Clinical efficacy of treatment for primary tracheal tumors by flexible bronchoscopy: Airway stenosis recanalization and quality of life

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Abstract. The aim of the present study was to evaluate the effectiveness of interventional treatment of primary tracheal tumors through flexible bronchoscopy. The clinical data of 38 patients with primary tracheal tumours who underwent flexible bronchoscopy intervention therapy between January 2011 and January 2017 were retrospectively analyzed. The average time interval from onset of symptoms to the appearance of actual clinical manifestations in the 38 patients ranged from 0 to 60 months, with an average of 8.1±11.6 months and a median of 4.2 months. The rate of misdiagnosis at the first visit was 36.8% (14/38). After interventional treatment, the overall efficiency (complete + partial response) of airway stenosis recanalization in the 38 patients was 89.5%. In 3 patients with benign tumors, the anhelation score was reduced following treatment (1.00±0.77 vs. 3.13±1.21 at the pre-treatment stage; P<0.001). The overall survival rates of the 35 patients at 1, 3 and 5 years were 69.3, 48.7 and 20.3%, respectively. Therefore, flexible bronchoscopic intervention may effectively smoothen the airways of patients and relieve the symptoms of anhelation. Combining radiotherapy and chemotherapy may improve patient prognosis and safety.

Introduction

Primary tracheal tumor is a rare type of respiratory-tract cancer. According to worldwide statistics, the annual incidence rate of primary tracheal tumors is approximately one case per million. Of all tracheal tumors, the rate of malignancy is ~90% in adults and ~30% in children. Tracheal malignancies account for ~0.2% of all respiratory-tract cancers and <0.05% of all malignancies (1-4). Treatments of common tracheal tumors include surgical resection, radiotherapy and chemotherapy. Surgery has been considered the treatment of choice for a long time (5). The 5-year survival rate for patients treated with surgical resection of tracheal malignant tumors has been reported to be 50%, compared to only 10% for non-surgically treated patients (6). However, this procedure has been limited due to the high risk associated with anaesthesia and surgery, the length of the tracheal resection and the extent of the lesion. Two large-sample studies reported a rate of surgical interventions of only 11.6 and 6.9% (2,3).

With the development of endoscopic intervention techniques, the treatment of tracheal tumors has also advanced. As a result, interventional therapies including bronchoscopic stent placement, electric snare resection, argon plasma coagulation knife (APC), laser treatment and CO_2 cryotherapy have been applied to the treatment of tracheal tumors. In particular, the application of bronchoscopic intervention prior to surgical treatment has been indicated to reduce tumors, improve airway stenosis, relieve anhelation and reduce the risk of surgery. In the present study, the clinical data and therapeutic effects of comprehensive interventional treatment with a flexible bronchoscope in patients with primary tracheal tumors at the Shandong Provincial Hospital (Jinan, China) in the past 7 years were retrospectively analysed.

Patients and methods

Patients. Patients with primary tracheal tumors who underwent bronchoscopic intervention between January 2011 and December 2017 at Shandong Provincial Hospital Affiliated to Shandong University (Jinan, China) were considered for inclusion. All patients provided written informed consent. This

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study was approved by the Ethics Committee of the Shandong Provincial Hospital Affiliated to Shandong University (Jinan, China).

All patients had been diagnosed via bronchoscopic biopsy. Except for secondary tracheal tumors, all patients had undergone interventional treatment with a flexible bronchoscope (IT260 Bronchovideoscope; Olympus Corp.). Of these patients, 3 had benign tumors, including 1 with schwannoma, 1 with glomus tumor and 1 with hamartoma. In addition, 35 patients had malignant tumors, including 1 with squamous cell carcinoma with short-term recurrence after surgery and 1 with adenoid cystic carcinoma that had relapsed 30 months after surgery plus radiotherapy; the remaining 33 patients presented with tracheal malignant tumors that were not eligible for surgical resection.

