

Interventional Bronchoscopic Therapy in Adult Patients with Tracheobronchial Mucoepidermoid Carcinoma

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Abstract

Background: Tracheobronchial mucoepidermoid carcinoma (MEC) is a rare airway tumor in adults for which surgery is considered a first-line treatment. However, some patients already lost the best opportunity of a surgical intervention when diagnoses are confirmed, and surgery causes considerable trauma resulting in partial loss of pulmonary function. Moreover, the tumor is resistant to radiotherapy and chemotherapy. These factors make the treatment of tracheobronchial MEC challenging. This study aimed to evaluate the safety and efficacy of interventional bronchoscopic therapy in adult patients with tracheobronchial MEC.

Methods: We retrospectively analyzed the clinical manifestations, bronchoscopic interventions, complications, and outcomes of 11 adult patients with tracheobronchial MEC. Paired *t*-test was used to analyze the parameters of the American Thoracic Society Dyspnea Index and the Karnofsky Score before and after the first interventional bronchoscopic therapy.

Results: All tumors occurred in the main bronchus and were easily visualized by bronchoscopy. After interventional bronchoscopic therapy, the symptoms of all patients showed significant improvement. The American Thoracic Society Dyspnea Index decreased from 1.91 ± 1.22 to 0.27 ± 0.47 ($t = 6.708$, $P < 0.001$) and the Karnofsky Score increased from 78.18 ± 16.62 to 95.46 ± 8.20 ($t = -5.190$, $P < 0.001$). Bronchoscopic intervention did not result in serious complications or mortality. During the follow-up period between 3 and 96 months after the first therapy, the following results were noted: (1) among the eight patients with low-grade tracheobronchial MEC, only one patient had a relapse and agreed to surgical treatment; (2) among the three patients with high-grade tracheobronchial MEC, one patient required repeated bronchoscopic interventions, one patient died of pulmonary infection, and one patient died of systemic failure owing to tumor metastasis.

Conclusions: Interventional bronchoscopic therapy, as an alternative treatment, shows promise in some adult patients with low-grade tracheobronchial MEC confined to the bronchus. However, for adult patients with high-grade tracheobronchial MEC, early diagnosis and surgical treatment are still strongly recommended.

Key words: Adult; Bronchoscopy; Bronchus; Mucoepidermoid Carcinoma

INTRODUCTION

Tracheobronchial mucoepidermoid carcinoma (MEC) is a rare airway tumor in adults.^[1] Currently, surgery is the preferred treatment for this disease.^[2] Patients with tracheobronchial MEC do not present with specific clinical manifestations. Consequently, in most of the cases, opportunities for surgical intervention are missed when diagnoses are confirmed. Surgical treatment results in significant trauma, and worsens pulmonary function, which is not suitable for all patients. Moreover, the tumor is resistant to radiotherapy and chemotherapy. These factors make the treatment of tracheobronchial MEC challenging. In the recent years, advancements in

interventional bronchoscopic therapy have highlighted its increasingly important role in the treatment of airway stenosis caused by malignant airway tumors. The aim of our study was to evaluate the safety and efficacy of interventional bronchoscopic therapy in adult patients with tracheobronchial MEC.

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METHODS

Ethical approval

This study was approved by the Institutional Ethics Committee of Beijing Tian Tan Hospital, Capital Medical University (NO. JS 2013-007-02). All patients signed an informed consent giving permission to use their medical data.

Patient selection

A total of 12 adult patients with tracheobronchial MEC who were admitted to the Department of Pulmonary Diseases from July 2008 to February 2016 were initially enrolled. All patients were diagnosed based on pathological examination of samples obtained through bronchoscopic biopsy at our hospital. Apart from one patient in whom bronchoscopic intervention was terminated because of significant bleeding during the procedure, the remaining 11 patients completed interventional bronchoscopic therapy. We retrospectively analyzed clinical data of the 11 adult patients with tracheobronchial MEC (seven men and four women). Their ages and medical history ranged from 23 to 69 years (mean: 45.0 ± 14.2 years) and 1–84 months (mean: 19.7 ± 25.1 months), respectively. Based on these pathological findings, these patients were divided into a low-grade tracheobronchial MEC group (cases 1–8) and a high-grade tracheobronchial MEC group (cases 9–11). Six patients (cases 1–6) refused surgical treatment and five patients (cases 7–11) were unsuitable for surgery or had missed a surgical opportunity, as assessed by the thoracic surgeons.

