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Original Article

Primary pulmonary adenoid cystic carcinoma: clinicopathological analyses of 12 cases

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Abstract: Background and objectives: Adenoid cystic primary pulmonary carcinomas (adenoid cystic carcinomas or ACCs) are rare tumors, so we described the clinical and pathological features of these tumors and related these findings with diagnosis and prognosis of ACC, comparing our data to the existing literature. Methods: Clinical and pathological features of 12 ACC cases were observed and described. Immunohistochemical EnVision staining, fluorescent PCR detection, and FISH were used to characterize tumor samples and the literature was reviewed. Results: Of the 12 ACC cases (7 male; average 53.1 years-of-age; range 33-78 years), the chief presentation symptom was cough, followed by expectoration, gasping, and bloody sputum. Microscopically, histopathology revealed cribriform, tubular, or solid cords. CD117 was overexpressed in glandular epithelia in 9 cases and calcitonin and thyroid transcription factor-1 (TTF-1) were overexpressed in 4 cases. One case was positive for *EML4 ALK* gene rearrangement. Conclusion: ACC is a low-grade malignant tumor with poor prognosis and high recurrence and metastases. TTF-1 expression indicates a primary tumor and CD117 expression is not significant to prognosis.

Keywords: Adenoid cystic carcinoma, diagnosis, prognosis; immunohistochemistry, fluorescence PCR, FISH

Introduction

Primary salivary-type lung tumors are rare, comprising approximately 0.1-0.2% of all lung cancers [1, 2]. These tumors are derived from small salivary glands in the respiratory system and are of three histological subtypes: adenoid cystic carcinomas (ACCs), mucoepidermoid carcinomas (MEC), and less common epithelial-myoepithelial carcinomas (EMC) [3-5]. ACCs usually occur in the trachea and central bronchi and few cases have been reported to arise peripherally in smaller bronchi [6, 7]. ACCs are well described low-grade malignant tumors that can extensively invade inside and beyond the bronchial wall. ACC prognosis is often poor and the survival rate is low. Also, resection is difficult because of the tumor location and its invasiveness. Thus, to better understand this rare tumor type, we studied 12 ACC cases of the primary trachea and bronchi.

Materials and methods

ACC samples (N=12) from the Department of Pathology in the First Affiliated Hospital of Xinjiang Medical University were collected from January 2003 to June 2014. All resected specimens were fixed in 10% neutral buffered formalin (pH 7. 4), embedded in paraffin, cut into 4-μm sections, and stained with hematoxylin and eosin (H&E).

Immunohistochemistry

Immunohistochemistry was used to measure protein expression in 12 paraffin-embedded primary pulmonary ACC tissues as previously described [8]. All markers were incubated with sections overnight at 4°C. Markers included CK (mouse monoclonal antihuman anti-body clone:C50; 1:50; Fuzhou Maixin Biotechnology, Fuzhou, China), P63 (mouse monoclonal antihuman anti-body clone:4A4; 1:100; Fuzhou Maixin Biotechnology, Fuzhou, China), TTF-1 (mouse monoclonal antihuman anti-body clone:SPT24; 1:50; Fuzhou Maixin Biotechnology, Fuzhou, China), CD117 (mouse monoclonal antihuman anti-body clone:YR145; 1:50; Fuzhou Maixin Biotechnology, Fuzhou, China), Ki-67 (mouse

monoclonal antihuman anti-body clone:MIB-1; 1:50; Fuzhou Maixin Biotechnology, Fuzhou, China). The second antibody was from an IHC reagent kit (Zhongshan Biotechnology Company, Beijing, China). After diaminobenzidine (DAB) staining, sections were counterstained with hematoxylin. Only the plasma membrane and cytoplasm stained positive for CK and CD117. For P63, TTF-1, Ki-67, only the nucleus was positively stained. Sections were evaluated by staining intensity (-, no positive cells; +, <10% positive cells; ++, 11%< positive cells <50%; +++, >50% positive cells)

Multiplex real-time quantitative PCR (RT-PCR)