Treatment methods. An individualized treatment plan was selected according to the location, size, shape and other characteristics of the primary tracheal tumor. A tracheal stent, high-frequency electric trap, electric knife, laser, APC, cryotherapy and balloon dilation were used. In cases with a more pronounced tracheal stenosis (stenosis >50%), parallel APC/laser and cryotherapy was performed, as the numerous lesions were difficult to completely remove, which had resulted in breathing difficulty and challenging tracheal stent placement. In cases with limited tumor lesions, the basement may be ligated and the tumur may be removed using a high-frequency electric snare and electric knife. The patient may then be treated with APC or cryotherapy to cauterize the basal area. In this way, 22 patients underwent bronchoscopy within 1 week after surgery and 17 patients underwent a second intervention for further removal of tumors present in the open airways. After interventional treatment of patients with malignant tumors, most of the follow-up patients underwent radiation therapy and/or chemotherapy. Certain patients discontinued due to intolerance to chemoradiography or by choice. All patients were followed up at the outpatient or inpatient clinics or via telephone.

Efficacy assessment. Differences in airway stenosis and anhelation prior to and after bronchoscopic intervention were evaluated and a follow-up analysis of patient survival was performed. i) The evaluation criteria of the curative effects of airway stenosis recanalization included the following: Complete response (CR), partial response (PR), mild response (MR) and no response (NR) (6). Overall efficiency=(cases of CR + cases of PR)/total patients. ii) Airiness symptom scores (7): Level 0: Normal; level 1: Breathing difficulties when walking fast; level 2: Breathing difficulties when walking at a normal speed; level 3: Unable to walk due to anhelation during normal speed; level 4: Anhelation after slight activity.

Statistical analysis. Statistical analysis was performed using SPSS 22.0 (IBM Corp.). Values are expressed as the mean ± standard deviation. The efficacy prior to and after treatment was compared using an unpaired Student's t-test. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. $P<0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics and circumstances of misdiagnosis. The basic clinical data of the 38 patients who underwent comprehensive interventional therapy along with flexible bronchoscopy are provided in Table I (age 24-76; male:female=23:15). Clinical symptoms mainly included a progressively worsening cough, dyspnea and wheezing. Approximately half of the patients developed a small amount of haemoptysis, with none developing severe haemoptysis. Due to the occurrence of non-specific symptoms, there was a high rate of misdiagnosis, and 36.8% (14/38) of patients were misdiagnosed at the first visit as having bronchial asthma or bronchitis (see Table II for details). The time from onset to diagnosis was 0-60 months, with an average of 8.1±11.6 months and a median of 4.2 months. Thoracic X-rays were performed in 8 patients, of which 2 patients (25%) displayed tracheal/superior mediastinum lesions. Prior to treatment, all 38 patients had tracheal tumors, as demonstrated by chest CT. Tracheal tumor sites were more common in the middle and lower segments, accounting for 84.2% (32/38) of all tumor sites. A total of 6 patients had tracheal tumors in the upper segment, accounting for only 15.8% of all patients. Furthermore, 35 (92.1%) underwent bronchoscopy, which demonstrated that >50% of the lumen was obstructed. In 20 patients (57.1%); >75% of the lumen was obstructed. Serious obstruction of the lumen may lead to dysfunction in ventilation.

Comparison of the different pathological subtypes of tracheal malignant tumors in 35 patients. Benign and malignant primary tracheal tumors are clinically rare, with malignant tumors being more common than benign ones in adults. A total of 3 cases of benign tumor were identified among the 38 patients, namely peripheral glioma, angiomyoneuroma and hamartoma. The tracheal tumors affecting the remaining 35 patients were malignant and were most commonly squamous cell carcinoma and adenoid cystic carcinoma, with squamous cell carcinoma accounting for 40.0% (14/35) and adenoid cystic carcinoma accounting for 37.1% (13/35). Overall, compared to other types of cancer, squamous cell carcinoma exhibited a stronger association with males and smoking. The age of onset for squamous cell carcinoma was higher than that for adenoid cystic carcinoma (Table III). Patients suffering from tracheal malignant tumors underwent immunohistochemical examination for different markers. Among them, 83.3% (15/18) were positive for P63 and 14.3% (2/14) were positive for thyroid transcription factor-1. Of the patients with adenoid cystic carcinoma, 88.9% (8/9) were positive for CD117. Of the patients with squamous cell carcinoma, adenoid cystic carcinoma, adenocarcinoma and small-cell carcinoma, 50-70, 1-20, 20-40 and 30-40% were positive for Ki-67, respectively. Squamous cell carcinoma had the highest proliferation index.

