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Original Article

Adenoid cystic carcinoma of the tracheobronchial tree: clinicopathologic and immunohistochemical studies of 21 cases

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Abstract: Aims: To review retrospectively 21 cases adenoid cystic carcinoma of the tracheobronchial tree (TACC) with emphasis on their clinical and pathologic features, treatment and the possible prognostic factors. Methods and results: 21 cases TACC diagnosed by surgical biopsy or resection at the Peking Union Medical College Hospital (PUMCH) over 10 years. Patients aged 24-69 years (median, 49 years), 6 men/15 women. Cough (18/21), dyspnea (14/21) and hemoptysis (10/21) were the most frequent manifestations. 15 patients had tumors in trachea. Ten patients had pathologically positive margin (n = 11). Immunohistochemically, BCL-2, CD117, P16, type IV collagen, SMA and P63 were positive (20/20); GFAP was focally positive (4/20); TTF-1 and P53 were negative (0/20). Ki-67 index ranged from 2% to 35%. Fifteen patients had followed up, 13 of which received postoperative radiotherapy. The median relapse-free survival (RFS) was 56.9 months and the 5-year RFS was 48.6%. By univariate analysis, postoperative radiotherapy had favorable prognostic significance ($P < 0.05$). Conclusions: TACC, which is mainly located in primary trachea or bronchus, is difficult to be detected at early stage. The tumors are not likely to be completely removed by surgery, and postoperative radiotherapy is helpful for reducing the likelihood of recurrence and metastasis.

Keywords: Tracheobronchial tree, adenoid cystic carcinoma, immunohistochemistry

Introduction

Adenoid cystic carcinoma (ACC), first described in the 1850s [1], is a low malignant tumor and accounts for 22% of all malignant salivary gland tumors [2], and represents about 10% of head and neck tumors [3, 4]. Primary ACC of the trachea is very uncommon. Tracheal malignancies occur in only 2 per 1,000,000 people per year, accounting for less than 0.1% of the cancer-induced deaths per year [1, 5]. Tracheal adenoid cystic carcinoma (TACC), which originates from the submucosal glands of the airway, accounts for about 10-20% of the malignant tracheal tumor [6]. Patients with ACC are often treated for asthma or chronic bronchitis for months to years before being correctly diagnosed [6, 7]. Tracheal tumors at the level of the thyroid can be misinterpreted as invasive thyroid cancer upon initial diagnosis [8].

In the current study, we have reviewed a retrospective series of 21 patients with primary ACC of the tracheobronchial tree in PUMCH from 2000 to 2013, with emphasis on their clinical and pathologic features, treatment and the possible prognostic factors.

Materials and methods

A total of 21 cases of primary TACC have been retrieved. All operations were carried out in PUMCH from 2000 to 2013, accounting for 0.21% of all the 9800 primary histologically diagnosed malignant pulmonary tumors. No patient had a history of salivary gland tumor.

The clinical data included gender, age, symptoms, period from first symptom to initial diagnosis, history of smoking, bronchoscopical findings, treatment and outcome were reviewed. All tissues were fixed in 10% neutral buffered for-

