

Peer Review File

Article information: <http://dx.doi.org/10.21037/apm-21-630>

Reviewer A

This is the manuscript about usefulness of interventional bronchoscopic therapy for tracheobronchial schwannoma. The effectiveness of bronchoscopic therapy for tracheobronchial schwannoma is unclear, and so this study might provide potentially useful information for readers. Meanwhile, it was not eligible for publishing because of the reasons mentioned below.

Major comments:

Comment 1: The authors showed 7 case in Table 1. Were all cases benign tracheobronchial schwannoma? Especially, there were multiple tumors in Case 5 (thyroid schwannoma). Please add more information about Case5, and discuss about bronchoscopic therapy for benign or malignant tracheobronchial schwannoma (which is better bronchoscopic therapy or surgery, respectively) in this manuscript.

Reply 1:

Nerve sheath tumors include neurofibroma, schwannoma and malignant peripheral nerve sheath tumor. The name of “malignant schwannoma” in literatures is not uniform. “Malignant schwannoma” is also called malignant peripheral nerve sheath tumor (MPNST) or spindle cell sarcoma (histopathology in correlation with immunohistochemistry studies was reported as spindle cell sarcoma with features suggestive of MPNST). Surgery remains the primary modality of treatment for the MPNST.

All cases in this study were benign tracheobronchial schwannaoma, and histochemical features had been added. Case5 was a multiple schwannoma and was still a benign schwannoma.

Changes in the text:

Page 3, line 93-97: Histochemically, the resected specimen tumor postinterventional had features consistent with benign schwannoma: exhibited an Antoni A growth pattern (composed of spindle cells with elongated palisading nuclei); a few hyalinized blood vessels, whereas no clear necrosis or mitotic activity was observed within these

areas; positive for S100 protein expression diffusely, but was negative for cytokeratin, desmin, cluster of differentiation 117 and smooth muscle actin.

Page 5, line 152-154: Solitary tumors were seen in six cases, and one case had multiple tumors (case 5, tumors were found in both the upper and middle trachea, and patient was also diagnosed with thyroid schwannoma).

Comment 2: In this report, authors recommended snare for resecting tracheobronchial schwannoma. In our experience, we had many cases with tracheobronchial hamartoma by APC and cryotherapy because of hard texture, unable to resect by snare. I want to know your opinion about it, and discuss in this manuscript.

Reply 2:

Yes. APC can be applied to resect tracheobronchial tumors. However, the coagulation depth of APC is shallow, and doctors have to clean the coagulated tissues using biopsy forceps during the procedure which will need longer time. In our experience, for pedunculated tumor, we prefer to use snare because it is time efficient and can achieve a more complete lesion resection, of course, it will need a longer trigger time for tumor with hard texture. For sessile tumor, we usually use high-frequency electric knife to do resection along the tumor's basement, or divide the big tumor into several small part, then use snare resect them separately. Then APC or cryotherapy can be applied to treat residual tumors. We do not recommend to use of APC or cryotherapy alone to ablate the entire tracheobronchial tumor.

Changes in the text: Page 7, line 222-227.

Minor comments:

Comment 3: How many cases do authors perform interventional bronchoscopic therapy in a year? Are you experts for the therapy? Please add more information in this manuscript.

Reply 3:

We perform about 800-1000 cases interventional bronchoscopic therapy one year, and our center is a famous interventional bronchoscopy center in China.

Changes in the text:

Page 3, line 88-91. All patients with pathologically diagnosed benign tracheobronchial schwannoma between January 2007 and December 2018, who

underwent interventional bronchoscopic therapy at bronchoscopy center of Beijing Tiantan Hospital, Capital Medical University were retrospectively reviewed.

Reviewer B

This is a retrospective study on the clinical utility of bronchoscopic intervention for tracheobronchial schwannoma. Because of its rarity, the published literatures were case reports or review articles. Thus this manuscript may provide some useful information for readers. I have a few comments.