Therapeutic effect of bronchoscopy intervention and recanalization of tracheal stenosis and complications. The curative effects of the comprehensive interventional treatments involving flexible bronchoscopes, tracheal stenosis recanalization and potential complications are presented in Table IV. Within 1 week after the operation, bronchoscopy was performed in 22 patients, of which 17 patients underwent a second interventional treatment

Table I. Baseline characteristics of the patients (n=38).

Characteristics	Value
Sex	
Male	23 (60.5)
Female	15 (39.5)
Age (years)	61 (24-76)
Smoking	21 (55.3)
Symptom	
Difficulty breathing	35 (92.1)
Cough with or without expectoration	37 (97.4)
Haemoptysis	19 (50.0)
Stridor wheezing	8 (21.1)
Hoarse voice	7 (18.4)
Chest pain	2 (5.3)
Feeling of a foreign body	1 (2.6)
Dysphagia, swallowing difficulty	2 (5.3)
Tumor site	
Upper section	6 (15.8)
Middle section	12 (31.6)
Lower section	17 (44.7)
Middle and lower segment	3 (7.9)
Tracheal stenosis degree (%)	
<50	3 (7.9)
50-74	15 (39.5)
75-89	17 (44.7)
90-100	3 (7.9)

Values are expressed as n (%) or ean (range).

Table II. Cases of misdiagnosis within the cohort.

Disease	n (%)
Bronchial asthma	4 (10.5)
Bronchitis	4 (10.5)
Chronic obstructive pulmonary disease	3 (7.9)
Pneumonia	1 (2.6)
Coronary heart disease	1 (2.6)
Pharyngitis	1 (2.6)
Total	14 (36.8)

to further clear the tumor-obstructed airways. The patients tolerated the course of treatment well with no serious complications noted. The most common intra-operative complication was haemorrhage. Altogether, 19 patients (34.5%) developed haemorrhage in 55 separate events. A total of 12 patients had a small amount of haemorrhage and haemostasis was achieved by washing with norepinephrine (1:10,000). Furthermore, 7 patients had a small amount of blood in their sputum after surgery, which stopped spontaneously after 2-3 days without treatment. In addition, 2 patients developed hypotension during surgery. After interventional therapy, the overall efficiency (CR+PR) of airway stenosis recanalization in the 38 patients was 89.5%. In Fig. 1, representative images of patients with Schwannoma (Fig. 1A-a and 1A-b), adenocarcinoma (Fig. 1B-a and 1B-b) and adenoid cystic carcinoma (Fig. 1C-a and 1C-b) who underwent endotracheal intervention are presented. Histopathological images of patients with Schwannoma (Fig. 1A-c), adenocarcinoma (Fig. 1B-c) and adenoid cystic carcinoma (Fig. 1C-c) are provided. The anhelation score was 3.13±1.21 prior to treatment and 1.00±0.77 after treatment (t=15.0, P<0.001).

Gastrin scores, treatment methods, pathological types and follow-up results of the patients with primary tracheal tumors. All 38 patients who received follow-ups from March 2017 to March 2018 were followed up either face-to-face or via telephone. Out of the 35 patients (20%) with malignant tracheal tumors, 7 of patients received radiotherapy combined with chemotherapy and 7 patients were followed up with radiotherapy alone (20.0%), while 11 patients were followed up with chemotherapy alone (31.4%). Among the patients, 1 case was lost to follow-up and 18 mortalities occurred. The overall 1-year survival rate of patients with malignant tracheal cancer was 69.3%, the 3-year survival rate was 48.7% and the 5-year survival rate was 20.3%. The survival curve is presented in Fig. 2, these results demonstrated that relief of airway obstruction increases the quality of life. The 14 patients diagnosed with squamous cell carcinoma had a 1-year survival rate of 71.4% and a 5-year survival rate of 38.1% and the median survival time was 15 months. Out of the 13 cases with adenoid cystic carcinoma, 1 patient was lost to follow-up and 3 patients died. The remaining patients received follow-up for 4-62 months. The median follow-up period was 39 months. The survival time of patients suffering from adenoid cystic carcinoma was significantly longer than that of patients diagnosed with squamous cell carcinoma. The survival curves are presented in Fig. 3.