Therapeutic methods

Preoperative preparation

Blood test findings, blood coagulation function, blood biochemical index, electrocardiograms, and enhanced computed tomography (CT) images of the chest were examined before interventional bronchoscopic therapy. All preoperative and anesthetic assessments were performed by a pulmonologist and an anesthesiologist, respectively. The patients were instructed to refrain from food and beverages for at least 6 h before initiation of the procedure.

Anesthesia selection and monitoring

All patients underwent interventional bronchoscopic therapy under general anesthesia, which was administered by an anesthesiologist using a regimen of propofol, midazolam, remifentanyl, and muscle relaxants in an operating room. Dynamic electrocardiogram, noninvasive blood pressure, and peripheral oxygen saturation were monitored throughout the treatment process.

Therapeutic procedures

The three patients with high-grade tracheobronchial MEC underwent interventional bronchoscopic therapy through an endotracheal tube. The remaining eight patients with low-grade tracheobronchial MEC underwent treatment through a laryngeal mask. A ventilator was connected to all patients to maintain the peripheral oxygen saturation of $>95\%$.

First, we removed the intraluminal lesions using a high-frequency electric knife (ERBE, Tubingen, Germany) and Holmium laser (VersaPulse PowerSuite 100W, Lumenis, USA) with an electronic bronchoscope (BF-1T260, Olympus, Tokyo, Japan). The power of the electric current was set at 60 W. The power and pulse frequency of laser were set at 8 W and 10 Hz, respectively. Then, the roots of the tumors were cauterized by argon plasma coagulation (APC; ERBE, Tubingen, Germany). The output power of the APC probe was 30 W and the flow rate of argon was 1.2/min. The coagulated tissues were removed using biopsy forceps. To prevent an airway fire, the concentration of inhaled oxygen during the various procedures was maintained at $<40\%$.

Since severe airway stenosis cannot be managed by the above methods, a Y-shaped silicone tracheal stent (NOVATECH SA, France) and Y-shaped nitinol alloy tracheal stent (MICRO-TECH, China) were placed in cases 9 and 10, respectively, using a rigid bronchoscope of 14-mm diameter (Karl Storz, Tuttlingen, Germany).

For clearance of all necrotic tissues and observation of the stent location, all patients were assessed using bronchoscopy performed 2–3 days after the procedure.

Response assessment

We used the American Thoracic Society Dyspnea Index and the Karnofsky Score in evaluating clinical effects.

Follow-up

After the first interventional bronchoscopic therapy, all patients underwent bronchoscopic inspections at intervals of 1–6 months to examine for restenosis of the airway. The follow-up period was 3–96 months (mean: 24.9 ± 25.4 months). The last follow-up was finished on January, 2017.

Statistical analysis

Statistical analyses were performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). Paired *t*-test was used to compare the changes in the American Thoracic Society Dyspnea Index and the Karnofsky Score before and after the first interventional bronchoscopic therapy. Quantitative data were expressed as mean \pm standard deviation (SD). A value of $P < 0.05$ was defined as statistically significant.

RESULTS

The chief complaints of patients included cough, hemoptysis, and exertional dyspnea. They were initially misdiagnosed with pneumonia, bronchitis, chronic obstructive pulmonary disease, or bronchial asthma, and antibiotic and asthma treatments were futile.

The symptoms of all patients improved significantly after bronchoscopic interventions. Most patients recorded a small amount of blood-stained sputum after interventional bronchoscopic therapy, and the bleeding spontaneously ceased in a week. Case 5 and case 10 reported chest pain after interventional bronchoscopic