RT-PCR was performed on paraffin-embedded sections from 12 ACC patients. Total DNA was extracted from ACC tissues using a QIAamp DNA Tissue Kit (Biomart; Beijing; China), according to the manufacturer's instructions. Extracted DNA was measured with a Micro-Ultraviolet Spectrophotometer (Thermo Nanodrop 2000). Then DNA was serially diluted to obtain standard solutions (20 ng/μl) for use. Amplification for TaqMan probes reactions was performed in a 30 μl reaction volume, using 3.0 μl TaqMan Universal Master Mix 2X (Biomart; Beijing; China). RT-PCR conditions were as follows: 95°C for 10 min; 40 cycles of 95°C for 15 s and 60°C for 60 s. If a mutation in the sample (FAM channel) was amplified and the value of Ct was <35, mutation results were positive; if the Ct value was >38 or there was no amplification, results were negative. If 35<Ct≤38, and was the same after repeated experiments, mutation results were suspected to be positive.

Fluorescence in situ hybridization (FISH)

The ALK copy number of can be determined by direct FISH. An ALK Dual Color Break Apart FISH Probe (DakoCytomation) was used to obtain the ALK gene copy number located on chromosome 2p23. A PathVysion ALK probe kit (LOT: 450607, Abbott Molecular, Chicago, Illinois) was used for FISH analysis. Slides were hybridized with prewarmed probes for the ALK gene (orange) overnight at 37°C. In brief, sections were de-paraffinized using xylene, rehydrated, and pretreated using a Vysis solution kit (Histology FISH Accessory kit). Probes were added to the sections, coverslipped, sealed with rubber cement, and placed in a Dako hybridizer. Sections and probes were co-denatured for 6 min at 78°C, followed by annealing at 42°C overnight. After hybridization slides were washed in 2 × SSC (with detergent) at 78°C for two min followed by two min in 2 × SSC at room temperature. Then, sections underwent dehydrating in ethanol three times for 3 min. Slides were counterstained and embedded with a 4,6-diamidino-2-phenylindol·2HCL (Vysis). FISH signals for each locus-specific FISH probe were assessed under an Olympus microscope (Olympus, Tokyo, Japan) equipped with a triple-pass filter (DAPI/green/orange). For a patient to be included, 100 evaluable cells were assessed. Signal quantification was performed under high magnification (× 1,000). The entire area of the tumor tissue was evaluated for each case, and all nuclei were assessed for orange (marker) and green (reference) signals.

Positive signals were indicated by 2 signals that were rearranged or "broken apart" more than 2 signal diameters apart. A sample was considered positive if >50 cells out of 100 (>50/100 or >50%) were positive and a sample was considered negative if <10 cells out of 100 (<10/100 or <10%) were positive. Samples were considered equivocal if 10-50 cells (10-50%) were positive. For equivocal samples, a second reader evaluated the slide and the first and second cell counts were added and a percent was calculated out of 200 cells (average percent of positive cells). If the average percent positive was <15% (<30/200), the sample was considered negative. If the average percent positive was >15% (>30/200), the sample was considered positive.

Results

Patient characteristics

Of the enrolled patients (N=12), 7 were male (mean age 53.1 years-of-age; 33-78 years-of-age). In 5 cases the tumor was in the trachea; in 3, the tumor was in the main bronchi (1 in left; 2 in right), and for 4 cases, the tumor appeared in the segmental bronchi (3 in left; 1 in right). Patients with these tumors complained of cough and bloody sputum lasting from 50 days to 20 years. Bloody sputum was observed in 7 ACCs occurring once or occurring over 60 days. Also, tight chest, shortness of breath, and wheezing were documented for 8 ACCs (lasting

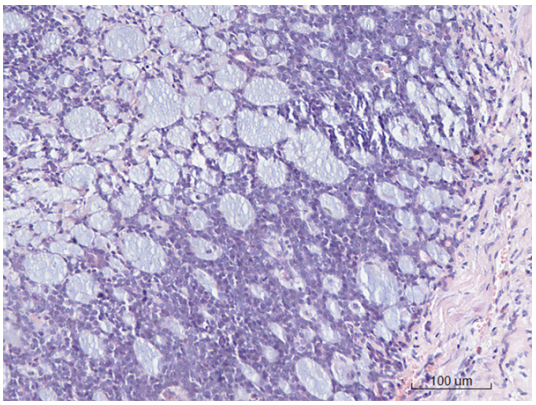

Figure 1. ACC show cribriform-like structures with mucus; H&E STAINING, 20 × magnification.