Discussion

The clinical manifestations of primary tracheal tumor commonly include symptoms of airway obstruction, e.g. cough, sputum, bloody sputum, dyspnea and wheezing. By the time these clinical manifestations are observed, airway stenosis has frequently exceeded half of the lumen (8). The low incidence of tracheal tumors, slow tumor growth and a lack of specific clinical manifestations appear to be the cause for patients not to seek timely medical attention. The sensitivity of chest X-rays in distinguishing tracheal tumors is low, ranging from only 18 to 28% (9), leading to frequent misdiagnosis. As a result, the rate of misdiagnosis at the first visit was as high as 36.8% in the 38 patients. Diagnosis was delayed for numerous patients by several months or even several years, with an average of 8.1±11.6 months. An analysis of a large sample undertaken using Shandong Provincial Hospital Affiliated to Shandong University's internal data between January 2001 and July 2017 reported an average delay of 2.5±8 months. While most patients were referred to a specialist for diagnosis in a timely manner, 10% of the patients faced delays of >6 months. The most common misdiagnosis for these patients was bronchial asthma and bronchitis. Of all misdiagnosed patients of the present study,

Table III. Comparison of demographics between different pathological types of 35 patients with tracheal malignant tumors.

Pathological type	Patients (n)	Mean age (years)	Sex (male/female)	Smoking (yes/no)
Squamous cell carcinoma	14	62.3±8.4	10/4	10/4
Adenoid cystic carcinoma	13	56.4±16.2	6/7	4/9
Adenocarcinoma	4	62.8±13.5	2/2	2/2
Small cell carcinoma	2	69.5±4.9	2/0	2/0
Adenosquamous carcinoma	1	72[a]	1/0	1/0
Plasmacytoma	1	65[a]	0/1	0/1

[a]The median value is provided; the other values are expressed as the mean ± standard deviation.

Table IV. Types of bronchoscopy intervention, complications and therapeutic effects of recanalization of tracheal stenosis.

Item	Patients (n)
Interventional treatment	
Tracheal stent	27
Electric trap	12
APC	39
CO_2 freezing	17
High-frequency electric knife	12
Laser	3
Balloon expansion	1
Anaesthetic method	
Local anaesthesia	47
Local anaesthesia + intravenous general anaesthesia	8
Complications	
Hemorrhage	19
Slight bleeding	12
Significant bleeding (>50 ml)	7
Hypotension	2
Tracheal stricture recanalization	
CR	9 (23.68%)
PR	25 (65.79%)
MR	4 (10.53%)
NR	0

CR, complete response; PR, partial response, MR, mild response; NR, no response; APC, argon plasma coagulation.

28.6% (4/14) were misdiagnosed as having bronchial asthma. Since delayed diagnosis and treatment may impair patient survival (10), these results suggest that clinicians should enhance their awareness of the disease. In cases of poorly controlled bronchial asthma and dyspnea, particularly those with chronic coughing and wheezing, a chest CT or bronchoscopy should be considered in order to exclude tracheal tumors (11,12).

According to the different pathological manifestations, primary tracheal tumors may be divided into different grades, including benign, low-grade or highly malignant. Adult tracheal malignancies are far more common than benign tumors. In accordance with the results of the present study, Urdaneta *et al* (13) reported that squamous cell carcinoma and adenoid cystic carcinoma are the two most common pathological types. In this cohort, the age of the patients suffering from squamous cell carcinoma was greater than that of patients with adenoid cystic carcinoma and the survival time was also shorter than that of patients with adenoid cystic carcinoma. Adenoid cystic carcinoma has a longer median survival and higher survival rate than squamous cell carcinoma, but distant metastasis is more common than in squamous cell carcinoma (14). The positive rate of CD117 in patients with adenoid cystic carcinoma was 88.9% (8/9). It has been previously reported that positive expression of CD117 may have a certain reference value for the diagnosis of adenoid cystic carcinoma (15).

