as “Previous studies have reported that age(young), lymph node involvement(N0), small tumor size, margin status (Negative), histology (ACC) and the use of radiotherapy were associated with an improved survival of tracheobronchial patients (8-12)”.

Please find changes on Page 4, Line 11-14.

2. Page 5 line 11: The authors are dividing their Groups in patients with E1:

primary tumor confined to the trachea/bronchus; E2: primary tumor spread outside the trachea/bronchus or spread to adjacent Organs. This is confusing, for my understanding patients in the E2 group do not have a primary TBT so they should not be included in this study.

**Reply:**

We would like to thank the reviewer pointed this out. Indeed, there is currently no recognized staging system for primary tracheobronchial tumors. Therefore, we evaluated the invasion degree based on previous studies, in which E1 was defined as “Spread outside the trachea but not to adjacent organs or structures”; E2 was defined as “Spread to adjacent organs or structures”. ( Ann Thorac Surg. 2019;108:873-882; J Surg Oncol. 115(2017):1004-1010). And we have added associated reference in the text.

**Changes in the text:**

It can be read as “E1: primary tumor confined to the trachea/bronchus; E2: primary tumor spread outside the trachea/bronchus or spread to adjacent organs (8,14).”

Please find changes on Page 5, Line 17.

3. Page 5 line 12-18: The authors are writing that patients with Nx were included to the Group of N0 patients, this is not correct and should be seen separated. Why was not a lymph node dissection performed in the Nx Group with a tracheobronchial cancer?

**Reply:**

We would like to thank the reviewer pointed this out. At present, there are

currently lacking of guidelines and norms for lymph node dissection in the surgery of primary tracheobronchial tumor. Whether and how to perform lymph node dissection for tracheobronchial tumor is still controversial. In our center, if no radiographic evidence before surgery or no enlarged lymph nodes during surgery was observed, the lymph node will not be dissected. In this study, those patients without dissecting lymph node was classified into Nx group. To make it clear for reader, we divided “N0+Nx” group into N0 group and Nx group for reanalyzing. And the result showed that there were 49 patients known lymph node status, and 20 patients didn’t. And lymph node metastases were found in 16.3% of patients with known lymph node status. We modified corresponding information in the text.

**Changes in the text:**

It can be read as “There were 49 patients known lymph node status, and 20 patients didn’t. And lymph node metastases were found in 16.3% of patients with known lymph node status.”

Please find changes on Page 8, Line 7-9; Table 2; Table 3; Figure 2.

4. page 5 line 15: Could the authors please write how (ct, mri?) and how often the follow-up was performed??

**Reply:**

We would like to thank the reviewer pointed this out. For patients with tracheobronchial neoplasm, the computed tomography scan examinations were conducted for evaluation after surgery. And the follow-up was generally performed every 3 months for the first two years, and then every 6 months. To make this clear to the readers, we have added related information in the text.



**Changes in the text:** It can be read as “Computed tomography scan examinations were conducted for evaluation after surgery. And the follow-up was generally performed every 3 months for the first two years, and then every 6 months.”

Please find changes on Page 6, Line 1-3.

5. page 6 line 8/9: The authors included benign tumors and furthermore mixed them in a group with malign tumors. This is also not correct. Furthermore, patients with a benign disease are influencing the survival rate and should be excluded.

**Reply:**

We would like to thank the reviewer pointed this out, which will make the text more clarity. Indeed, it is not accurate to analyze the prognostic factor if including benign case. Therefore, we reanalyzed the data after excluding the benign cases. Specifically, 7 benign cases were excluded, and 62 malignant cases were included in the univariate analysis and multivariate analysis. And we have modified corresponding information in the text.

**Changes in the text:**

It can be read as “For patients with malignant tumors, the estimated 5-year OS of the overall population was 77.2% and the estimated 5-year OS of SCC patients was 73.8% especially. The multivariate analysis showed that age ( $\leq 50$  years or  $> 50$  years) was independent prognostic factor for OS ( $P < 0.05$ ). Conclusions: Age is independent factor affecting the OS of primary TBT treated by surgery. Patients of TBT with younger age should be much more referred for surgery.” and “And the univariate analysis and multivariate analysis were conducted on the malignant cases.” and “Of all 69 patients, there were 62 malignant cases (SCC 16, ACC 26, mucoepidermoid

carcinoma 10, carcinoids 4, adenocarcinoma 4, epithelia-myoepithelial carcinoma 1, sarcoma 1) and 7 benign cases (inflammatory pseudotumor 3, vascular tumor 1, leiomyoma 1, schwannoma 1, plasmacytoma 1).” And “For patients with malignant tumors, the median length of follow up was 74.7 months for the overall cohort, 48.1 months for patients with ACC, 57.0 months for patients SCC and 89.7 months for patients in the other category. Estimated 1-year, 3-year, and 5-year OS of the overall population was 88.6%, 79.4%, and 77.2%, respectively, with an estimated mean survival time of 133.7 months (95% CI 115.5-151.9) (Figure 1). And all patients with benign tumors were still alive at the deadline for follow-up (range 42.67-122.90 months).” and “For patients with malignant tumors, the univariate Cox regression analysis identified that age and tumor size had significant effects on OS. Further multivariate Cox regression analysis confirmed age was the independent prognostic factor.” and “In our study, estimated 5-year OS of the patients with malignant tumor was 77.2%”.