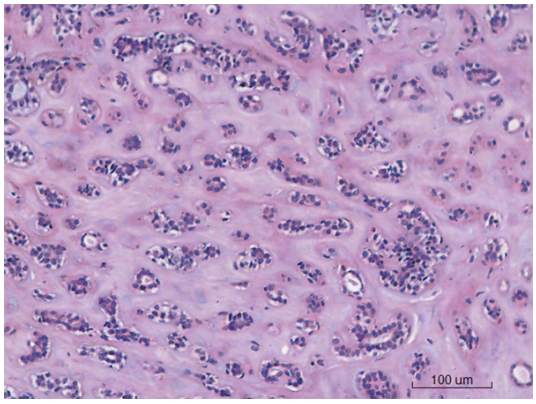

Figure 2. Focal tubular structure in ACC; H&E STAINING, 20 × magnification.

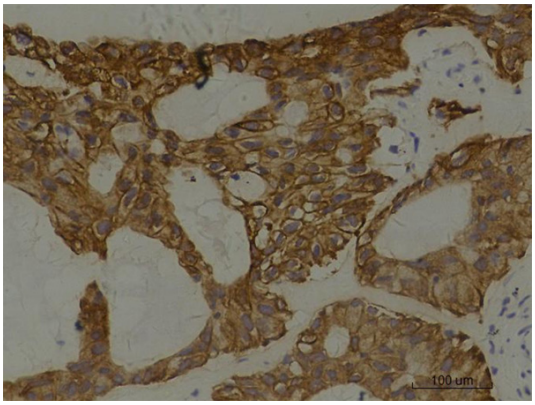

Figure 3. Expression of AE1/AE3 in ACC; H&E STAINING, 20 × magnification.

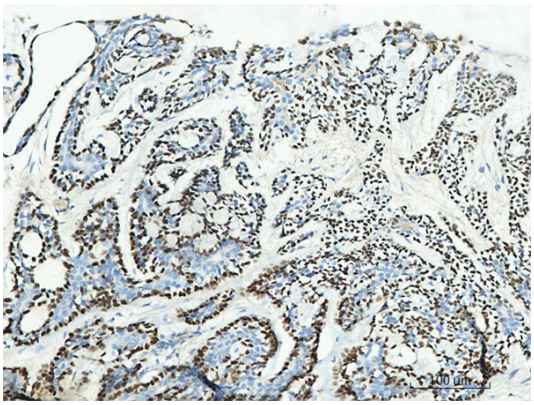

Figure 4. Expression of P63 in ACC; H&E STAINING, 20 × magnification.

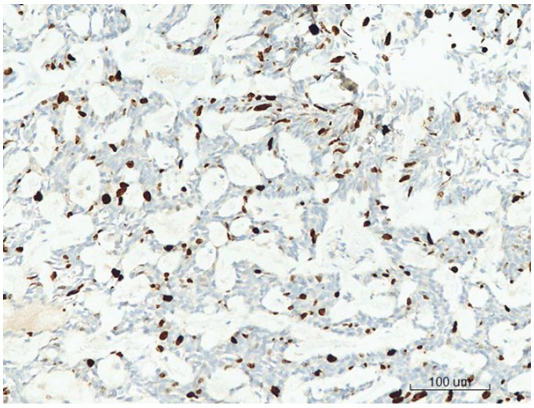

Figure 5. Expression of Ki-67 in ACC; H&E STAINING, 20 × magnification.

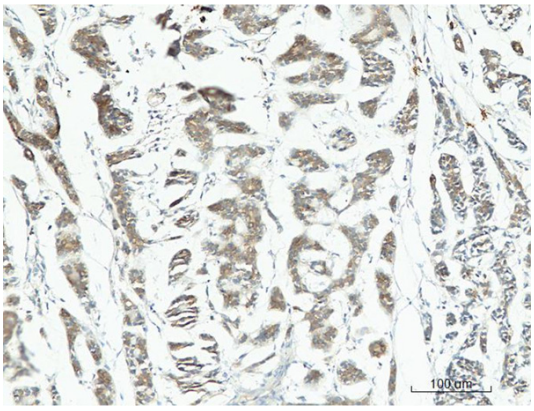

Figure 6. Expression of CD117 in ACC; H&E STAINING, 20 × magnification.