The first treatment of choice for primary tracheal tumors is surgery. For patients with symptoms of severe tracheal obstruction, pre-operative bronchoscopic intervention may effectively improve these symptoms. Studies including that by Chhajed *et al* (16) indicated that in patients with malignant airway obstruction, prior bronchoscopic intervention may improve lung function and may allow lung cancer patients to undergo lung parenchymal preservation surgeries. The length of a tracheotomy is usually limited to 6 cm due to the lack of ideal substitute material. As a consequence, if a tumor involving the trachea is too long and cannot be anastomosed without tension, or it the tumor cannot be removed completely, or by the time the tumor has metastasized and other serious complications arise, the opportunity for surgical resection and the associated benefits are lost (17). Radiotherapy is an alternative treatment for this subset of patients with inoperable malignancies. However, early radiotherapy may not be preferred in cases with severe airway stenosis due to the risk of local tissue swelling, further increase in airway stenosis and even suffocation due to radiography. Recently, a case report on a tracheal primary tumor was published, demonstrating the efficacy of radiation therapy without chemotherapy (18). However, to avoid these risks, pre-operative bronchoscopic interventional therapy may be performed, which may effectively relieve airway obstruction, particularly during tracheal stent placement.

Bronchoscopic intervention has become an important method for the treatment of central airway stenosis.