Please find changes on Page3, Line 10-15; Page 5, Line 6-7; Page 6, Line 19-22; Page 9, Line 5-10; Page 9, Line 21-22; Page 10, Line 1; Page 10, Line 18; Table 3; Table 4; Figure 1; Figure 2.

6. Could the authors please describe when a chemotherapy or radiotherapy was performed?

**Reply:**

We would like to thank the review to point this out. Due to the low incidence of primary trachea neoplasm, there is no consensus on adjuvant therapy for patients with primary tracheal neoplasm after surgery. Although some studies showed that adjuvant

therapy postoperatively did not improve the overall survival for patients with primary tracheal neoplasm (Ann Thorac Surg. 109(2020):1026-1032), most studies demonstrated patients with adjuvant therapy have better overall survival than those patients without adjuvant therapy (Int J Radiat Oncol Biol Phys. 84(2012):464-470). However, the characters of patients received adjuvant therapy were not consistent in different centers. Not only patients had either R1 or N1 status received adjuvant therapy, but also patients with the neoplasm spreading to the adjacent tissues or organs received adjuvant therapy (Asia Pac J Clin Oncol. 15(2019):244-249; Int J Radiat Oncol Biol Phys. 84(2012):464-470). In our center, other than patients with R1 or N1 status, patients with primary neoplasm that spread to adjacent organs and other structures (E2) will be taken into consideration for adjuvant therapy. And the decision of conducting adjuvant therapy for patients with E2 status was made based on the Multi-disciplinary Treatment (MDT).

**Changes in the text:**

It can be read as “Adjuvant therapy was performed for patients with R1 or N1 status. And the decision of conducting adjuvant therapy for patients with E2 status was made based on the Multi-disciplinary Treatment (MDT).”

Please find changes on Page 5, Line 20-22.

7. Regarding patients with ACC it is well known, that a radiotherapy with additional C12 boost has excellent survival rates. Was an additional C12 boost performed in these patients? This should be discussed in the discussion part.

**Reply:**

We would like to thank the reviewer pointed this out. However, in our center,

additional C12 boost was not carried out for patients with ACC. And we will pay attention to this technology to improve the survival rate of patients with ACC in future. And we have added corresponding information in the Section of discussion.

**Changes in the text:**

It can be read as “There were still some controversial issues about the treatment of tracheal surgery. Firstly, the adjuvant treatment (radiotherapy and/or chemotherapy) of tracheal tumors after surgery was controversial. there is no consensus on adjuvant therapy for patients with primary tracheal neoplasm after surgery. Although some studies showed that adjuvant therapy postoperatively did not improve the overall survival for patients with primary tracheal neoplasm (20), most studies demonstrated patients with adjuvant therapy have better overall survival than those patients without adjuvant therapy (21). However, the characters of patients received adjuvant therapy were not consistent in different centers. Not only patients had either R1 or N1 status received adjuvant therapy, but also patients with the neoplasm spreading to the adjacent tissues or organs received adjuvant therapy (21,22). In our center, other than patients with R1 or N1 status, patients with primary neoplasm that spread to adjacent organs and other structures (E2) will be taken into consideration for adjuvant therapy. And the decision of conducting adjuvant therapy for patients with E2 status was made based on the Multi-disciplinary Treatment (MDT). Many studies in recent years have also proposed many effective adjuvant therapies. For example, some studies have shown that radiotherapy with additional carbon ion radiotherapy boost has a good effect on local tumor control of ACC (23). And neoadjuvant therapy was effective in tracheal tumors according to some reports (24). Meanwhile, the immunotherapy proposed in recent years may also be one of the

tracheal tumor treatments. Therefore, it is necessary to standardize the postoperative adjuvant treatment of tracheal tumors, and it is hoped that effective postoperative treatment can improve the prognosis of patients.”

Please find changes on Page 11, Line 17-22; Page 12, Line 1-15.