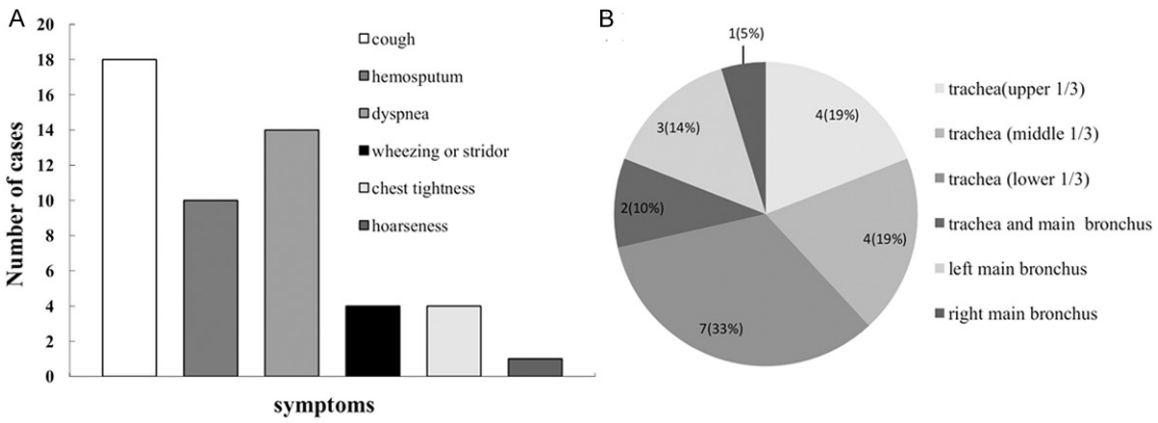

Figure 1. A: The symptoms of the TACC. B: The locations of the TACC.

malin, routinely processed, and embedded in paraffin. Hematoxylin-eosin stained sections were reviewed by two experienced pathologists independently and the tumors were graded as proposition defined by Batsakis et al. [9]. The investigated parameters included anatomical location, histologic type, neural and/or vascular involvement, lymph nodes metastasis, mitotic count, and necrosis status.

The immunohistochemical staining of CD117, BCL-2, P63, P53, P16, TTF-1, Ki-67, SMA, GFAP, type IV Collagen were performed in 20 cases. They were performed on 4 μm thick unstained sections cut from representative formalin-fixed paraffin-embedded blocks. For all markers, positive control and negative control were used. For GFAP and SMA, signals appeared as tan particles in cytoplasm were positive. For BCL-2 and CD117, tan granules on membrane or in cytoplasm were positive. For P63, P53, TTF-1, Ki-67, tan particles in nucleus were positive. For P16, tan particle in nucleus and/ or cytoplasm was positive. No tan particle in corresponding locations was negative.

Statistical analysis

The 15 patients who had follow-up data were further subjected to survival analysis. Survival curves were calculated according to the Kaplan-Meier method and compared using the log-rank test. The level of significance was defined as $P \leq 0.05$ (two tailed). Patient follow-up time was calculated using reverse Kaplan-Meier analysis. All statistical analyses were performed using SPSS software for windows, version 20 (SPSS Inc., Chicago, IL) for windows.

Results

Clinical data

Twenty-one TACC patients aged 24-69 years (median, 49 years), are composed of 6 men and 15 women. 5 men had history of smoking. All patients were symptomatic. The most common symptoms were cough, dyspnea and hemoptysis (**Figure 1A**). The time of diagnosis from the onset of symptoms ranged 1-84 months (median, 7 months) and 8 patients (38%) were more than 1 year. One patient was first treated as chronic obstructive pulmonary disease; two other patients were considered as thyroid tumors, and the remaining 18 patients were considered as tracheal neoplastic lesions. The location of tumors had been shown in **Figure 1B**. 8 patients experienced pulmonary function test, 5 (62.5%) of which showed obstructive ventilation dysfunction, 2 (25%) showed mixed ventilation dysfunction and 21 patients underwent bronchoscopy, 20 of which revealed the mass growing into lumen of trachea (**Figure 2A**). Tracheal lumen was only mild narrow without any nodule in the remaining patient whose pulmonary function test was normal. Six patients received biopsy by bronchoscopy, 4 patients experienced partial resection of tumor, 10 patients had tracheal or bronchial segmental resection and 1 patient had laryngotracheal resection.

Pathologic findings

In 11 patients received tracheal or bronchial resection or laryngotracheal resection, the length of resected trachea ranged 1.5-4.0 cm