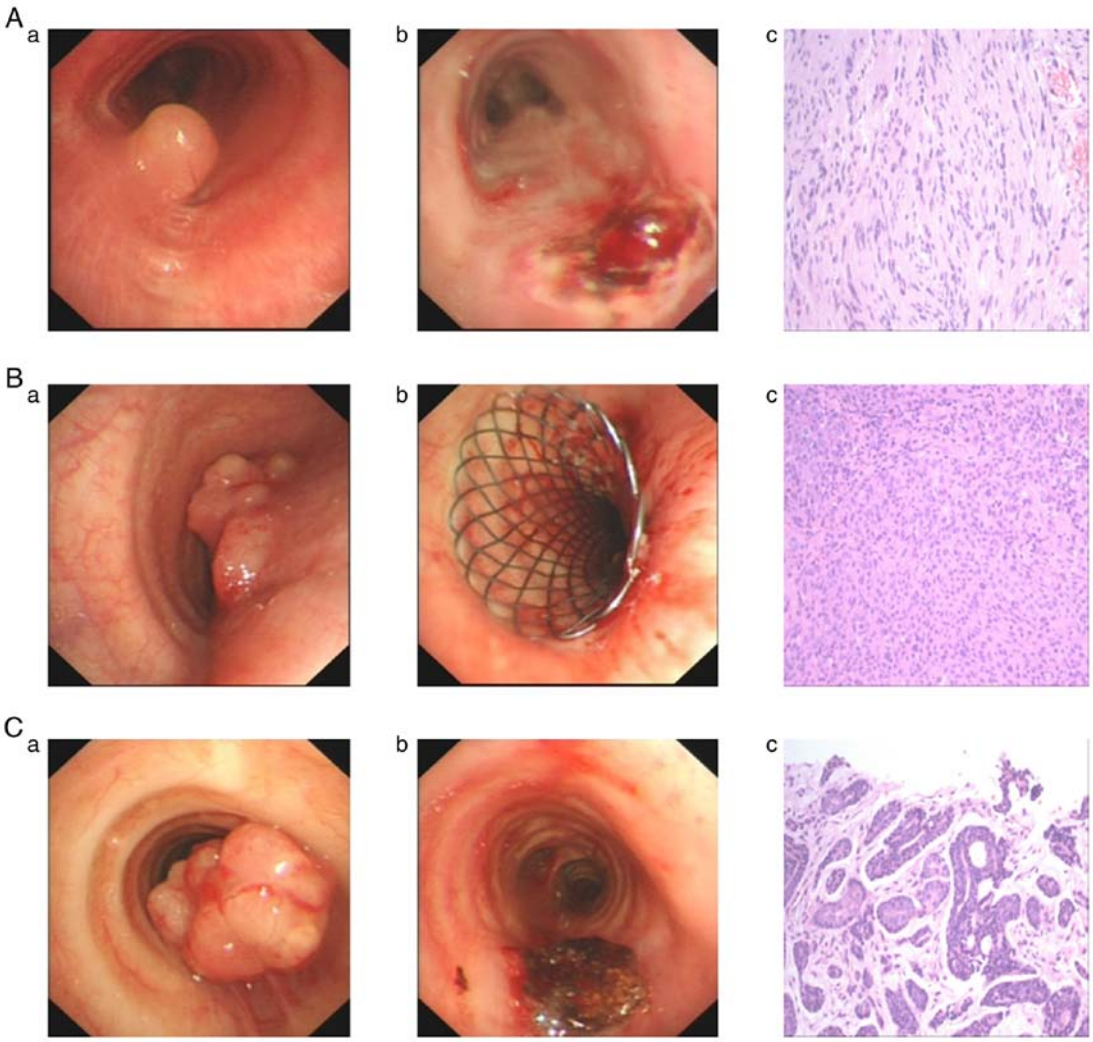

Figure 1. Representative images of typical patients subjected to endotracheal intervention. (A) Schwannoma (A-a) prior to and (A-b) after interventional treatment with bronchoscopy and (A-c) histopathological images. (B) Adenocarcinoma (B-a) prior to and (B-b) after interventional treatment with bronchoscopy and (B-c) histopathological images. C. Adenoid cystic carcinoma (C-a) prior to and (C-b) after interventional treatment with bronchoscopy and (C-c) histopathological images. Histopathological images with HE staining (magnification, x400).

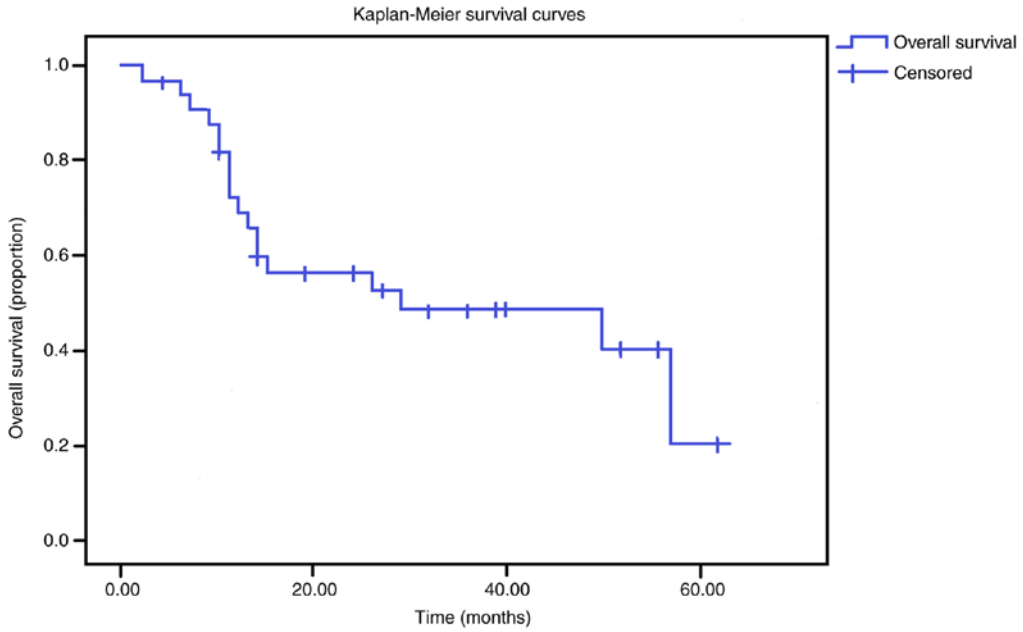

Figure 2. Kaplan-Meier survival curve of 35 patients with primary tracheal malignancies.

