

# Analysis of clinicopathological characteristics, *MYB* rearrangement and prognostic factors in salivary adenoid cystic carcinoma

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**Abstract.** Recent studies have indicated that a recurrent t(6;9)(q22-23;p23-24) chromosomal translocation in salivary adenoid cystic carcinoma (ACC) results in a *MYB* proto-oncogene transcription factor-nuclear factor I/B (*MYB-NFIB*) gene fusion, which has not previously been detected in any non-ACC carcinomas of the head and neck. In the present study, data on clinical factors affecting the survival rate of patients with salivary ACC from a single institution was retrospectively analyzed, and the frequency of *MYB* gene rearrangement determined. A total of 97 patient cases were analyzed, and young adults presenting with ACC (<40 years old) accounted for 19.6% of all patients (n=19). A total of 70.1% (n=68) displayed neurological symptoms, including pain, paraesthesia, tongue deviation, and facial paralysis. A marked majority of the analyzed tumors (85.6%) displayed evidence of *MYB* rearrangement. *MYB* rearrangement was significantly higher in patients with late Tumor-Node-Metastasis (TNM) stage cancer compared with that in patients with early TNM stage (P=0.033), as detected by a dual color *MYB* break-apart fluorescence *in situ* hybridization probe. Kaplan-Meier analysis revealed significant differences in patient overall survival (OS) time with regard to age, gender, TNM stage,

neurological symptoms, margin status and *MYB* rearrangement. Specifically, young age was significantly associated with a shorter OS time. In summary, the present study suggested that young patients with salivary ACC presented with a worse prognosis, in contrast to the majority of patients with salivary ACC. Moreover, *MYB* alterations exhibited a high positive rate in salivary ACC, and therefore, the absence of *MYB* rearrangements may be associated with a better prognosis.

## Introduction

Adenoid cystic carcinoma (ACC) is a rare malignancy that is able to exist at various sites within the body, although it is most commonly localized to the salivary gland (1). Salivary ACC displays characteristic features, including biological behavior diversity and histological heterogeneity (2). Patients diagnosed with salivary ACC usually present with a poor prognosis due to metastasis to distant organs, the high risk of relapse and the propensity of the tumor to invade the peripheral nerves. The majority of patients diagnosed with salivary ACC succumb between 5 and 20 years post-diagnosis (3-5).

To understand the course and behavior of the disease, a number of studies have focused on identifying specific prognostic factors for salivary ACC. However, few clinical parameters are associated with a poor prognosis, including advanced Tumor-Node-Metastasis (TNM) stage (6), perineural invasion and solid histological pattern (5,7-10). Moreover, assessment of the clinical parameters alone is not sufficient to accurately predict the clinical outcome of patients with salivary ACC. Therefore, molecular prognostic factors may be beneficial for a more accurate prediction of clinical outcome.

Previous studies have demonstrated that a recurrent t(6;9)(q22-23;p23-24) chromosomal translocation in salivary ACC results in the fusion of the *MYB* proto-oncogene transcription factor (*MYB*) gene with the nuclear factor I/B (*NFIB*) gene. Notably, the *MYB-NFIB* gene fusion has not been observed in any non-ACC carcinomas of the head and neck to date (11). The fusion gene fragment is predominantly *MYB*, leading to the overexpression of *MYB* mRNA and a subsequent increase in protein expression level (12). Clinical and differential diagnoses of ACC have relied on the detection of molecular

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biomarkers, including *MYB-NFIB* gene fusion or *MYB* activation by fluorescence *in situ* hybridization (FISH) analysis, or immunohistochemical staining of *MYB* proteins (13-15). However, due to the small number of cases (and the potential possession of multiple primary cancer sites), the association between *MYB* rearrangement and clinical prognosis remains controversial (2,16-21).

The purpose of the present study was to retrospectively analyze the clinical factors affecting the survival of patients with salivary ACC, and to identify the frequency of the rearrangement of *MYB* using FISH, in order to establish the association between *MYB* rearrangement and the survival rate or prognosis of patients with salivary ACC.

## Materials and methods

**Participants and recruitment.** A total of 97 records of patients with ACC of the head and neck were analyzed. All patients were treated from January 2007 to December 2014 at the Shanghai Ninth People's Hospital, Shanghai Jiao Tong University. The inclusion criteria were as follows: i) Location of the tumor in major or minor salivary gland; ii) demographic and complete clinicopathological data; iii) radical surgery without preoperative therapy; and iv) availability of surgical specimens in formalin-fixed paraffin-embedded blocks. The study was approved by the Review Board of the Shanghai Ninth People's Hospital. Clinical, pathological, treatment and follow-up data were obtained from patient medical records. Young adult (YA) ACC patients were classed as <40 years old (n=19), middle-aged (MA) patients were between 41 and 65 years old at disease onset (n=60) and old-aged (OA) patients were >65 years of age at onset (n=18). Two experienced pathologists reviewed the histological specimens. The histological grade was determined according to the following criteria: Grade 1, no solid component; grade 2, solid component <30%; and grade 3, solid component ≥30%. Margins were defined as positive if the tumor was detected at the resection margin. Patient information is displayed in Table I.

