

## Adenoid Cystic Carcinoma of the Trachea: a Report of Seven Cases and Literature Review

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**Background:** Adenoid cystic carcinoma (ACC) of the trachea is rare. The clinical manifestations, natural history, and responses to therapy differ from those of other malignant tracheal tumors.

**Method:** In this retrospective study, we examined pathological records of patients in the Department of Pathology at Chang Gung Memorial Hospital from 1990 through 2002. There were five male patients and two female patients with ages that ranged from 21 to 55 years. For these seven patients the clinical manifestations and period from initial symptoms to diagnosis, treatment and outcome are presented.

**Results:** Hemoptysis, nonproductive cough, dyspnea, chest pain and weight loss were the frequent early manifestations. Five patients had tumors in the lower area of the trachea, two had tumors in the upper area of the trachea. In a patient with the tumor in the upper area of the trachea, the tumor involved the cricoid ring, larynx, and subglottic area. In one patient with the tumor in the lower area of the trachea, the tumor invaded the right lower lobe of the lung. The longest survival time was more than 10 years.

**Conclusions:** ACC is a rare primary tracheal malignancy. The time from first symptoms to diagnosis varied, ranging from weeks to more than 1 year. Complete surgical resection provides the patient with the best chance of prolonged survival or even complete remission.

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**Keywords:** adenoid cystic carcinoma, trachea.

Primary tumors of the trachea are rare. Tracheal malignancies occur in only 0.2 per 100000 people per year accounting for under 0.1% of the cancer deaths per year.<sup>(1)</sup> Adenoid cystic carcinoma (ACC) is the second most common malignant tracheal tumor after squamous cell carcinoma.<sup>(2)</sup> The clinical symptoms, natural history, and responses to different therapeutic approaches to ACC of the trachea differ from those of other malignant tracheal tumors. The

clinical and pathologic features of ACC of the trachea were initially reported in 1859 by Billroth.<sup>(3)</sup> Characteristically, ACC is a gradual, low malignancy tumor usually associated with prolonged survival. However, when it is associated with distant metastases survival is frequently less than 2 years.<sup>(4)</sup> Complete surgical resection offers the patient a better opportunity of prolonged survival or complete remission. The addition of photon- or electron-beam

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radiation seems to influence local control but does not affect survival. In this study, we presented seven cases of primary ACC of the trachea that were found during the previous 13 years at the Chang Gung Memorial Hospital and reviewed reports published in the literature. The clinical manifestations, diagnostic approaches, therapy selections, and actuarial data are discussed. This study provides more information about the rare primary tracheal malignancy in Chinese people in Taiwan.

### METHODS

In this retrospective study, we examined pathological records of patients in the Department of Pathology at the Chang Gung Memorial Hospital from 1990 through 2002. Eight patients had the histopathological diagnosis of ACC of the trachea. Of these patients, the medical records of seven were available. For these seven patients the clinical manifestations including sex, age, symptoms and period from initial symptoms to diagnosis, treatment and outcome are presented. The results were illustrated and were compared with results presented from previous studies.

### RESULTS

There were five male patients and two female patients whose ages ranged from 21 to 55 years. Hemoptysis (5/7) and nonproductive cough (4/7) were the most common clinical symptoms, followed

by dyspnea (2/7), chest pain (2/7), and weight loss (2/7) (Table 1). The time from first symptoms to diagnosis of ACC ranged from 1 to 12 months (average = 6 months). Two patients were treated as asthma for 1 year because of chronic cough, even though one of the patients had coexistent hemoptysis. Five patients had tumors in the lower part of the trachea, two in the upper part of the trachea. In a patient with a tumor in the upper part of the trachea, the tumor involved the cricoid ring, larynx, and subglottic area. In one patient with a tumor in the lower part of the trachea, the tumor invaded to right lower lobe of the lung. Three patients (cases 1, 3, and 4) received surgical or bronchoscopic resections of their tumors and postoperative radiation therapy (Table 2). Case 1 underwent laryngotracheal resection and total thyroidectomy. Case 3 refused laryngotracheal resection and underwent bronchoscopic tumor excision. Case 4 received right pneumonectomy due to involvement of the right lung. The postoperative complications included pharyngeal leak and symptomatic hypocalcemia (case 1), and ileus (case 4). Cases 1, 3 and 4 received radiotherapy after their operations. Two patients (cases 2 and 5) received radiation treatment only. Case 7 received chemotherapy with FLEP (5-Fluorouracil, Leucovorin, Etoposide and Cisplatin).