Minor:

Comment 1: The conclusions seem that the bronchoscopic intervention is the second procedure for patients with a high risk of surgery. Did you perform bronchoscopic resection in high-risk patients? The conclusions should be elicited from the study results. From this study results, bronchoscopic intervention seems to be a useful alternative to surgical resection, and be considered as a first procedure. Please describe the role of bronchoscopic intervention more clearly.

Reply 1:

We have modified our text as advised (see Page 8, line 262-270)

Changes in the text:

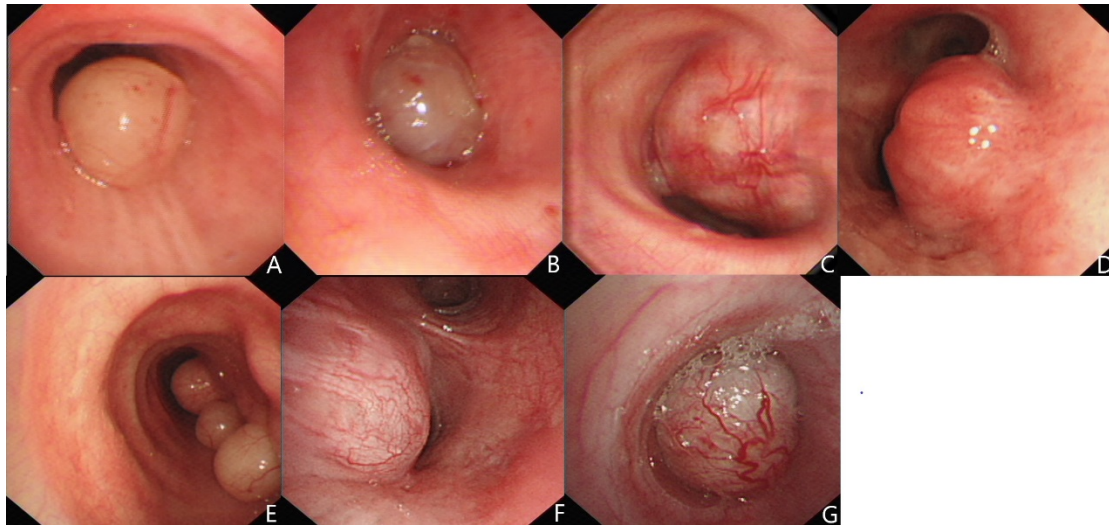
In conclusion, interventional bronchoscopic therapy is an acceptable approaches for the management of tracheobronchial schwannoma and is a useful alternative to surgical resection, especially for those who are at a high risk of surgery or are unwilling to undergo surgery. However, long-range bronchoscopic surveillance is necessary because of the possibility of tumor recurrence. Due to its benign nature, repeat endoscopic resection can still be considered after recurrence.

Comment 2: Figure 1. Bronchoscopic findings are one of the highlights of this manuscript. Please show the bronchoscopic findings of all seven cases. In addition, please describe the case number of each figure in the figure legend. I think CT images can be omitted as they seem not to be informative.

Reply 2:

We have added the manifestation on bronchoscopy of case 1-7 in Figure 2. According to the classification of tracheal schwannomas, tracheal schwannomas are classified as intraluminal type (tumor that exists only in the intraluminal space) and combined type (tumors that occur in both intraluminal and extraluminal spaces). Therefore, chest CT images are helpful for the classification and we suggest not to delete them.

Changes in the text: Figure 2.



Minor:

Comment 3: Figure 2. Please reduce the figures to understand easily. In addition, the lesions in the CT scans are difficult to see. Please magnify the lesions.

Reply 3:

Red arrow had been added to help readers to see the lesions in the CT.

Comment 4: Line 260. I think APC can be used effectively for hard tracheobronchial tumors.

Reply 4:

Yes. APC can be applied to resect tracheobronchial tumors. However, the coagulation depth of APC is shallow, and doctors have to clean the coagulated tissues repeatedly using biopsy forceps during the procedure which will need longer time. Therefore, we do not recommend to use of APC alone to ablate the entire tracheobronchial tumor.