50-120 days). Sternal tenderness was observed for 3 ACCs and weight loss was observed for 2 ACCs. Moreover, of the 7 male patients, 6 were previous smokers from ten years to several decades. Of the 12 patients, 2 were initially diagnosed as having bronchial asthma and were treated for this. Also, 6 patients were ini-

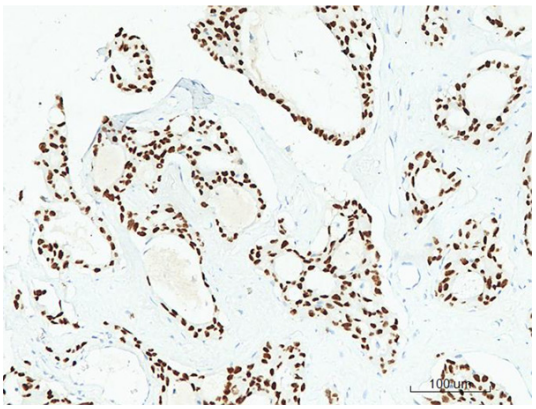

Figure 7. Expression of TTF-1 in ACC; H&E STAINING, 20 × magnification.

tially diagnosed as having chronic bronchitis and were treated for this. However, clinical outcomes for these people were unsatisfactory.

All patients were given a computed tomography (CT) scan and 8 ACCs were documented to be trachea-space occupying lesions; others were centric pulmonary carcinomas and/or peripheral pulmonary carcinomas. Bronchoscopy revealed that tracheal mucous had thickened irregularly; and the airway was obstructed by papillary neoplasms or tracheal neoplasms. Surgically, 8 ACCs were treated using fiberoptic bronchoscopy for lump resection and 2 ACCs were treated with whole or part pulmonary lobectomy. Two ACCs were obtained after tracheal resection. 3 ACCs were stage II; 6 were stage III; and 3 were stage IV. Of the tissues samples, 5 were from ACC survivors and 2 were from deceased patients. Five ACC cases were lost to follow-up. For the 5 survivors, 2 cases were recurrent and included one patient who had 4 recurrences. For the 2 deaths, one patient died due to recurrence within 6 months after discharge and the other death was due to hepatic metastatic recurrences 3 years after discharge, and this person died 6 years after discharge.

Pathology

Morphology

Tissues were obtained from patients who underwent fiberoptic bronchoscopy for lump resection or whole or part pulmonary lobectomy. Therefore, tumor sizes were diverse (0.1 cm × 0.1 cm × 0.1 cm to 4.0 cm × 4.0 cm × 4.0 cm). Tumors from pulmonary lobectomies were closely associated with segmental bronchi extended into the surrounding lung parenchyma and lacked definite margins.

Microscopic histopathology

All 12 ACCs had similar pathologic characteristics: being cribriform, tubular, or solid cords with mucus. Tumor cells had smaller cell volume, less cytoplasm, an oval or polygonal nucleus, stronger straining, and less mitosis (**Figure 1**). Some tissue was tubular and involved cylindrical or cuboidal inner cells and outer cells with clear cytoplasms (**Figure 2**). WHO [9] classification suggests four grades for ACCS: I had only cribriform and tubular structures; II had consolidated areas that represented less than 30% of the sample; III tumors had consolidated areas exceeding 30% of the sample; and IV samples had greater malignant transformation. Vascular and nerve invasion was not seen in grades I and II and 2 tumor tissues from a pulmonary lobectomy never extended into the bronchi margin but lymph node metastases were observed in one tissue.

Immunohistochemistry, FISH, and fluorescent PCR

Immunohistochemical findings showed that tumor tissues were immuno-positive for CK (+++) (**Figure 3**), P63 (++-+++) (**Figure 4**), and Ki-67 (+-++) (**Figure 5**) in all tumor tissues. In addition, 9 cases were positive for CD117 (+-++) in the epithelium (Figure 6), 4 cases were positive for TTF-1 (++-+++) (**Figure 7**). Data show that the mutated *EGFR* gene in exons of 18, 19, 20 and 21 was negative according to TaqMan probes reactions in all ACCs. Rose curve was the positive control (**Figure 8**). FISH revealed only 1 case had the EML4-ALK fusion (**Figure 9**).