therapy and this symptom disappeared in 3 days. Case 2 presented with recurrence of the tumor a month after interventional bronchoscopic therapy, necessitating surgical treatment [Figure 1]. Consequently, this patient underwent surgery during a 3-month follow-up period. The remaining seven patients with low-grade tracheobronchial MEC did not show tumor recurrence. The longest follow-up period was 96 months (case 1) [Figure 2]. Among the three patients with high-grade tracheobronchial MEC, case 10 complained of intermittent, small amount of hemoptysis, at 3 months after stent implantation. Bronchoscopy revealed that the intraluminal lesions had relapsed to cause lumen restenosis, lumen blockage in the distal stent, and fracture of the stent in the right main bronchus [Figure 3]. Therefore, the patient received repeated bronchoscopic interventions. Case 10 needed interventional bronchoscopic therapy at intervals of 1–3 months. Case 9 exhibited mediastinal lymph node enlargement that resulted in extrinsic stenosis of the lumen. Therefore, a silicone stent, which is easy to remove, was placed in the patient. We intended to remove the stent after radiotherapy. However, the efficacy of the radiotherapy was poor, and we decided to leave the airway stent. Although the silicone stent caused retention of secretions, the patient refused to undergo replacement with a bare-metal stent. Repeated episodes of pneumonia and severe pulmonary infection eventually led to the death of this patient at 10 months of follow-up. Case 11 re-experienced severe dyspnea, 9 months after the first interventional operation, because of relapse of intraluminal lesions. The patient received a second bronchoscopic intervention and died of systemic failure caused by tumor

metastasis at 11 months after the first operation. The general informations and clinical characteristics of the 11 patients are summarized in Table 1.

All patients showed significant improvement of symptoms after therapy. The American Thoracic Society Dyspnea Index markedly decreased from 1.91 ± 1.22 to 0.27 ± 0.47 ($t = 6.708$, $P < 0.001$) and the Karnofsky score markedly increased from 78.18 ± 16.62 to 95.46 ± 8.20 ($t = -5.190$, $P < 0.001$) after the first bronchoscopic intervention [Table 2].

DISCUSSION

MEC of the lung is derived from minor salivary gland tissue of the tracheobronchial tree,^[3] and was first described by Smetana in 1952.^[4] The World Health Organization classifies pulmonary MEC, pulmonary adenoid cystic carcinoma, and epithelial-myoepithelial lung carcinoma as “salivary gland type” tumors. Histologically, MEC comprises a mixture of different cell types, including mucus-secreting glandular cells, squamous cells, and intermediate cells. Based on the morphology and cytology, MEC is classified as low grade and high grade.^[5-7] Low-grade MEC exhibits a long natural history with rare occurrence of metastasis, whereas high-grade MEC is aggressive and prone to local invasion and early metastasis.^[8,9] Tracheobronchial MEC is extremely rare in adults. It affects men and women equally, with the median age at presentation being approximately 40 years.^[10] The tumor preferentially occurs in the major airway, particularly in the segmental bronchi, main bronchus, and trachea.^[11-14] In the study, the tumors in all patients were located in the main airway, providing adequate space for an interventional bronchoscopic therapy.

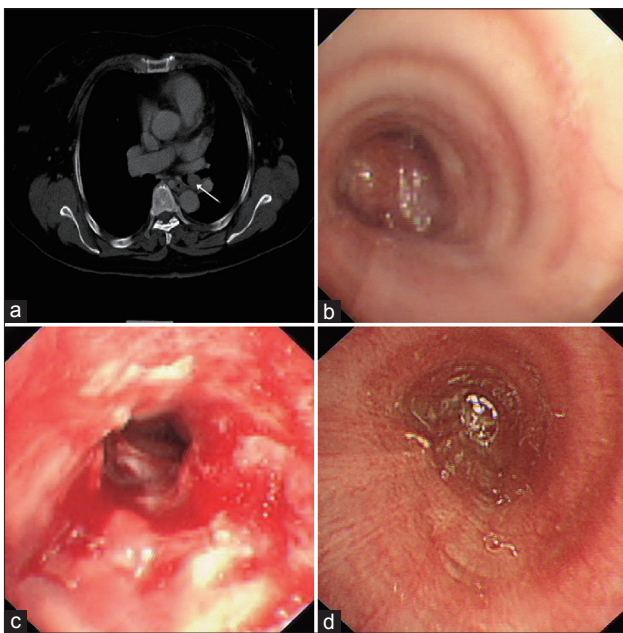


Figure 1: Clinical characteristics of case 2. (a) Chest computed tomography showing a mass located in the left main bronchus that induces bronchial obstruction (white arrow); (b) bronchoscopic findings before bronchoscopic therapy; (c) bronchoscopic findings after bronchoscopic therapy; (d) local tumor recurrence in the left main bronchus.