The longest survival time was more than 10 years (case 2) (Table 2).

### DISCUSSIONS

We presented seven patients with primary tra-

**Table 1.** Presenting Symptoms and Duration of Symptoms

	Patient No.							Total
	1	2	3	4	5	6	7	
Age	38	35	27	21	51	31	55	
Gender	♀	♂	♀	♂	♂	♂	♂	
Tumor location	lower	upper	lower	upper	lower	lower	lower	
Dyspnea	-	+	+	-	-	-	-	2
Hoarseness	-	-	-	-	-	-	-	0
Wheeze	-	-	-	-	-	-	-	0
Stridor	-	-	-	-	-	-	-	0
Hemoptysis	-	+	+	-	+	+	+	5
Chest pain	+	-	+	-	-	-	-	2
Weight loss	+	+	-	-	-	-	-	2
Cough	+	-	-	+	+	+	-	4
Time from first symptoms to diagnosis (mo)	6	6	1	12	12	1	6	Average 6

**Table 2.** Treatment Modalities of Seven Patients

Patient No.	Surgery Alone	Chemo-therapy	Radiation	Surgery + Radiation	Local recurrence and Metastasis	Survival time
1	-	-	-	Total larynx, total thyroid, and tracheal resection with primary anastomosis + XRT† (10,500 cGy)	-	1 y 4 mo
2	-	-	XRT (4400cGy)	-	Recurrence 4y	10 y 3 mo
3	-	-	-	Tracheostomy, bronchoscopic coring + XRT (6600cGy)	Recurrence 3y	7 y 6mo
4	-	-	-	Right pneumoectomy + XRT (6600cGy)	-	5 mo
5	-	-	XRT (5000 cGy)	-	-	2 y 2mo
6	-	-	-	-	-	1 y 2mo
7*	-	FLEP	-	-	-	2y 15 d

Tumor location: patient 1,3,5,6,7 all in lower portion of trachea, 2, 4 upper portion of trachea.

\* Only chemotherapy FLEP (5-Fluorouracil, Leucovorin, Etoposide and Cisplatin) done two years after diagnosis.

† XRT: radiation therapy

cheal ACC and reviewed the reports in the literature. In contrast to tracheal squamous cell carcinoma (SCC) that occur in men approximately 90% of the time, primary tracheal ACC is found in men and women with almost equal frequency.<sup>(1,5,6)</sup> The results of a previous study of 174 patients with tracheal ACC showed a female-to-male ratio of 1.1:1.0 (90 women and 84 men).<sup>(1)</sup> However, there were more male patients in our study (ratio 5:2). The limited number of patients may account for the difference. The ages reported for tracheal ACC ranged from 45 to 60 years. The ages for our seven patients ranged from 21 to 55 years. In a previous study, the two youngest reported patients were 15 and 18 years of age, and the oldest was 80 years old.<sup>(1,7)</sup> Patients with ACC usually present with symptoms such as coughing, wheezing and dyspnea and are often treated for asthma for months to years before being correctly diagnosed.<sup>(8)</sup> Patients with tracheal malignancies demonstrated the most frequent symptoms such as wheezing or stridor, dyspnea, hemoptysis, and coughing. Few patients presented with hoarseness and weight loss.<sup>(5,9)</sup> Two studies that specifically considered people with ACC of the trachea found similar complaints, mainly dyspnea, hoarseness, and wheezing or stridor. Few patients had hemoptysis, coughing or weight loss.<sup>(1,7)</sup> In our seven patients, hemoptysis and coughing were the most common presenting complaints. The presenting course of tracheal ACC appeared much more indolent than that of tracheal SCC.<sup>(10)</sup> In a review of 208 patients with tracheal tumors, patients with ACC had symptoms three

times as long as patients with SCC (12 months versus 4 months, respectively).<sup>(5)</sup> In our seven patients the average time for presenting symptoms was 6 months prior to diagnosis. In 44 previously reported patients with tracheal ACC, the location was 45.5% (n = 20) in the upper part of the trachea, 20.5% (n = 9) in the middle part of the trachea, and 34% (n = 15) in the lower part of the trachea.<sup>(6,7, 11)</sup> The site of the tumors in our seven patients included two in the upper part of the trachea and five in the lower part of the trachea. In this study one patient (case 4) had a tumor in the lower part of the trachea, and the tumor invaded to right lower lobe of the lung. The patient died 5 months after he underwent pneumonectomy. Houston et al. presented that tumor location correlated with prognosis.<sup>(12)</sup>