Reviewer C

The article is interesting and valuable, as it shows possible variations in clinical manifestations which might be treated by interventional bronchoscopy. Details of the clinical course and alternative treatments are provided.

There are some minor concerns, which should be easy to address:

Comment 1: The study's design is described in the introduction as retrospective (Strobe Checklist item1) it should also be described as observational short study.

The basis of this article is a correct diagnosis of schwannoma. The only mention about diagnosis is line 76 ("...pathologically diagnosed..."). But were all schwannoma "typical", conventional schwannoma or were there subforms? What criteria were applied for diagnosis? Were there difficulties or uncertainties?

Was the pathological diagnosis done postinterventional on the resected specimen or were biopsies taken before the intervention?

Reply 1:

Histochemical features had been added.

Changes in the text:

Page 3, line 93-97: Histochemically, the resected specimen tumor postinterventional had features consistent with benign schwannoma: exhibited an Antoni A growth pattern (composed of spindle cells with elongated palisading nuclei); a few hyalinized blood vessels, whereas no clear necrosis or mitotic activity was observed within these areas; positive for S100 protein expression diffusely, but was negative for cytokeratin, desmin, cluster of differentiation 117 and smooth muscle actin.

Comment 2: In the opinion of the authors: are there limits to the size of the tumor to be resected? Or is this method applicable to all endoluminal tumors regardless of morphological criteria?

Reply 2:

In this study, the maximum diameters of tumors measured by CT images are approximately 1.5–4cm (see Page 5, line 151, and Table 1). In our opinion, if the maximum diameter of tumor is larger than 5cm, the difficulty of interventional bronchoscopic therapy will be increased.

Changes in the text:

In the previous literature, surgical resection is recommended for patients with sessile tumors, or extraluminal extension (reference 13) in order to reduce the risk of recurrence. However, in this study, five cases presented with sessile tumors and six had extraluminal extension, and the follow-up results suggest that for these patients, interventional bronchoscopic therapy may be also a useful and acceptable alternative to surgical resection (Page 7, line 234-241).

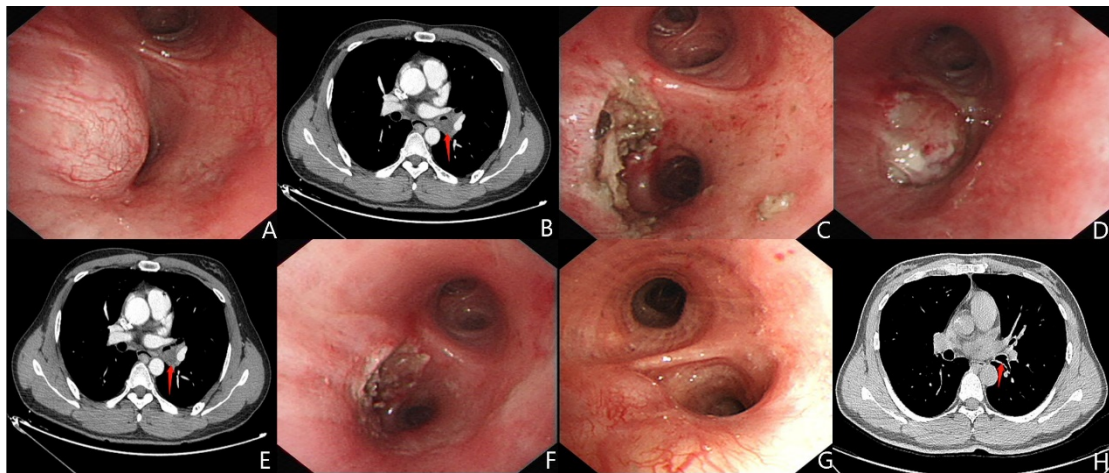
Comment 3: Follow up was based on bronchoscopy and imaging data (line 108).

Were there any clinical symptoms of the patients in the follow up? Because, after resection of intraluminal tumor parts there might have been symptomatic extraluminal tumor growth. If there was intraluminal recurrence it would be expected that the non-

resected, extraluminal tumor would become symptomatic. That again would be an argument for primary surgery, so it should be addressed.