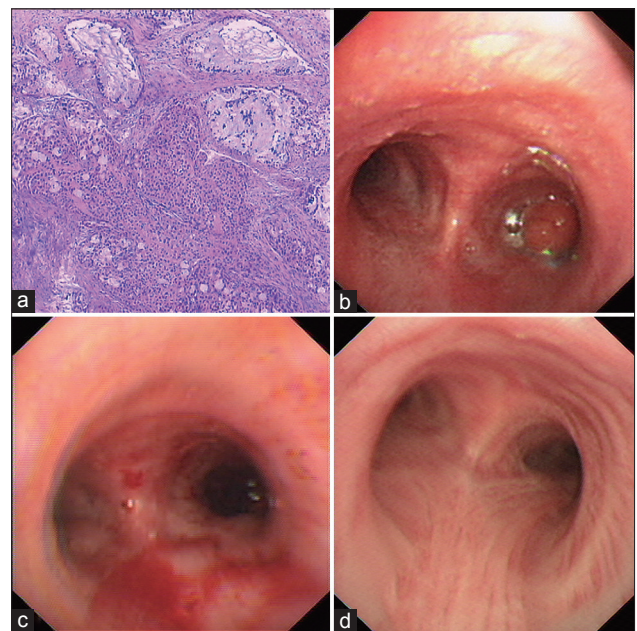


Figure 2: Clinical characteristics of case 1. (a) Pathology indicating a diagnosis of low-grade mucoepidermoid carcinoma (H and E, original magnification $\times 100$); (b) bronchoscopy showing a polypoid mass located in the right main bronchus; (c) bronchoscopic findings after bronchoscopic therapy; (d) bronchoscopic findings 96 months after bronchoscopic therapy.

The common symptoms of tracheobronchial MEC include cough, hemoptysis, wheezing, fever, and chest pain.^[15] Cough is believed to be the most common clinical symptom, occurring in approximately 70% of cases of bronchial MEC.^[12] In the study, nine of the 11 patients presented with cough, which accounted for 82% of the total cases. Therefore, when a patient has an unexplained cough for a long time, the possibility of tracheobronchial MEC should be considered.

CT plays an important role in the diagnosis of tracheobronchial MEC, which usually presents as a solitary nodule or an

endobronchial mass, with or without postobstructive pneumonia or atelectasis.^[16] A study by Wang *et al.*^[17] reported that chest CT scans of low-grade MEC often revealed intraluminal homogeneous, smooth, and oval or spherical tumors with well-defined margins. In our study, chest CT scans of the eight patients with low-grade tracheobronchial MEC revealed well-distinguished, homogeneous, and smooth masses in the bronchus, similar to results of the CT scan in the previous study. In contrast, the three patients with high-grade tracheobronchial MEC presented with bronchial stenosis and rough airway walls, accompanied by mediastinal lymph node enlargement. However, chest radiographs did not provide significant insights, with only a few patients presenting with distal atelectasis or obstructive pneumonia.^[10] In this study, chest radiographs of cases 3, 5, and 7 revealed no abnormalities. Therefore, we recommended immediate chest CT for the patients suspected to have tracheobronchial MEC.

Bronchoscopic examination and biopsy are helpful in diagnosing tracheobronchial MEC.^[18] Bronchoscopes of the eight patients with low-grade tracheobronchial MEC in our study revealed well-circumscribed smooth neoplasms confined to the bronchus, with the mucosa around the mass not showing any obvious abnormalities. The three patients with high-grade tracheobronchial MEC had bronchus soakage of neoplasms that caused evident and rough bronchial wall thickening, without any clear demarcation from the surrounding mucosa. Broadening of carina and extrinsic stenosis of the lumen were often visible due to mediastinal lymph node enlargement.