8. Could the authors please add the morbidity and mortality rate?

**Reply:**

We would like to thank the reviewer pointed this out. In our center, a total of 72 patients with primary TBT were treated by surgery from 2004 to 2020. And the surgery was successfully performed for all patients. However, there were 3 patients died of serious complications within 30 days. Therefore, the operative and 30 day mortality were 0% and 4.17% respectively. And in our study, the incidence of postoperative complications was 44.9%. Pneumonia was the most common postoperative complications in this study, which accounted for 17.4%. And the incidence of tracheal anastomotic fistula was 10.1%, which was secondly to the pneumonia. Other complications including tracheal stenosis, recurrent laryngeal nerve palsy, chylothorax, fat liquefaction and postoperative bleeding, accounted for 7.2%, 5.8%, 1.4%, 1.4% and 1.4% respectively. To make it clear for readers, we have added corresponding information in the text.

**Changes in the text:**

It can be read as “A total of 72 patients with primary TBT were treated by surgery from 2004 to 2020. And the operative and 30-day mortality were 0% and 4.17% respectively. Finally, 69 patients were included in analysis.” and “The incidence of postoperative complications was 44.9%. Pneumonia was the most

common postoperative complications in this study, which accounted for 17.4%. And the incidence of tracheal anastomotic fistula was 10.1%, which was secondly to the pneumonia. Other complications including tracheal stenosis, recurrent laryngeal nerve palsy, chylothorax, fat liquefaction and postoperative bleeding, accounted for 7.2%, 5.8%, 1.4%, 1.4% and 1.4% respectively.”

Please find changes on Page 6, Line 16-18; Page 7, Line 10-15.

9. Page 7 line 12: Patients without dissection of lymph nodes promised a good prognosis: this sentence implies that lymph node dissection should not be performed and is wrong.

**Reply:**

We would like to thank the reviewer pointed this out. At present, there are currently lacking of guidelines and norms for lymph node dissection in the surgery of primary tracheobronchial tumor. Whether and how to perform lymph node dissection for tracheobronchial tumor is still controversial. In our center, if no radiographic evidence before surgery or no enlarged lymph nodes during surgery was observed, the lymph node will not be dissected. In this study, those patients without dissecting lymph node was classified into Nx group. Although the result in this study showed that patients in “N0+Nx” group have a better prognosis, it did not indicate that lymph node dissection should not be performed and is wrong. The reason for this result may due to the small sample size in this study. Lymph node dissection should still be performed for lymph nodes with significant enlargement and obvious positive indications (such as PET-CT). Therefore, it is urgent to establish a standard lymph node dissection method similar to lung cancer in future based on larger cohort of

tracheobronchial tumors cases.

To make it clear for reader, we divided “N0+Nx” group into N0 group and Nx group for reanalyzing. And the result showed that there were 49 patients known lymph node status, and 20 patients didn't. And lymph node metastases were found in 16.3% of patients with known lymph node status. We modified corresponding information in the text.

**Changes in the text:**

It can be read as “There were 49 patients known lymph node status, and 20 patients didn't. And lymph node metastases were found in 16.3% of patients with known lymph node status.”

Please find changes on Page 8, Line 7-9; Table 2; Table 3; Figure 2.

10. Table 2: 30.8% of the ACC group had an incomplete resection, this is very high. What were the reasons? What happened with these patients?

**Reply:**

We would like to thank the reviewer pointed this out. Indeed, the objective in resectable cases is to obtain a complete and potentially curative operation. However, adenoid cystic tumors of the upper airway frequently spread 1 cm or more beyond the palpable and visible confines of the neoplasm. However, the anastomotic tension will increase with the length of trachea resected, which will increase the risk of surgical failure (J Thorac Cardiovasc Surg. 112(1996):1522-1531). Therefore, positive margins was regarded as an acceptable factor for ACC in order to obtain a more secure anastomosis tension (Ann Thorac Surg. 96(2013): 1998-2004). In this study, of all 8 patients with positive margin, the positive margin of 5 patients was due to the

large anastomotic tension. And the cause of positive margin in the other 3 patients was that the tumor was closed to the larynx. To avoid damaging laryngeal function, the tumor was not resected completely. The ratio of the positive margins was between 8.0% and 84.9 reported in the literature, and our positive rate of 30.8% is within the range. (Am J Otolaryngol. 33(2012):226-231; Ann Thorac Surg. 96(2013) : 1998-2004). To make it clear for readers, we have added corresponding information in the Section of discussion.

**Changes in the text:**

It can be read as “Thirdly, the effect of complete resection on survival remains controversial in primary tracheobronchial neoplasm. Usually, R0 resected is required, and many studies have also proved that R0 resection has a better prognosis than R1(6). However, several studies indicated that the overall survival between patients with having complete resection and incomplete resection was not significant (25,26). Yang et al pointed that patients with ACC which was a kind of low-grade malignant tumor can receive R1 during surgery, because tension-free anastomosis is more important for patients than R0 resection for ACC (25). And our result also demonstrated that there was no survival difference between R0 and R1 disease. The reason maybe that patients with R1 disease were mainly ACC (8/10). In our ACC group, positive margin was encountered in 30.8% of patients, which was similar to previous studies (25,27)”.

Please find changes on Page 13, Line 3-13.