ACC spreads most commonly by direct extension, submucosal or perineural invasion, or hematogenous metastasis. More than 50% of patients with tracheal ACC have hematogenous metastases. Pulmonary metastases are the most common and can remain asymptomatic for many years. Metastases to the brain, bone, liver, kidney, skin, abdomen, and heart have also been reported.<sup>(2,5,13)</sup> Local recurrence of tracheal ACC is common and occurs at an average of 51 months after the primary treatment.<sup>(5)</sup> Metastases occurred in two of our patients, and the site of metastasis was the lung. The metastases occurred 36 to 48 months after diagnosis of ACC. Lymphatic spread is uncommon in patients with tracheal ACC. Only one author reported lymphatic spread in tracheal ACC. Five of 38 patients (13%)

**Table 3.** Reported Results of Resection for Adenoid Cystic Carcinoma of the Airway

	Grillo	Perelman	Regnard	Pearson
No. of patients	60	56	65	38
Years of follow-up	26	20	23	32
Operative mortality	8 (13%)	8 (14%)		3 (9%)
Actuarial survival (%)				
5 yr		66	73	79
10 yr		56	57	51
Mean survival (mo)				
Radiation only	39			74
Resection and radiation	108			88

had regional nodes positive for metastases.<sup>(2)</sup> Positive nodes in the head and neck ACC correlated with decreased 10-year survival.<sup>(13)</sup> However, the effects of positive nodes on the survival of tracheal ACC are unclear. Treatment options include surgery alone, radiation therapy alone, or a combination.<sup>(2,5,6,8,13)</sup> The surgical operations are primary tracheal resection and reconstruction, primary tumor resection, and endoscopic resection, either by coring or using a laser. However, Grillo and Marthisen<sup>(14)</sup> recommended tracheal resection and primary reconstruction. Both complete and incomplete resections can be done with an acceptably low operative mortality rate and with the expectation of long periods of

survival in a majority of patients.<sup>(14)</sup> Maziak et al. demonstrated a trend of better survival with complete rather than incomplete resection, 69% vs. 30% of 10-year survival, respectively.<sup>(1)</sup> Complete resection is defined as no remaining gross, palpable, or microscopic tumors.<sup>(5)</sup> In previous studies the operative mortality rate was an average of 12% (range, 5%-14%).<sup>(2,15,16)</sup> In this study, one patient (case 1) received total larynx, thyroid and tracheal resection due to tumor invading and died 1 year and 4 months after the surgery. One patient (case 4) received right pneumonectomy due to lung involvement and died 5 months after surgery. One patient (case 3) underwent bronchoscopic coring and had survived for 7 years and 6 months at the time of this writing. There were no operative deaths in our patients and the extent of tumor involvement seemed to be predisposing to the survival time. ACC usually has significant local invasion at the time of detection, making surgical resections more extensive. Reported complications include tracheoesophageal fistula, pharyngeal or esophageal leak, anastomotic separation, wound dehiscence, vocal cord paralysis, temporary tracheotomy, dysphagia, ileus, and pneumonia.<sup>(2,16)</sup> Case 1 experienced three of the complications (tracheoesophageal fistula, tracheal stenosis, and pharyngeal leak) mentioned above and case 7 had esophageal

**Table 4.** Percentage of Patients with Different Presenting Complaints

Symptom	% Patients with symptom (n =7)	% Patients with symptom (n = 6)*	% Patients with tracheal ACC with symptom (n = 51) <sup>†</sup>	% Patients with tracheal malignancies with symptom (n = 285) <sup>‡</sup>
Dyspnea	28.6	66.7	72	49
Hoarseness	-	33.3	43	22
Wheezing or stridor	-	33.3	39	60
Cough	57.1	66.7	23	41
Hemoptysis	71.4	16.7	20	44
Weight loss	28.6	16.7	14	18.2
Throat pain	-	-	-	22.6

**Abbreviations:** ACC = adenoid cystic carcinoma.

\* Data from Azar et al. (6 patients) (Taraneh Azar, Fadi w. Abdul-Karim, Harvey M. Tucker. Adenoid cystic carcinoma of the trachea. Laryngoscope 1998;108:1297-1300)

† Data compiled from two studies: Hajdu et al. (7 patients) (Hajdu SI, Huvos AG, Goodner JT, Foote FW, Beattie EJ. Carcinoma of the trachea: Clinicopathologic study of 41 cases. Cancer 1970;25:1448-56.; Maziak et al. (38 patients) (Maziak DE, Todd TRJ, Keshavjee SH, Winton TL, Norstrand PV, Pearson FG, Adenoid cystic carcinoma of the airway: thirty-two year experience. J Thorac Cardiovasc Surg 1996;112:1522-32.)