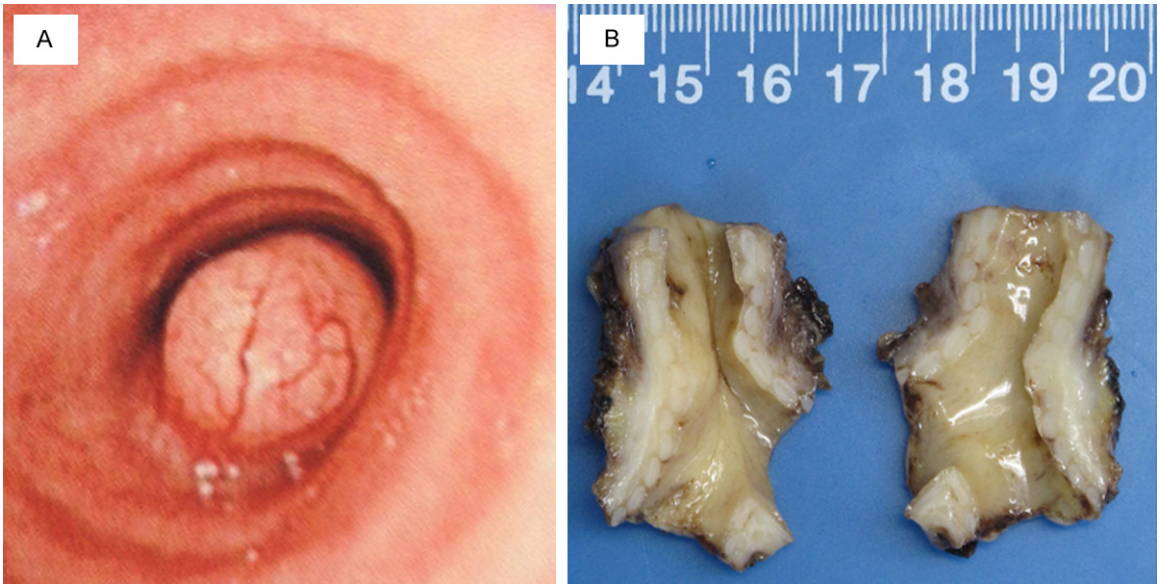

Figure 2. A: Intraluminal adenoid cystic carcinoma of the middle trachea diagnosed in one patient who had a cough and dyspnea for six months. B: Gross appearance of a resected tracheobronchial specimen of adenoid cystic carcinoma. The wall of the lower of the trachea near carina became thicken and airway was stenosis.

