Primary major airway tumors; management and results

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Abstract

Objective: Primary major airway tumors are rare. A retrospective analysis of referral centers experience could be helpful for their management. Methods: Fifty-one patients, including 44 (86%) malignant and seven (14%) benign with primary tumors of subglottis, trachea, carina, and main stem bronchi, were managed in a 14-year period. Based on computed tomography (CT) scan and rigid bronchoscopy findings, those who evaluated as resectable underwent airway resection and reconstruction. The others were managed by one or a combination of these methods: core out, laser, chemotherapy, radiotherapy, and tracheostomy. Follow-up was completed in 88.2%, mean (35.2 ± 33.2 months). Results: Extraluminal extension of the tumor found in CT scan was significantly associated with unresectability (p = 0.006). Thirty-two patients underwent resection with three complications (9%) and one mortality (3%). Nineteen were managed by non-resectional methods; of these, 15 were found unresectable, because of tumor length, extensive local invasion or diffuse distant metastases, and four due to risk–benefit ratio or patient preference. Among 18 patients with adenoid cystic carcinoma 13 (72%) were resected (seven with negative margins). Overall 1-, 2-, 5-, and 8-year survival was 90.9%, 90.9%, 77.9%, and 19.5%, respectively. In unresectable tumors with adenoid cystic carcinoma, overall 1- and 2-year survival was 60% and 40%, respectively. Data analysis found significant association of long-term survival with resection (p = 0.005) but not with negative margins in adenoid cystic carcinoma. Among 15 patients with carcinoid tumors, all were alive at the end of follow-up, except one who died after surgery. Conclusions: Airway resection, if feasible, may extend survival and may even be curative, with low morbidity and mortality, in most patients with major airway tumors. © 2010 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Airway; Tumors; Trachea; Bronchi; Resection; Survival

1. Introduction

Primary major airway tumors are rare and account for less than 0.1% of all tumors [1–3]. They are usually malignant in adults, but benign in children [4]. The most common histologic types are squamous cell carcinoma (SCC) and adenoidcystic carcinoma (ACC), which account for about 2/3 of these tumors [3,5,6].

As they frequently cause nonspecific symptoms and signs and are difficult to be seen in chest X-rays, the patients are usually diagnosed late, with a long history of management for other diseases such as asthma [1,2,5]. The most useful imaging study is computed tomography (CT) scan [1,2,5,7]. It shows the tumor itself, its invasion to the surrounding structures, and distant metastases [1,5,6]. Bronchoscopy is the most important procedure for both tissue diagnosis and initial assessment of tumor resectability [1,3,5–8]. Airway resection and reconstruction can be curative for all benign and slow-growing malignant tumors, such as carcinoids. It may also extend survival or even be curative for most ACCs and SCCs, if they are diagnosed at early stages [1,3,5,8,9].

However, in some cases, resection and reconstruction are not practicable, due to the long segment of the involved airway, the invasion of the tumor to the vital structures, distant metastasis, or poor general condition of the patient [5–9]. In this group of patients, other procedures such as core out via rigid bronchoscopy, laser, stent placement, tracheostomy, T-tube, cryosurgery, photodynamic therapy,
brachytherapy, radiotherapy, and chemotherapy could be beneficial as palliative treatments [5–7]. Because these tumors are rare, it takes a very long time for a center to collect a significant number of patients for valuable data analysis [5,9]. This study describes our experience in the management of these tumors, from a referral academic center.

2. Materials and methods

A retrospective study of our General Thoracic Surgery database was performed for all patients with major airway tumors, from 1994 to 2008. The CT scan reports, bronchoscopic findings, operative notes, and pathology reports were reviewed. All secondary tumors from primary lung cancers, thyroid cancers, esophageal cancers, mediastinal malignancies, as well as metastatic lesions were excluded. Fifty-one patients were then enrolled in the study with primary tumors of the subglottic airway, trachea, and main stem bronchi. All available CT scans were reviewed by a chest radiologist.