Discussion

Primary malignant tumors of the trachea are very uncommon. Squamous cell carcinoma is the most common primary tumor followed by ACCs, and these two tumor types comprise 86% of primary malignant tracheal tumors in adults [10]. ACC is a malignant salivary gland tumor, representing the most common type found in the parotid gland and accounting for 10% of all head and neck tumors. However,

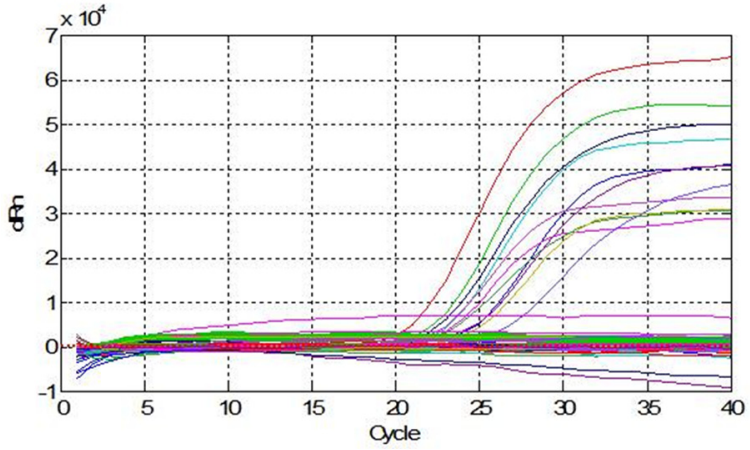

Figure 8. Mutated *EGFR* gene show negative in ACCs; RT-PCR of TaqMan probes reactions.

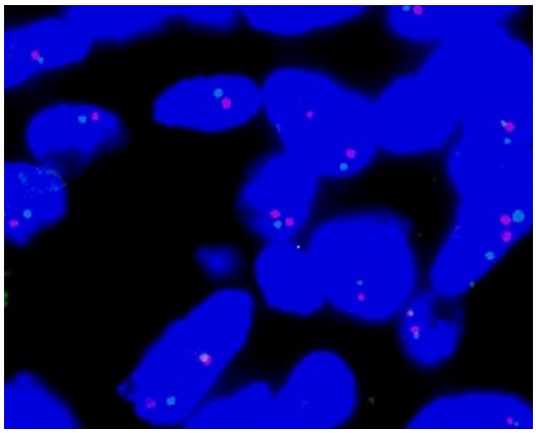

Figure 9. Detection of ALK fusion gene positive in ACC; FISH, 1000 × magnification.

ACCs of the trachea are rare neoplasm and originate from submucosal glands of the tracheobronchial tree [11].

Research suggests that occurrences of ACCs do not differ between men and women and are not correlated with cigarette smoking, unlike squamous cell carcinomas [10, 12, 13]. Patients with ACCs are typically 40-50 years-of-age. In our sample, we studied more men than women and we studied 6 smokers and 6 non-smokers. Our subjects ranged in age from 33-78 years-of-age (median 50.5 years) Thus, our sample represented those depicted in the literature. Tracheal tumors depicted in the literature for adults were usually malignant, and pediatric tumors were typically benign [11]. We studied adults only who had malignant tumors.

We categorized primary tracheal ACCs into 2 subtypes: laryngeal and tracheal with laryngeal types extending from the epiglottal edge to the inferior border of the cricoid cartilage. Tracheal types extended from the trachea to the inferior border of the cricoid cartilage. All of our cases were tracheal with tumors occurring in the trachea, bronchi, and segmental bronchi, similar to cases reported by Julian and colleagues [14]. Ismail's group [15] suggested that ACC patients have certain clinical symptoms depending on tumor obstructions: dyspnea, cough, hemoptysis, asthma, hoarseness, stridor or repeated lung infections. Symptoms of our patients included these with the exception of hoarseness and wheezing. Honings' group [16] reported that many ACC patients would be misdiagnosed as having asthma or chronic obstructive lung disease treated inappropriately for a long time before being properly diagnosed. In our study, 8 patients had been previously diagnosed with asthma or chronic bronchitis and treated for this prior to a proper diagnosis of ACC. Thus, ACC presentation is easily confused with other common respiratory diseases.

Ratto et al [17] described histologically identified solid lumps in ACCs related to more aggressive clinical courses and early metastasis and that cribriform morphology suggested a mild clinical course. Here, we microscopically observed a typical mesh and a tubular structure in 2 ACC cases for patients who died and we saw mesh and tubular structures in 4 cases with central or peripheral lung carcinoma imaged diagnosis. These data disagreed with Ratto's group [17] and this may be explained by limitations in our study caused by fiberoptic bronchoscopy.