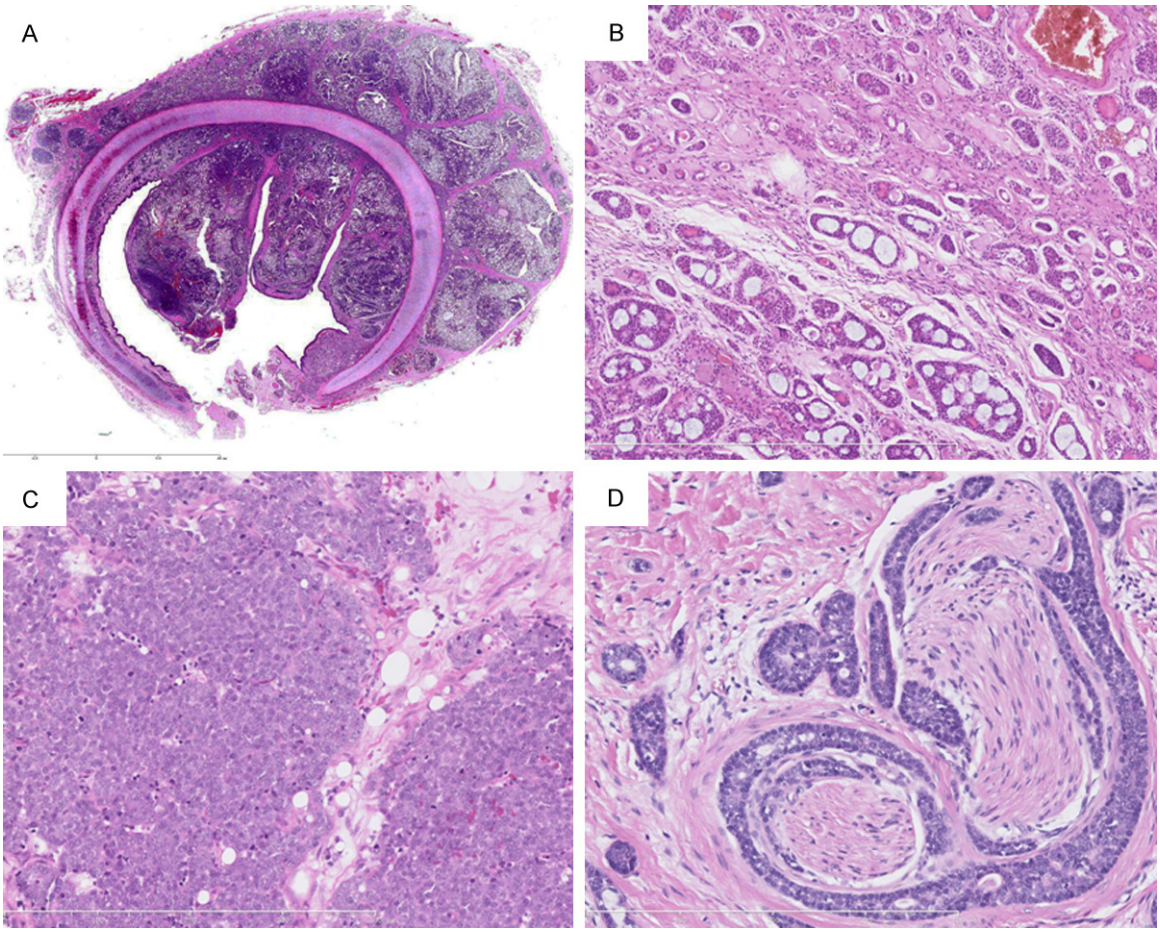

Figure 3. A: Cross-section of the trachea demonstrating adenoid cystic carcinoma with intraluminal growth pattern and infiltration of the trachea wall. The tumor cells exhibiting cribriform pattern (H&E, lower power). B: Adenoid cys-

tic carcinoma showing cribriform/tubular pattern with excessive extracellular basal lamina material and mucinous material (H&E, x 150). C: A solid pattern demonstrated diffuse tumor cells with heavy nuclear chromatin distribution (H&E, x 300). D: High power illustrating TACC grew with perineural invasion (H&E, x 300).