All patients, even those who referred to us with a definite tissue diagnosis, underwent a rigid bronchoscopy as an initial evaluation. Precise measurement of the length of the tumor and its distance from the vocal cords and carina, as well as coring out the tumor for a temporary palliation and providing tissue for pathologic diagnosis, were performed by rigid bronchoscopy. If the patient had dysphonia or the tumor was suspected to be at the level of the subglottis, laryngoscopy would be performed right before bronchoscopy. All patients with malignant tumors were evaluated for distant metastasis. Surgical resection was considered according to the length of the tumor, its locoregional invasion, the extent of distant metastases, and general condition of the patient.

After segmental resection of the airway, if more resection were possible, margins would be checked by frozen section. Unresectable tumors were managed with one or some of these modalities: core out by rigid bronchoscopy, laser, tracheostomy, chemotherapy, or radiotherapy.

Based on the location of the tumor, surgical approach was through a transverse collar incision with or without partial sternotomy, or thoracotomy.

Exploration without resection and tracheostomy alone were not considered as surgical treatments.

During tracheal resection, extensive regional lymph node dissection was not performed, because it might destroy the segmental blood supply of the remaining trachea for anastomosis. Although the adjacent lymph nodes were resected with the tumor, for malignant main stem bronchial tumors, however, mediastinal lymphadenectomy was performed.

All patients with resected tumors underwent a fibroptic bronchoscopy 1 month after surgery, to make sure that the anastomosis was well healed. Then, those who required adjuvant therapy were referred to the radiotherapy—oncology department.

Follow-up was based on medical records and was completed by direct patient contact. Survival was calculated from the day of surgery or the day of bronchoscopy in unresected cases. The study was approved by the Ethics Committee and the informed consent was waived by the chairman of the Ethics Committee. In this study, t-test, Fisher’s exact, log-rank, nonparametric Kruskal–Wallis, and Mann–Whitney tests were used for data analysis.

3. Results

There were 51 patients (27 men), with a mean age of 41.4 ± 19 (6 months to 81 years). Forty-four (86.3%) patients had malignant and seven (13.7%) had benign tumors. Benign tumors occurred in younger patients (t-test, p < 0.01). Table 1 summarizes the histologic types and location of the tumors. The most common histologic type was ACC (35.3%).
The vast majority of tumors, 26 (51%) were in the trachea. The most common histologic type in main stem bronchi was carcinoid tumors (82%). The chief complaint was dyspnea in all patients except those with carcinoids, who mostly presented with cough. The mean duration of symptoms was 8.4 ± 8.7, 21.5 ± 24.3, and 24.5 ± 32.6 months in patients with SCC, ACC, and carcinoid tumors, respectively (non-parametric Kruskal–Wallis test, \( p = 0.43 \)). This symptom duration was significantly longer in unresected ACCs (42.7 months) than in resected ACCs (13.4 months) (Mann–Whitney test, \( p = 0.03 \)). Cigarette smoking was found in 66.7%, 27.8%, and 26.7% of patients with SCCs, ACCs, and carcinoids, respectively (Fisher’s exact test, \( p < 0.01 \)).

Findings of 41 available CT scans are presented in Fig. 1. Extraluminal extension of the tumor showed increased risk of unresectability (Fisher’s exact test, \( p < 0.01 \)).

Fifteen (29.4%) out of 51 tumors were found unresectable—of them 12 based on their CT scan and bronchoscopic findings, and three after surgical exploration. Irrespective of resectability, airway resection was not performed in four patients (two carcinoids, one inflammatory myofibroblastic tumor, and one hamartoma) because of risk–benefit ratio or patient preference.

Resection was performed in 32 (62.7%) patients. None of the SCCs were resectable; however, 13 (72.2%) ACCs and 12 (80%) carcinoids were resected. Eight patients with malignant tumors were found to have distant metastases—of them four (two ACCs and two carcinoids) with lung metastases underwent surgical resection; laryngectomy, tracheal resection, left main stem bronchus resection, and left-upper lobectomy, respectively.