CD117 is mainly expressed in the glandular epithelium of tumor tissue [18], and is restricted to certain subtypes of salivary gland carcinomas, such as ACCs, lymphoepithelial carcinomas, and myoepithelial carcinomas, but is not expressed in other types of salivary gland carci-

nomas [19]. Hotte's group [20] indicated that tumor cells had strong expression of CD117 with ACC recurrence or metastases. Similarly, Zhou and colleagues [21] reported that CD117 can be expressed in the epithelium and myoepithelium and that myoepithelial expression indirectly indicates poor prognosis. According to our findings, expression of CD117 in 9 cases was noted, ranging from + to ++, and that this was unrelated with histological grade and Ki-67 expression intensity and these data agreed with published findings [21, 22]. However, we observed no explicit myoepithelial expression of CD117, and this disagreed with data from Zhou et al [21]. In addition, for 7 cases (2 deaths, 3 of imaged prompt has been transferred When seeing a doctor, 2 relapsed patients) had expression intensity from - to ++, and no correlation could be found with this expression and prognosis. These data were inconsistent with Hotte et al [20]. Such discrepancies warrant further study.

For primary lung cancer, TTF-1 is a highly sensitive and specific marker expressed in the thyroid and lung. TTF-1 is expressed in 60-70% of pulmonary adenocarcinomas, but not in metastatic lung tumors. Thus, it is a useful indicator for distinguishing pulmonary primary tumors from metastatic tumors [23, 24]. Here, TTF-1 was expressed in only 4 cases. In 8 cases of primary pulmonary ACC, TTF-1 was not expressed which had been excluded transfer through clinical examination. Decreased TTF-1 expression may be associated with individual differences in expression and less research object, except specimen storage time because negative cases from 2003 to 2013.

Non-small cell lung cancer (NSCLC) accounts for most lung cancers and the prognosis is poor even with multiple treatment modalities. Now, lung adenocarcinoma is one of the most common pathological types of lung cancer. Using molecular targeted drugs such as epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) depends mainly on the EGFR mutation rates. EGFR mutations in Chinese lung ACC patients are reported to be 44.3% [25]. However, in this study, an EGFR mutation did not occur in all 12 ACC cases. Because primary pulmonary ACCs are rare, whether this mutation can be measured conventionally is uncertain.

NSCLC patients have been documented to have echinoderm microtubule-associated protein-like (EML4) anaplastic lymphoma kinase (ALK) which has tumorigenic activity as reported by Soda et al [26]. This fusion gene occurs in adenocarcinomas, and is mutually exclusive to EGFR and KRAS mutations [27]. The incidence of ALK rearrangement in NSCLC patients is reported to be 0.5-7%, and other studies suggest an incidence of 4.9% measured by RT-PCR [27], 11.6% according to RACE coupled PCR sequencing technology [28], and 16.1% in lung adenocarcinomas [25]. We used FISH to detect *ALK* gene rearrangement and found only one, much less than the 11.3% documented by Liu et al [29] measured. It was needed to work in the future to clarify that whether the race of ALK gene rearrangement in ACC was consistent without its particularity to which in NSCLC.

ACC should be differentiated from polymorphous low-grade adenocarcinomas which have better prognoses than ACC and CD117 is helpful in this regard. ACC is a low-grade malignant tumor prone to distant metastasis, with high of 5-year survival rate and low of 10-15 years survival rate, so WHO classified it as a "high risk" tumor. Chief treatments of ACCs are excision and focal radiotherapy. Of those studied, three patients were stage II; 6 were stage III; and 3 were stage IV. Of them, 2 had complete or partially resected lobes and the others were treated with radiotherapy and chemotherapy because complete surgical excision was difficult. Of those studied, 7 had follow-up data from 6 months to 6 years, and 2 patients died within 5 years due to ACC (5-year survival rate 0%). Two of the 5 survivors had recurrent tumors. All patients studied had poor prognoses and 5- and 10-year survival rates with ACC were 35%, 7~10% respectively reported by WHO, which higher than this group, mainly relevant with most of the long medical history patients lost to follow-up in our study, looking forward to accumulate more cases further verification.

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Disclosure of conflict of interest

None.

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