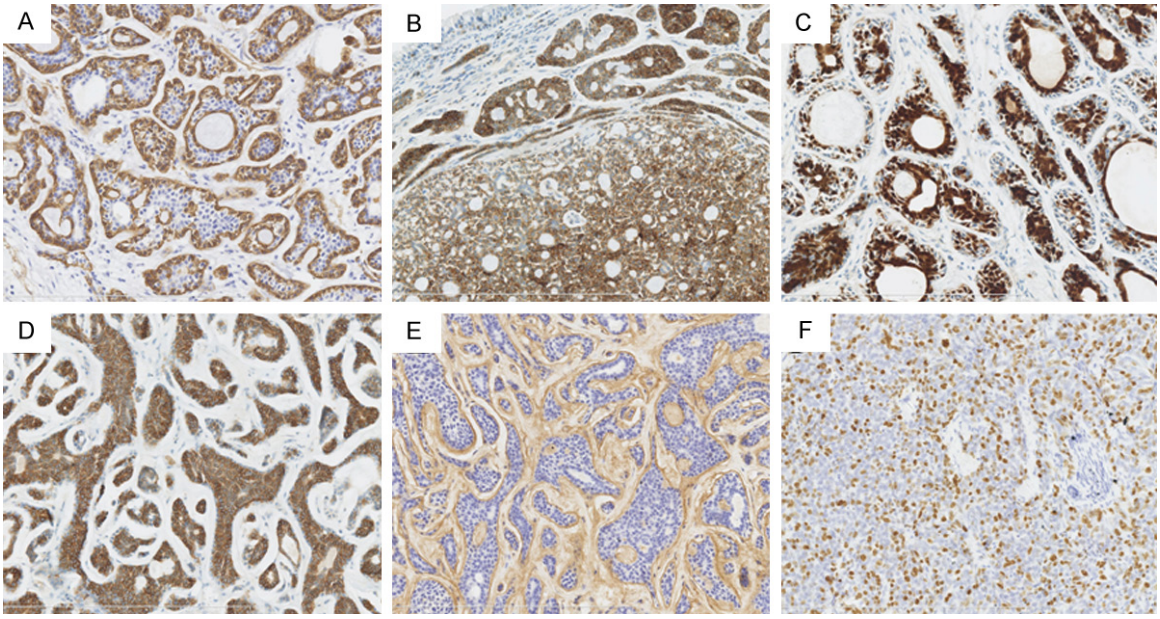

Figure 4. A-F: Immunohistochemistry. A: SMA highlighted the myoepithelial cells within the tumours (x 300). B: Bcl-2 showing positive in both epithelial cells and myoepithelial cells (x 300). C: P16 showing positive in epithelial cells (x 300). D: CD117 showing positive in epithelial cells (x 300). E: Collagen IV showing the basal lamina material (x 300). F: Ki-67 showing positive of nuclear in a solid pattern and the index is 35% (x 300).

(median, 2.5 cm), in which 10 tumors had intraluminal growth pattern, and 1 tumor was wall-infiltration (**Figure 2B**); 8 tumors were single nodule (**Figure 3A**) and 2 were multiple. The tumor surface was usually smooth and the size ranged 1.0-2.5 cm (median, 1.5 cm). The cut surface was solid with tan-gray color. Local invasion through the tracheal wall were observed in all 11 patients (11/11). Microscopically, in all 21 cases, 8 cases showed predominantly cribriform pattern, 5 cases showed tubular pattern predominantly, and 8 cases showed mixture pattern (**Figure 3B**). 17 cases were grade I, 3 cases were grade II, a case was grade III (**Figure 3C**). Uniform cytomorphology within the tumor, including basaloid cells with small, angulated, hyperchromatic nuclei, indistinct nucleolus and scant cytoplasm. The mean mitotic figure was 1.7/mm^2, however, > 10/mm^2 in solid area of a grade III tumor. Necrosis was only observed in two tumors. Perineural invasion (**Figure 3D**) was found in 10 patients (10/11), lymph node metastasis in 2 (2/11), vascular involvement in 2 (2/11), and pathologically positive margin was found in 10 (10/11). Except for the 6 biopsy cases, in the remaining 15 cases including 4 cases partial resection of tumor, thyroid gland invasion was found in 3 patients.

Immunohistochemical findings: SMA (**Figure 4A**) and P63 were positive in myoepithelial cells (20/20), BCL-2 (**Figure 4B**) was expressed in both epithelial and myoepithelial cells ranging 10%-95% of all tumor cells (20/20, median, 70%); P16 (**Figure 4C**) was expressed mainly in epithelial cells ranging 10%-80% of all tumor cells (20/20, median, 35%); CD117 (**Figure 4D**) was expressed mainly in epithelial cells, with positive cells ranging 5%-90% of all tumor cells (20/20, median, 60%) and was focally expressed in myoepithelial cells in 4 patients. Type IV collagen (**Figure 4E**) was positive in all cases (20/20). GFAP was positive focally in myoepithelial cells (4/20). TTF-1 and P53 were negative in all patients (0/20). Ki-67 (**Figure 4F**) index ranged 2%-35% (median, 12%).

Outcomes and survival analysis

Fifteen patients had follow-up data (range: 4-120 months), 13 of which received radiother-

Table 1. Results of 15 follow-up patients with TACC

No.	Age/ gender	Solid area	Necrosis	Ki-67 index	Follow-up time (months)	RT (dose)	CHT	Time of recurrence, metastasis or died after resection (months)	Recurrence or metastasis (sites) or died
1	38/M	25%		10%	113	56 Gy		96	Recurrence
2	49/M			15%	9			8	Recurrence
3	37/F		Yes	12%	24			24	Metastasis (lung, pleura)
4	52/F	60%	Yes	35%	39	56 Gy	Yes	24	Metastasis (lung, bone)
5	35/F			15%	50	60 Gy	Yes	12	Metastasis (lung)
6	56/F			8%	47	56 Gy			No
7	62/F	10%		18%	4	56 Gy			No
8	44/F			12%	93	50 Gy			No
9	45/F			10%	44	56 Gy	Yes		No
10	38/F	10%		8%	120	60 Gy			No
11	60/F			15%	49	48 Gy			No
12	33/F			12%	40	56 Gy	Yes		No
13	51/M			12%	19	56 Gy			No
14	57/F			10%	5	60 Gy			No
15	56/M			6%	6	18 Gy		6	Died of surgery complication

RT: Radiotherapy; CHT: Chemotherapy.