4. Unresected tumors

Fifteen tumors were found unresectable due to one or two of these reasons: tumor length in 11, mean 70.7 mm (40–120 mm), locoregional invasion to vital structures in six, and distant metastasis in four. Non-resectional management of these patients and those four patients who did not undergo surgery because of risk–benefit or patient choice is shown in Table 2. In this group of patients, one patient who had an ACC with tracheoesophageal fistula died in hospital due to the progression of the disease and its complications.

5. Resected tumors

A total of 32 patients underwent airway resection; of them 28 had malignant tumors. Neoadjuvant therapy was performed in none of them. Malignant tumors were 13 ACCs, 12 carcinoids, and one of each synovial sarcoma, embryonal rhabdomyosarcoma, and mucoepidermoid carcinoma. Benign tumors were one of each granular cell tumor, hemangioma, leiomyoma, and chondroma.

Frozen-section examination of resected airway margins was done for all patients except three with ACCs in whom more airway resection was not feasible. The final pathology results of all patients showed microscopic airway margin involvement in four patients, including those three patients and the patient with mucoepidermoid carcinoma. There were also microscopic deep margin involvements in four patients (three ACCs and one leiomyoma). The mean length of the resected airway in 18 cases of tracheal and laryngotracheal resection was 32.3 ± 10.2 (15–55) mm. All resection and reconstruction procedures are shown in Table 3.

Mediastinal lymphadenectomy was performed in all 11 patients with carcinoid tumors of main stem bronchi. In nine patients, all lymph nodes were free of tumor, and in two

![Fig. 1. CT scan findings in patients with resected and unresected tumors.](https://academic.oup.com/ejcts/article-abstract/39/5/749/353339)

### Table 2. Non-resectional managements.

<table>
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<tr>
<th>Pathology</th>
<th>Core out</th>
<th>Core out + Tracheostomy</th>
<th>Core out + Chemo radiotherapy</th>
<th>Core out + Laser</th>
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</table>

\(^a\) SCC: Squamous cell carcinoma.

\(^b\) ACC: Adenoid cystic carcinoma.
patients, only one lymph node in each was positive for tumor metastasis.

Three complications occurred. There was one anastomotic stricture, which responded well to one time of rigid bronchoscopy and dilatation. The second complication was a fistula between the end tracheostomy site and the esophagus in a patient who underwent a laryngectomy. That patient had an ACC of the subglottic airway, who had undergone laser therapy many times before surgery. This complication was managed by gastrostomy, jejunostomy, and supportive care. The fistula healed spontaneously. The third complication was a massive hemoptysis in a patient, who had undergone a left-upper-sleeve lobectomy for a carcinoid tumor on the 22nd postoperative day. The patient was emergently transferred to the operating room and was found to have a fistula between the pulmonary artery and bronchial suture line. Unfortunately, the patient died (mortality, 3.1%).

Eleven of 13 resected ACCs and the patient with synovial sarcoma underwent postoperative radiotherapy, with a dose of 5000 rads for margin-negative and 5500 rads for margin-positive cases.

6. Follow-up

Follow-up was complete in 88.2% of patients. The mean follow-up time was 35.2 ± 33.2 months. In patients with resected ACCs 1-, 2-, 3-, 5-, and 8-year survival was 91 + 1%, 91 + 1%, 78 + 1%, 78 + 1%, and 19.5%, respectively. In patients with unresected ACCs, 1- and 2-year survival was 60% and 40%, respectively. The last patient in this group died after 3 years.

Median survival was 68.8 ± 1 months in resected and 21.2 ± 20.8 months in unresected ACCs (p < 0.01). Fig. 2 compares the survival of resected and unresected ACCs. Median survival was 68 ± 22.7 months in margin-negative and 92.8 month in margin-positive ACCs.