At present, surgical resection is the mainstay of tracheobronchial MEC treatment. The goal of this treatment is to completely remove the tumor with nodal dissection and to preserve functional parenchyma. Tracheobronchial MEC is surgically treated with pneumonectomy, lobectomy, and sleeve lobectomy.^[19,20] A review of 34 surgical cases

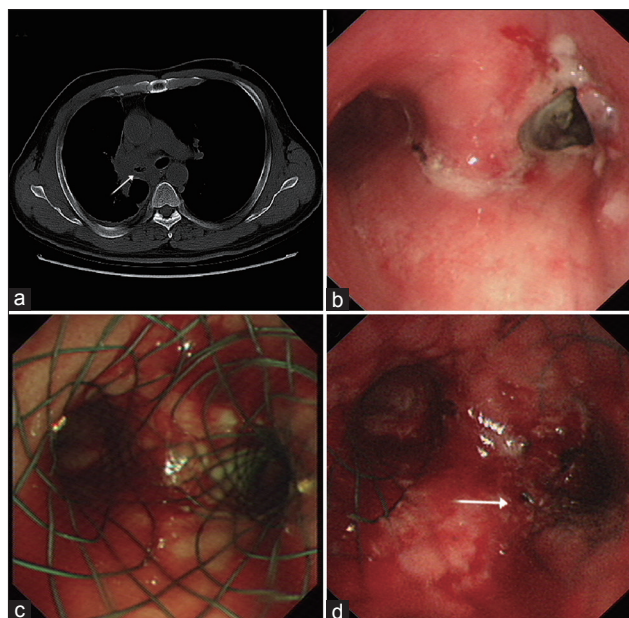


Figure 3: Clinical characteristics of case 10. (a) Chest computed tomography showing tumors invading the carina and both main bronchi, narrow main right bronchus (white arrow), and mediastinal lymph node enlargement; (b) bronchoscopic findings before bronchoscopic therapy; (c) Y-shaped metal stent was placed; (d) distal stent lumen blockage and right main bronchus stent fracture (white arrow).

Table 1: General informations and clinical characteristics of 11 patients with tracheobronchial mucoepidermoid carcinoma

Number	Gender	Age (years)	Tumor location	Chief complaints	Therapeutic frequency (times)	Complications after therapy	Follow-up (months)	Prognosis
1	Male	44	Right MB	Cough	1	Hemoptysis	96	No relapse
2	Female	62	Left MB	Cough, dyspnea	1	Hemoptysis	3	Relapse
3	Male	35	Right LL	Cough	1	Hemoptysis	36	No relapse
4	Male	28	Left MB	Cough, dyspnea	1	Hemoptysis	29	No relapse
5	Male	39	Right BI	Hemoptysis	1	Hemoptysis, chest pain	24	No relapse
6	Female	40	Right MB	Cough, dyspnea	1	Hemoptysis	20	No relapse
7	Female	58	Left UL	Hemoptysis	1	Hemoptysis	19	No relapse
8	Male	69	Right UL	Cough, hemoptysis	1	Hemoptysis	15	No relapse
9	Female	23	Ca and both MB	Cough, dyspnea	2	Secretion retention	10	Died
10	Male	52	Ca and both MB	Cough, dyspnea, hemoptysis	5	Hemoptysis, chest pain	11	Relapse
11	Male	45	Ca and both MB	Cough, dyspnea, hemoptysis	2	Hemoptysis	11	Died

BI: Bronchus intermedius; Ca: Carina; LL: Lower lobe; MB: Main bronchus; UL: Upper lobe.

Table 2: ADI and KPS of 11 patients with tracheobronchial mucoepidermoid carcinoma before and after the first interventional bronchoscopic therapy

Number	ADI		KPS	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment
1	1	0	90	100
2	2	0	80	100
3	1	0	90	100
4	1	0	90	100
5	1	0	90	100
6	1	0	90	100
7	2	0	80	100
8	1	0	90	100
9	4	1	50	80
10	3	1	60	100
11	4	1	50	80

ADI: American Thoracic Society Dyspnea Index; KPS: Karnofsky score; SD: Standard deviation.

suggested that patients with low-grade tracheobronchial MEC could expect to be cured following complete resection. However, the patients with high-grade tracheobronchial MEC had a poor prognosis.^[2] Since large airways are typically involved,^[21] a surgical operation may pose a great risk with serious postoperative complications; moreover, partial loss of pulmonary function is unavoidable. In addition, some patients miss opportunities for surgical intervention at the time of diagnosis or are unsuitable for surgery. In the study, the pathological stage of the tumors in cases 1–8 was Ib. However, cases 1–6 refused surgery and cases 7 and 8 were considered unsuitable for surgical treatment because of severe cardiovascular disease and renal dysfunction, respectively. The pathological stage of cases 9–11 was determined to be IIIb, and thoracic surgeons deemed these patients ineligible for surgery.