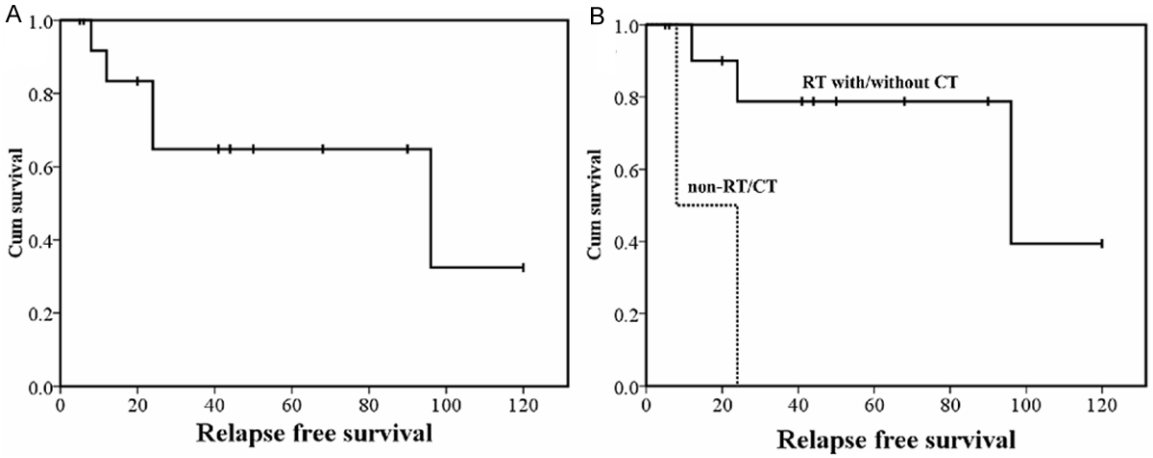

Figure 5. A: Relapse free survival of the 15 TACC patients with follow-up. B: Relapse free survival according to RT treatment.

apy (RT) alone; 4 received both RT and chemotherapy (CT). Only one patient died of surgical complication at the sixth months after tracheal resection; three patients had metastasis; two patients had local recurrence; nine patients had no proof of recurrence or metastasis (details in **Table 1**). The median RFS was 56.9 months, and the 5-year RFS was 48.6%. 6 patients were lost to follow-up after biopsy or resection.

The RFS curves of the patients were shown in **Figure 5A**, **5B**. By univariate analysis, RT had favorable prognostic significance ($P < 0.05$). Age, location, solid pattern, necrosis and operational manner had no prognostic significance. Ki-67 index of more than 10% had some tendency with higher RFS, but the result did not reach statistical significance ($P > 0.05$) (**Table 2**).

Discussions

ACC in the tracheobronchial tree is rare. We reported 21 patients of primary TACC, whose incidence among all primary pulmonary tumors was 0.21% in our hospital and represented approximately 12.4% of ACC of the whole body.

Table 2. Univariate analysis of prognostic factors for patients with TACC

Parameter	RFS		
	RR	95%CI	*P* value
Age			0.803
≥ 40	Reference group		
< 40	0.786	0.111-5.582	
Site			0.407
Bronchi	Reference group		
Trachea	2.468	0.253-24.077	
Solid area			0.440
≥ 10%	Reference group		
< 10%	0.494	0.077-3.191	
Necrosis			0.116
Yes	Reference group		
No	0.245	0.034-1.753	
Ki-67 index			0.092
≥ 10%	Reference group		
< 10%	0.021	0.000-87.960	
RT/CHT treatment			0.015
RT with/without CHT	Reference group		
Non-RT/CHT	7.528	1.044-54.277	
Surgery			0.508
Local resection	Reference group		
Segmental resection	0.547	0.086-3.486	

RFS: relapse-free survival; RR: relative risk; CI: confidence interval.