In the resected ACC group, there were two patients with lung metastasis at diagnosis. The first one was a 37-year-old female with diffuse bilateral lung metastases. She underwent tracheal resection and reconstruction. Airway margins were positive in microscopic examination. At follow-up, she had been very well for 6 years after surgery. Then, she gradually developed dyspnea and finally died 8 years after surgery with dyspnea and dysphonia. The second case was a 41-year-old male with unilateral lung metastases, who underwent laryngectomy. He had been very well for 7 years, but died 8 years after surgery because of progressive dyspnea secondary to bilateral diffuse lung metastases.

At the end of follow-up, all patients with resected carcinoid tumors were alive with no symptoms and no recurrence, even the patient with one positive mediastinal lymph node.

Of three patients with unresected carcinoids, one, who decided not to undergo surgery and left the hospital by her choice, was lost in follow-up. Two other patients were alive 19 and 28 months at the end of follow-up with no symptom or sign. Both patients with carcinoid tumor and lung metastasis were alive and symptom free 1 and 7 years after surgery.

The patient with synovial sarcoma developed a local recurrence in the neck 7 years after surgery. She underwent surgical resection of the mass (no airway resection) and adjuvant chemoradiotherapy. She has been alive and symptom free at the end of follow-up.

Two patients with mucoepidermoid carcinoma and rhabdomyosarcoma, who underwent tracheal resection and reconstruction, were alive after 7 years with no complaint. Median survival of six patients with SCC, who were all unresectable, was 17.7 ± 7.5 months.

The patient with poorly differentiated carcinoma with neuroendocrine differentiation died after 2 months due to congestive heart failure. The patient with clear cell carcinoma died after 9 months in his home due to a massive hemoptysis.
At the end of follow-up, patients with resected benign tumors were alive, symptom free and with no recurrence. Of those with unresected benign tumors, the patient with inflammatory myofibroblastic tumor was symptom free. The patient with hamartoma had a recurrence after 3 years and underwent a re-endoscopic resection. He was symptom free with no recurrence at the end of follow-up. The patient with tracheal papillomatosis had a complaint regarding his tracheostomy tube.

7. Discussion

Major airway tumors are rare; hence, designing a prospective clinical trial to find the most reliable guidelines for managing these tumors is impractical. Retrospective data analysis of referral centers may be useful for the management of this rare group of patients.

In our patients, benign tumors were seen more in younger patients as observed by others [1,4]. However, in young patients, we have to keep the malignant tumors in our differential diagnosis as we had four carcinoids and three other types of malignant tumors in patients younger than 20 years old.

The vast majority of benign tumors and slow-growing malignant tumors (such as carcinoids and ACCs) are treated as asthma for dyspnea and cough in a long period of time. However, rapidly growing malignant tumors are usually diagnosed sooner because of airway obstruction and hemoptysis. This time difference has been shown in our patients and another study [5], although it was not statistically significant in our series. There was a statistically significant difference between the symptom duration of resected ACCs and unresected ACCs. This shows that earlier diagnosis may lead to a more effective treatment. When a major airway tumor is suspected, rigid bronchoscopy and CT scan are performed. In our center, if a tumor was found to invade more than 50% of the length of the trachea during rigid bronchoscopy, it is considered unresectable. This is because the submucosal and extraluminal extension of tumors are usually further than their intraluminal growth and it will be very difficult to resect more than 50% of the trachea and make a tension-free anastomosis. This safe limit is 4 cm between the lower trachea and the contralateral main bronchus for carinal tumors in our center.

The extraluminal extension of the tumor found in the CT scan was associated with increased risk of unresectability in our patients. Although this finding per se is not a contraindication for surgical resection, it may be helpful for definite decision making in borderline cases, such as those who are very high-risk patients or whose tumors invade about 50% of tracheal length.

In spite of precise rigid bronchoscopy under general anesthesia and taking multiple biopsy specimens for evaluation of the exact length of the tumors, as well as taking a chest CT scan for all patients, 3 (8.6%) of our 35 surgically explored patients, were found to have unresectable tumors. To decrease this negative exploration rate, other diagnostic procedures such as virtual bronchoscopy, endoluminal ultrasound, and magnetic resonance imaging (MRI) have been proposed by others [2,10,11]; however, none of them is capable to predict all cases. For submucosal extension of tumors such as ACCs, optical coherence tomography may be helpful in future [12].