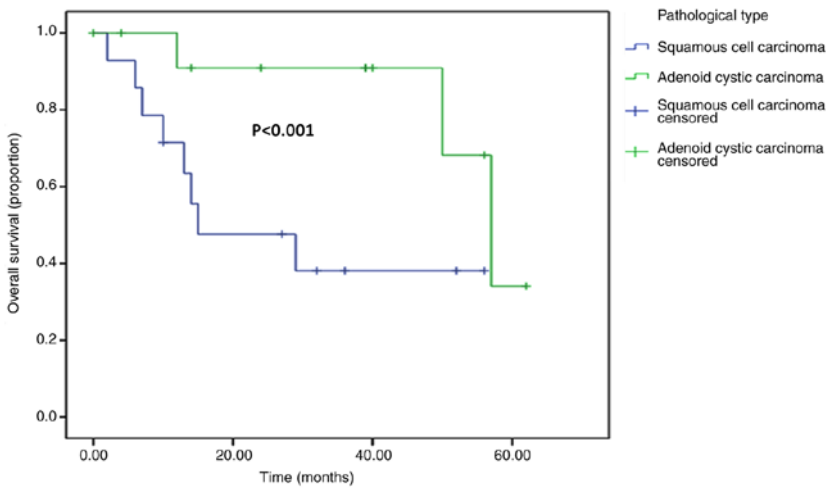

Figure 3. Comparison of survival curves between squamous cell carcinoma and adenoid cystic carcinoma.

Interventional therapy has a unique advantage over surgery in that it leads to the rapid removal of any obstruction caused by tracheal tumors and improves the palliative conditions (19). In the present study, different integrated interventions were used for different clinical manifestations in patients with tracheal tumors, including tracheal stent, high-frequency electric knife, electric snare resection, cryogenic therapy or APC. Laser, electrocautery and APC of bronchial ablations use heat to solidify or evaporate tissues, resulting in tissue damage (20). After interventional treatment, airway obstruction and anhelation symptoms were effectively relieved, which is consistent with the efficacy of interventional treatments in benign and malignant central airway stenosis reported in the literature (21,22).

Interventional treatment of tracheal tumors involving a bronchoscope has been reported to be safe, with the most common complications typically including a relatively small amount of bleeding, which may be easily controlled. Compared to rigid bronchoscopy, flexible bronchoscopy has the advantage of causing less trauma, being more tolerable, having a lower risk and being of lower cost. Based on the present assessment, it is suggested that special attention must be paid to the following considerations during the application of respiratory intervention for primary tracheal tumors: Pre-operative assessment of the existence of large blood vessels should be carefully performed and adequate preparations should be made to prevent the occurrence of life-threatening haemorrhage. One patient of the present study suffered from bronchial artery embolization prior to surgery.

In the field of tracheal tumors, unified TNM staging is yet to be formulated. While survival analyses have proven useful, the results are not comparable between studies due to their differences. A previous study reported that the overall 5-year survival rate of tracheal malignancies was 5-15% and that the 10-year survival rate was 6-7% (23). The prognosis therefore remains poor. Another study reported that patients with surgically treated tracheal squamous cell carcinomas had a 5-year survival rate ranging from 40 to 50% and a 10-year survival rate ranging from 20 to 40% (5). For this group, the overall 1-year survival rate was 69.3%, the 3-year survival rate was 48.7% and the 5-year survival rate was 20.3% (5). The 1-year survival rate of the squamous cell carcinoma patients of the present study was 71.4% and the 5-year survival rate was 38.1%. In recent years, studies have indicated improved survival rates of patients with tracheal tumors with an early definitive diagnosis, specialist surgery and the availability of endotracheal interventional therapy. Overall, previous studies and the present study suggest that endotracheal treatment is a new avenue for providing treatment and relief for patients unsuitable for surgery (24).

In conclusion, treatment of patients with primary tracheal tumor with bronchoscopy intervention therapy results in effectively unobstructed airways, alleviates the symptoms of anhelation, has broad application prospects and may be considered safe. Bronchoscopic intervention may effectively relieve the symptoms of the disease in patients with relevant surgical restrictions and missed surgical opportunities, particularly in combination with radiotherapy or chemotherapy, and may prolong patient survival.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ZRH and DJL designed the experiment. ZHY, JQZ, DZL, YYW and YMK carried out data acquisition, data analysis and statistical analysis together. ZRH, ZHY and DJL carried out literature search and manuscript editing. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Shandong Provincial Hospital Affiliated to Shandong University (Jinan, China).

Patient consent for publication

All patients provided written informed consent.

Competing interests

The authors declare that they have no competing interests.

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