Clinically, in accordance with literature [3, 5, 9], TACC occurred mainly in the main trachea (71.5%) in our series, especially in the lower 1/3 section of trachea (33.3%). In contrast to the reports in the literature of ACC with no gender predilection [10, 11], there was a female predominance in our series (15:6). Productive cough (85.7%), dyspnea (66.7%) and hemoptysis (47.6%) were the most common manifestations. The time of diagnosis from the onset of symptoms in 8 patients (38%) were more than 1 year, which suggest that TACC is difficult to be detected at early stage. Although 87.5% of patients who experienced pulmonary function test were abnormal in our series, 61.9% of patients regretted that they did not undergo pulmonary function test. Even the tumors (95%) mainly manifested as intraluminal growth pattern via bronchoscopy, it is helpful to avoid misdiagnosis via pulmonary function test and bronchoscopy examination.

Because of mucosal or sub-mucosal spread along the airways, TACC usually has an invasive growth pattern and is likely to invade the nerve at an early stage [4]. In our series, histopathologically, 90.9% of cases underwent segmental bronchial or tracheal resection were margin positive and had perineural invasion, indicating that tumor was likely to invade nerve and therefore was difficult to be resected totally. Only one patient had negative margin but who was aphonia. Cervical lymph node metastasis is a rare event in ACC [2, 10]. Instead, the tumor spreads through a hematogenous route with distant metastasis [2, 10]. In our series, 18.2% of cases underwent lymph node dissection were found positive, which is consistent with the literature, but the same rate were found vascular tumor thrombus or vascular invasion. So we do not have the proof that tumor is easier to spread by hematogenous route than by lymph node. ACC is composed of 2 cell types: adenoid and myoepithelial cells, but the 2 cell types are hard to be distinguished microscopically [2]. In our series, we could easily see the outer layer of myoepithelial cells and inner layer of adenoid cells in tubular pattern, but difficult to distinguish in cribriform pattern. Recently, more and more cases have been reported of malignant transformation [12, 13], thus ACC has been classified to 4 grades according to the proportion of solid area and if there is high grade transformation [14]. In our study, there was no tumor with high grade transformation and this is consistent with the literature that high grade transformation is very rare [12, 13].

Immunohistochemically, the related studies have focused on CD117, p16, BCL-2, p53 and Ki-67 etc., especially the relationship of markers' expression and prognosis at present [12, 15, 17-20]. It was reported that CD117 plays an auxiliary role, over-expression of EGFR and lack of CD117 expression were associated with worse prognosis [15]. Zhou et al. [14] proposed that CD117 and p63 was positive simultaneously, indicating the patient has a worse prognosis. In our study, all cases expressed CD117 in focal or patchy pattern, only one grade III case expressed CD117 and p63 simultaneously, and the patient relapsed and metastasized

24 months after resection. P16 can be expressed in many tumors, but rare studies were published about p16 and ACC [16, 17], which suggested that p16 protein over-expression was frequently observed in ACC of the head and neck, through a non-HPV-related mechanisms. However, in a minority of cases-p16 staining was diffuse and strong positive in more than 70% of the tumor cells, which was supposedly associated with co-existing HPV infection [16]. In our series, 80% of cases expressed P16, indicating that P16 played some roles in the tumorigenesis of ACC, but it was not clear if it is relevant to HPV infection, and HPV status detection is needed in the future study. We also observed that P16 were variably expressed in the epithelial cells, and rarely in the myoepithelial cells. BCL-2 in ACC was expressed more strongly than some of the benign tumors of salivary, and it can be used when combined with p53 [17]. In our series, BCL-2 was positive in both 2 type cells, but more myoepithelial cells were positive than epithelial cells. Increased P53 expression may also be an independent marker for poor prognosis [2]. In our study, P53 was negative in all cases. Increased Ki-67 expression may also be an independent marker for poor prognosis [18]. In our study, Ki-67 index ranged from 2% to 35% (median, 12%). We would tend to presume that a Ki-67 index of more than 10% had some correlation with higher RFS, but the result does not reach statistical significance. It is reported that GFAP can be positive in ACC [2], but only focally positive could be seen in a few cases. In this connection, we draw the conclusion that GFAP is not helpful for diagnosing the disease.