Reply 3:

In fact, in this study, we find that, for combined type of tracheobronchial schwannomas, if the extraluminal part of the tumor was large, it will squeeze into the intraluminal space after endoscopic resection of intraluminal part in a short-term follow-up (cases 2, 3, and 6) (Page 6, line 172-175). After a second interventional bronchoscopy therapy, the large part of the extraluminal part will be resect (see Figure 3).



A and B: The manifestation on bronchoscopy and chest CT before therapy. D. Follow-up bronchoscopy found intraluminal tumor reappeared 4 days later. E: CT scan showed the extraluminal part of tumor squeezed into intraluminal space again. G and H: The manifestation on bronchoscopy and chest CT 1 month later after the second interventional bronchoscopic therapy.

Comment 4: Were there any complications? Bleeding? Bronchial obstruction?

Technical difficulties? The risk of repeated intervention bronchoscopy is stated to be lower than that of surgery, but there is no mention of complications in the cohort and no data on the risk of repeated bronchoscopic intervention in general. so this should be complemented.

Reply 4:

Complications about bronchoscopic intervention has been added as advised.

Changes in the text:

Page 5, line 161-164. Four patients complained of small amounts of bloody sputum, and 4 complained of sore throat, which were all relieved without special treatment 2–3 days after operation. No serious complications such as asphyxia, airway collapse, or

airway perforation occurred.

Page 6, line 176-178. No serious complications such as asphyxia, airway collapse, or airway perforation occurred during the second interventional bronchoscopy therapy.

Comment 5: The range of follow up periods are very variable. There might be an even higher rate of recurrences if follow up of all tumors was longer, especially because schwannoma usually show a slow growth (underestimation of recurrence risk). In addition, more than half of the combined type schwannoma showed short term recurrence (4 days to 1 month, line 148-149), and in addition a substantial number of clinically intraluminal classified schwannoma have mural or even extraluminal parts and are actually combined type schwannoma (line 194) there is also a risk for undertreatment. This is shortly discussed in line 190-200 but these seem to be main arguments against interventional bronchoscopy. The concise pro-arguments for interventional bronchoscopy are given in lines 228-231 but their deliberations are not very detailed. The "pros" in the discussion are even shorter than in the conclusion, so more room should be given to discuss these arguments.

Reply 5:

Intraluminal tumors were found subsequently in 3 cases (cases 2, 3, and 6) during the short-term follow-up (4 days to 1 month). However, based on the slow growth characteristics of schwannomas, it was speculated that the intraluminal tumor that reappeared was not recurrence but the extraluminal part that squeezed into the intraluminal space after endoscopic resection of intraluminal lesions. After the second bronchoscopic therapy, two patients (cases 3 and 6) were followed up for 3 years and 12 years, respectively (case 2 underwent surgery). No recurrence was found. We modified the manuscript as advised, and the advantages of interventional bronchoscopic therapy have been emphasized in the article.

Changes in the text:

Page 7, line 234-240: Although surgical resection is the best option for patients with no reported cases of recurrence and is recommended for patients with sessile tumors and low surgical risk, or extraluminal extension, the choice of treatment is still influenced by the risk of tracheal resection. In contrast, compared with surgery, patients who underwent endoscopic resection experienced less trauma and shorter postoperative recovery time. In this study, five cases presented with sessile tumors and six had extraluminal extension, and the follow-up results suggest that for these patients, interventional bronchoscopic therapy may be a useful and acceptable alternative to surgical resection.

Page 8, line 252-255: However, surgery may not be the only treatment method for recurrent cases, especially for patients in poor conditions. Our experience emphasizes on the benign nature and slow growth characteristic of tracheal schwannomas illustrating that a second endoscopic resection can still be considered after recurrence. In short, it would be beneficial if a little more information about pathological diagnosis, clinical symptoms and complications/difficulties would be given and some more emphasis would be seen in the discussion part on limits of the procedure (technical, high recurrence rate, extraluminal symptoms etc) but also on the pro arguments (low risk option of repeated intervention), slow growth).