Many studies in different parts of the world have shown that resection extends the survival of patients with ACC [3,5,8,9,13–17]. In our ACCs, the resected group had a significantly longer survival as well. In the resected ACC group, those with positive margin had, surprisingly, a longer survival than those with negative margins. Massachusetts General Hospital experience reported by Gaissert and colleagues [5], which is the largest series with the longest follow-ups, showed that the negative margin is associated with longer survival. Therefore, our result in this regard seems to be unreliable due to the low number of patients. However, if we put all margin-negative and margin-positive resected patients in one group and compare them with unresected patients, the survival will be significantly longer in the resected group [3,5,14]. Therefore, it seems that resection of ACCs even with positive microscopic margins is beneficial to patients.

Because ACCs are slow-growing tumors and their lung metastases may remain silent for several years [3], we believe that the presence of a couple of lung metastases is not a contraindication for airway resection [1,9]. This could prevent airway obstruction and its dreadful suffocation until the patient dies from his lung metastases [3]. The rationale of this approach resembles airway resection for papillary or follicular thyroid cancers invading the airway, accompanied by some lung metastases [5]. Surgical resection in two patients with ACC and multiple lung metastases led to approximately 8 years’ survival with no airway obstruction.

We recommended adjuvant radiotherapy to all 13 patients with resected ACC [3,5,9,13]; of them, 11 completed the full course of their radiotherapy. Although the exact role of adjuvant radiotherapy in improving survival is not clear [3,5,9,18], it is recommended to all patients with ACC, even those with negative margins, because, sometimes, the microscopic tumor is very close to the margins and the tumor itself is very radiosensitive.

Some epidemiologic studies in the USA and Europe showed that the majority of primary tracheal tumors, which were locally advanced and unresectable at the time of diagnosis, were SCCs and managed by nonsurgical procedures [1,19,20]. This was the same in our SCC patients, although Gaissert and colleagues [5] showed that 60% of their SCCs were resectable.

The most frequent histologic type of tumors in main stem bronchi was carcinoid in our patients (82%), as observed by others [6]. Resection and anastomosis of airway with or without pulmonary resection could be a curative treatment for carcinoid tumors [21,22], even in node-positive patients [21], although mediastinal lymph node involvement may worsen the prognosis [23].

In medically high-risk patients with carcinoid tumors and those who do not want to undergo surgical resection, endoscopic resection could give the patient a long disease-free survival, or even be curative if the tumor is limited to the inside of the lumen of the airway [21,24].

Benign airway tumors, if resectable, are cured by resection and reconstruction and most of them do not have any tendency for recurrence [8].
In case of unresectability or when the risk of surgery is high, endoscopic procedures could also be successful treatments [8, 9].

Finally, we have to consider the novel approaches for tracheal replacement in those patients, who have a long segment tumor and no locoregional or distant metastases [25].

8. Conclusion

Major airway resection and reconstruction, if feasible, is potentially curative in all patients with benign tumors and in most patients with carcinoid tumors. It may also extend survival in patients with ACCs with low morbidity and mortality.

References


Editorial comment

Primary major airway tumors: management and results

Keywords: Airway; Trachea; Tracheal tumor; Tracheal surgery; Bronchial diseases; Statistics; Survival analysis

In a retrospective single-center study, Shadmehr and colleagues from Tehran, Iran, proposed to analyze their experience with primary tumors of the airways [1]. Over a 14-year period, 51 patients with primary (malignant, n = 44; benign, n = 7) tumors of subglottis, trachea, carina, and main stem bronchi were managed in their reference center. A total of 32 patients underwent surgical resection with a mortality rate of 3% (n = 1). Nineteen patients were treated by nonsurgical methods. Fifteen of them were not resectable because of tumor length, extensive local invasion, or diffuse distant metastases. Four of them were not operated upon because of risk—benefit balance or patient preference. For