**Information collection.** The follow-up information for 94 cases was obtained by case record review and return visits. Follow-up time was defined as the time from initial presentation at the institution for the tumor of interest to the date of last contact or mortality for overall survival (OS) assessments. The endpoint investigated was OS, which was defined as the time in months from surgery to mortality from any cause.

**FISH analysis.** FISH was performed on formalin-fixed paraffin-embedded sections with a thickness of 5 μm using a commercially available *MYB* Dual Color Break-Apart Probe (cat no. ZTV-Z-2143-200; Zytovision GmbH, Bremerhaven, Germany). The probe is designed to detect translocations involving the chromosomal region 6q23.3 harboring the *MYB* gene, and has two probes labeled with green and orange fluorochromes that hybridize at the 5' and 3' ends of the *MYB* gene, respectively. Analysis was conducted as described previously (19). A cell number >30 among 100 isolated cells indicated *MYB* abnormalities (16). Cells with a normal pattern presented as two fusion signals. *MYB* abnormalities present either with typical rearrangement (one fusion and another with separate orange and green signals), deletion (one fusion and

only one other orange or green signal) or amplification (more than two orange and/or green signals).

**Statistical analysis.** Statistical analyses were performed using the SPSS software package (version 13.0; SPSS, Chicago, IL, USA). The association of *MYB* with clinical parameters was determined using the  $\chi^2$  test. Kaplan-Meier survival analysis and Cox multivariate analysis were used to evaluate the association between the clinical factors and OS of the patients with salivary ACC. The P-values in Table IV were obtained by log-rank (Mantel-Cox) test during Kaplan-Meier survival analysis. P<0.05 was considered to indicate a statistically significant difference.

## Results

**Clinicopathological features and follow-up information.** The clinical data and histological features of 97 patients with salivary ACC are presented in Table I. Notably, among the 97 patients, follow-up information could only be collected from 94 patients. The cohort included 45 females (46%) and 52 males (54%), resulting in a male-to-female (M:F) ratio of 1:0.87. The age of the patients at the time of diagnosis ranged from 20 to 83 years, with a mean age of 53.9 years. YA patients with salivary ACC (n=19; 19.6%) were defined as those <40 years of age, MA patients (n=60; 61.9%) as between 41 and 65 years of age at onset and OA patients (n=18; 18.6%) as >65 years of age at onset. The incidence of ACC in the minor salivary glands (n=63; 64.9%) was higher compared with that in the major salivary glands (n=34; 35.1%). The palate was the most frequent location for salivary ACC (n=28; 28.9%). Overall, the tumor evaluation according to the TNM staging system identified 12 cases (12.4%) of T1, 27 cases (27.8%) of T2, 26 cases (26.8%) of T3 and 32 cases (33.0%) of T4 cancer at diagnosis.

The median time to presentation for treatment was 6 months (range, 0.5-125 months). There were 7 cases in which the presentation was delayed for over 60 months, including certain patients presenting with slow-growing tumors, 1 patient initially diagnosed with trigeminal neuralgia and another patient treated for glossopharyngeal neuralgia.

The majority of patients (n=68; 70.1%) presented with neurological symptoms, including pain, paresthesia, tongue deviation and facial paralysis, while the remainder (n=29; 29.9%) had no apparent symptoms or presented with other symptoms, including rapid growth of a mass, nasal obstruction or bleeding, and ulceration. The lesions of the palate frequently manifested as ulcers with numbness or pain. Parotid lesions frequently appeared as facial skin needle- or electric shock-like pain, in addition to facial paralysis. The floor of the mouth, tongue and sublingual gland lesions displayed different symptoms, including tongue numbness, pain and tongue deviation. The lesions of the maxillary sinus were frequently accompanied by epistaxis and diplopia. Histopathological evaluation of the tumor specimens identified 66 cases at grade 1, 14 cases at grade 2 and 17 cases at grade 3. A total of 63 cases (64.9%) displayed evidence of perineural invasion, while vascular infiltration was observed in 16 cases (16.5%). Moreover, 42 cases (43.3%) presented with positive surgical margins. Metastases to the regional lymph nodes were noted in 5 cases (5.2%). All the cervical lymph node metastases occurred in T3 and T4

Table I. Clinical and histological characteristics (n=97), and follow-up information (n=94) of patients with salivary adenoid cystic carcinoma.