‡ Data compiled from three studies: Regnard et al. (208 patients) (Regnard JF, Fourquier P, Levasseur P. Results and prognostic factors in resections of primary tracheal tumors: a multicenter retrospective study. J thorac Cardiovasc Surg 1996;111:808-13.); Houston et al. (53 patients) (Houston HE, Payne WS, Harrison EG, Olsen AM. Primary cancer of the trachea. Arch Surg 1969;99:132-9.); Fields et al. (24 patients) (Fields JN, Rigard G, Emami B. primary tumors of the trachea: results of the radiation therapy. Cancer 1989;63:2429-33.)

stricture.

Radiation therapy for ACC of salivary glands has been found to provide improved local control of tumors but did not affect survival.<sup>(5, 17)</sup> This treatment has not been investigated for tracheal ACC. Clinically many patients are amenable to receiving resection of the airway with removal of diseased tissues. Most tumors respond to radiotherapy which often results in long periods of remission for patients treated with radiotherapy alone. Two patients in this study (cases 2 and 5) received radiotherapy only and had survival of 10 years and 3 months and 2 years and 2 months, respectively. Although radiotherapy alone is not recommended in treatment of tracheal ACC, it might provide local disease control.

The role of post-operative adjuvant radiotherapy remains uncertain. It is reasonable to assume that adjuvant radiation therapy may be beneficial and likely delays or reduces the incidence of local recurrence in the airway. Adjuvant radiation was performed in all three patients (cases 1, 3 and 4) who received primary resection in this study. Although two of them died within 5 months (case 4) and 1 year and 4 months (case 1) after surgery, the cause of death should be attributed to extensive involvement of the upper airway and lungs. With limitations of randomized comparison, it still seems reasonable to recommend adjuvant radiotherapy for all patients undergoing resection, and certainly for those in whom the final pathologic examination identifies residual tumors at the resection margins.

The number of patients who have received chemotherapy is limited, and the results are considered unfavorable. According to the results of the few investigations, chemotherapy does not appear to have a role in the treatment of ACC of the trachea.<sup>(18)</sup> One of our patient (case 7) received chemotherapy only with 5-fluorouracil, Leucovorin, Etoposide, and cisplatin due to symptomatic pulmonary metastases. The symptoms improved and she survived for 2 years.

According to the results of previous studies the 5-year survival ranged from 66% to 100% and the 10-year survival ranged from 51% to 62% for patients with tracheal ACC regardless of the treatment.<sup>(12, 16)</sup> Two of our patients survived for more than 5 years. Case 2 survived for 10 years and 3 months, although, pulmonary metastasis developed 4 years, after the diagnosis of tracheal ACC (Table 2).

Similarly, case 3 survived for 7 years and 6 months, although, local recurrence developed 3 years after the initial diagnosis of tracheal ACC.

In summary, ACC is a rare primary tracheal malignancy. Hemoptysis, nonproductive cough, dyspnea, chest pain and weight loss are the common initial symptoms. The time from first symptoms to diagnosis varied, ranging from weeks to more than 1 year. This disease is commonly misdiagnosed as asthma. Complete surgical resection provides the patient with the best chance of prolonged survival or even complete remission. Post-operative radiotherapy may have some effect on local control but did not affect survival rate.

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## 氣管腺樣囊狀癌七個病例報告及文獻回顧

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**背景：**氣管腺樣囊狀癌非常少見。臨床表徵、病程和對治療的反應與其他類型的氣管癌症不同。

**方法：**我們蒐集七個病例報告，以及回顧早期文獻。

**結果：**在本篇報告以及過去的研究顯示咳血、乾咳、喘、胸痛和體重下降為最常見的初始症狀。從病人表現初始症狀到被診斷疾病的時間為數週到一年。這些病人剛開始容易被誤診為氣喘而治療一段時間。因此在臨床上對於不明原因慢性咳嗽的病人需考慮接受支氣管鏡檢查。

**結論：**完全手術切除能給予病人較長存活時間的機會，甚至有些病人可被治癒。放射治療對局部控制也有一些效果。

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**關鍵字：**腺樣囊狀癌，氣管。

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