Evidence for the effect of chemotherapy and radiotherapy has not been reported yet.^[22] A few cases reported that tyrosine-kinase inhibitor (gefitinib) shows good response in patients with MEC having EGFR gene mutations.^[23] However, tracheobronchial MEC is rare and lacks large-scale clinical research data. Thus, the efficacy of tyrosine kinase has not been established accurately. In the study, case 10 received six cycles of chemotherapy (pemetrexed combined with cisplatin) before admission to our hospital. Moreover, because of the presence of EGFR gene mutations, the patient underwent targeted therapy with gefitinib for 2 months after the first bronchoscopic intervention; however, the efficacy was poor.

The field of interventional bronchoscopic therapy has grown significantly over the past several years, especially in the treatment of malignant airway tumors. High-frequency electrotome, APC, cryotherapy, laser, and tracheal stents can rapidly improve airway stenosis with a lower incidence of adverse events.^[24,25] A study by Li *et al.*^[26] recommended the bronchoscopic laser method as an alternative to radical surgery in MEC confined to the bronchus; moreover, they

successfully used Nd-YAG laser in two patients. A study by Wang *et al.*^[27] reported the efficacy of bronchoscopic therapy in six children with bronchial MEC. However, all patients in the above-mentioned studies exhibited low-grade tracheobronchial MEC, and only one of these was an adult. To our knowledge, to date, there is no study focusing on the safety and efficacy of interventional bronchoscopic therapies in adult patients with tracheobronchial MEC. In this study, the symptoms of all patients improved after interventional bronchoscopic therapy. All patients who completed the procedure exhibited some bleeding (5–50 ml) that occurred during the operation. Bleeding was successfully controlled with APC and adrenaline irrigation; uncontrollable hemorrhage was not observed. Some patients had a small amount of blood in the phlegm and reported chest pain postoperatively; however, they did not have any serious complications such as pneumothorax, mediastinal emphysema, or tracheoesophageal fistula. Interventional bronchoscopic therapy did not lead to mortality in any of the cases. However, interventional bronchoscopic therapy in adult patients with high-grade tracheobronchial MEC was not as effective as it was in adult patients with low-grade MEC. After bronchoscopic intervention, regular bronchoscopic inspections are necessary. In cases of tumor recurrence, bronchoscopic intervention can be performed again. Surgery may also be performed when necessary for cases of low-grade MEC.

Hence, we found that interventional bronchoscopic therapy in adult patients with tracheobronchial MEC has the following advantages. First, interventional bronchoscopy is relatively simple to perform. For patients with severe airway stenosis, it can rapidly open the airway and improve symptoms. Second, bronchoscopic interventions resulted in less damage; moreover, it resulted in preservation of the pulmonary function. Third, the operation can be repeated, especially in inoperable patients with high-grade tracheobronchial MEC who are prone to future relapses. Bronchoscopic interventions can also be repeated to improve symptoms of patients, without resulting in serious complications. However, we suggest the placement of a bare-metal stent because of its benefits during expectoration in patients requiring an airway stent.

One disadvantage of interventional bronchoscopic therapy was that complete resection of the tumor could not be ensured during the procedure, which might lead to local tumor recurrence. In the present study, the recurrence rate of low-grade tracheobronchial MEC was 1/8, and the recurrence rate of high-grade tracheobronchial MEC was 2/3. Another disadvantage is that the risk of uncontrollable hemorrhage may occur during the procedure. One patient failed to complete interventional bronchoscopic therapy because of massive bleeding during the procedure (30 min, >50 ml). The patient soon underwent surgical treatment and was excluded from this study.

In conclusion, interventional bronchoscopic therapy, as an alternative treatment, demonstrates the potential to

achieve an effect similar to surgical effect in some adult patients with low-grade tracheobronchial MEC confined to the bronchus, based on this study. One limitation of this study was that the number of cases was relatively small, and large-scale, multicentric studies with longer follow-up periods are required to further validate the results. However, for adult patients with high-grade tracheobronchial MEC, bronchoscopic intervention resulted in a poor prognosis and only served as palliative treatment to relieve symptoms. Early diagnosis and surgical treatment are still strongly recommended in cases of high-grade MEC.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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