Recently, a number of salivary gland neoplasms have been associated with recurrent chromosomal abnormalities and resulting gene fusions. This includes the translocation t (6; 9) resulting in MYB-NFIB fusion in ACC [21, 22]. This fusion leads to the deregulation of the expression of Myb and is likely to be a critical step in oncogenesis for ACC. West RB et al. [22] found that over 50% of ACC harbor MYB translocation and increased Myb expression. MYB translocation by FISH and Myb expression by immunohistochemistry are needed in our future study.

The differential diagnosis of TACC includes several tumors originating from trachea and bronchus [2, 20], especially, basal cell adenoma, pleomorphic adenoma, mucoepidermoid carcinoma, basal cell adenocarcinoma, epithelial myoepithelial carcinoma, neuroendocrine carcinoma and adenocarcinoma, etc. Morphology and immunohistochemistry are very useful. Thyroid carcinoma with tracheal invasion is uncommon and TACC at the level of the thyroid can be misinterpreted as invasive thyroid tumor upon initial diagnosis [8]. 3 cases in our series were found to have upper tracheal wall and thyroid gland invasion and it was difficult to distinguish it from thyroid cancer before pathological examination, and TTF-1 is helpful. Because the relatively high extent of p16-positive cases in our series, the differential diagnosis also includes HPV-related carcinoma with adenoid cystic-like features, although this small series only identified sinonasal primary sites [23].

Although ACC is a low malignant tumor and complete resection is the best management, more often than not this is impossible because of the late diagnosis and its special location [11, 24]. TACC of more than 6 cm of the trachea along with the relative failure of tracheal grafts is difficult to be resected [3], different from ACC of salivary gland. ACC can recurrence locally or spread hematogenously with distant metastasis to lung, bone, and brain [2]. The 5 and 10 years overall survival rate is 52%-91%, 29%-76%, respectively [1, 3, 5, 6, 10, 11]. Studies reveal that RT plays an important role in the treatment of ACC which is unresectable, so RT is the most favorable treatment to these patients [21]. Combination operation with radiotherapy can be more effective treatment [11]. Chemotherapy is not effective for ACC [25]. In our series, median length of trachea resection was 2.5 cm. The surgery was more conservative than literature, but 1 patient was aphonia who received laryngotracheal resection radically. Fifteen cases had follow-up data; the median RFS was 56.9 months and the 5-year RFS was 48.6%, 13 of which received postoperative radiotherapy (RT), with median dose was 56 Gy. Our studies confirmed the role of RT, which has prognostic significance ($P < 0.05$). In the three metastasizing patients, the lung was involved in all patients, the bone and the pleura in 1 patient respectively. However, 9.3-13.3% of operative deaths were reported [1, 26], arguing that surgery is extremely complicated and requires a prudent study and punctilious surgical technique. In our series, only one patient died of the surgical complica-

tion. We believe that our operative deaths are lower because surgery was more conservative and treatment relied on RT more. The result confirmed that RT combined with resection can delay patients relapse and metastasis.

The prognostic factors include P53 expression, Ki-67 index, solid pattern, high grade transformation and tumor location [2, 10, 12, 13, 18]. In our series, P53 was negative in all cases. Age, location, solid pattern, necrosis and operational manner had no prognostic significance. Ki-67 index of more than 10% have some tendency with higher RFS, but the result did not reach statistical significance. Owing to the limited number of cases, we could only find some tendency. More cases were needed to get a reasonable conclusion.

In conclusion, TACC is mainly located in the primary trachea or bronchus and difficult to detect at early stage. It often takes a long time from the first symptoms to initial diagnosis. The tumors are not likely to be completely removed by operation. Postoperative radiotherapy is very helpful for reducing the recurrence and metastasis.

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Disclosure of conflict of interest

None.

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