Characteristic	Cases, n
Age, years	
≤40	19
41-65	60
>65	18
Sex	
Male	52
Female	45
Site	
Major	34
Minor	63
TNM stage	
I	12
II	27
III	26
IV	32
Neurological symptoms	
Yes	68
No	29
Histopathological grade	
1	66
2	14
3	17
Perineural invasion	
Yes	63
No	34
Vascular invasion	
Yes	16
No	81
Margin status	
Positive	42
Negative	55
Lymph node metastasis	
Positive	5
Negative	92
Treatment	
Surgery	16
Surgery and radiation	62
Surgery and chemoradiation	16
New recurrence	
Yes	31
No	63
Distant metastasis	
Prior to treatment	8
Following initial treatment	45
No	41

Table I. Continued.

Characteristic	Cases, n
Last known vital status	
Alive free of tumor	32
Alive with tumor	38
Succumbed	24

TNM, Tumor-Node-Metastasis.

Table II. Rearrangements of *MYB* detected by fluorescence *in situ* hybridization.

MYB rearrangements	Number
Split signal	71
Split and 5'-part amplification	5
Loss of 3'-part	4
Loss of 5'-part	2
Copy number amplification	1
Normal	14

*MYB*, MYB proto-oncogene transcription factor.

tumors, with 4 originating from the floor of the mouth and 1 case from the buccal mucosa.

All patients underwent surgery, and of the 94 patients with available follow-up information, 62 (66%) received postoperative radiotherapy. Patients with metastasis or positive margins (n=16; 17.0%) received concomitant chemotherapy. The mean follow-up time was 45.1 months (range, 4-104 months). At the end of the follow-up, 24 patients (25.5%) succumbed due to distant metastasis and/or local recurrence (LR), while of the remaining 70 patients (74.5%), 38 possessed residual disease. There were 53 patients (56.4%) with distant metastasis; 46 cases (48.9%) metastasized to the lung, 2 cases to the lungs and brain, 2 cases to the lungs, liver and bone, 1 case to the lungs and sternum, 1 case to the lungs and liver, and 1 case to lungs, kidney and bone. The median time for metastasis identification was 11 months (range, 0-101 months). There were no cases of lymph node metastasis development following surgery. The LR rate was 33.0% (31 out of 94 cases). The median time until LR was 12 months (range, 1-48 months).

**MYB rearrangement.** Using a dual color MYB break-apart FISH probe, *MYB* rearrangements were detected in 83 of the 97 cases. The typical patterns of *MYB* rearrangements with an intact signal (fused orange/green signals) (Fig. 1A) and a split signal (separated orange and green signals), indicating a breakpoint within the *MYB* gene (Fig. 1B), compared with the intact signal, were observed in 71 tumors. Gain of one or more green signals was apparent in 5 cases, indicating selective amplification of the 5' end of *MYB* (Fig. 1C), and multiple pairs of fusion signals were observed in one case, indicating gain of MYB copies (Fig. 1D) (Table II). A typical pattern with one

Table III. Associations between clinicopathological parameters and *MYB* rearrangement.

Parameter	<i>MYB</i> rearrangement, n (%)		P-value
	With (n=81)	Without (n=13)	
Age, years			0.157
≤40	18 (100.0)	0 (0.0)	
41-65	48 (82.8)	10 (17.2)	
>65	15 (83.3)	3 (16.7)	
Sex			0.372
Male	38 (90.5)	4 (9.5)	
Female	43 (82.7)	9 (17.3)	
Site			0.788
Major	28 (87.5)	4 (12.5)	
Minor	53 (85.5)	9 (14.5)	
TNM stage			0.033
I/II	29 (76.3)	9 (23.7)	
III/IV	52 (92.9)	4 (7.1)	
Neurological symptoms			0.995
Yes	56 (86.2)	9 (13.8)	
No	25 (86.2)	4 (13.8)	
Histopathological grade			0.332
1	54 (83.1)	11 (16.9)	
2/3	27 (93.1)	2 (6.9)	
Perineural invasion			0.764
Yes	53 (86.9)	8 (13.1)	
No	28 (84.8)	5 (15.2)	
Vascular invasion			0.119
Yes	15 (100.0)	0 (0.0)	
No	66 (86.2)	13 (13.8)	

TNM, Tumor-Node-Metastasis; *MYB*, MYB proto-oncogene transcription factor.

fusion signal and one green/ orange signal, indicating the loss of the 3' end, was observed in 4 cases (Fig. 1E) and the loss of the 5' end was observed in 2 cases (Fig. 1F).

The statistical significance between clinicopathological characteristics and *MYB* rearrangement in patients with salivary ACC patients was subsequently assessed (summarized in Table III). Only TNM stage was significantly associated with *MYB* rearrangement, wherein the late TNM stage was associated with higher *MYB* rearrangement ( $P=0.033$ ). These results suggest that *MYB* rearrangement is associated with the progression of salivary ACC, which may be interpreted as an indicator of poor prognosis. Notably, *MYB* gene rearrangement was not statistically associated with any other clinicopathological variable.

**Survival analyses.** Kaplan-Meier analysis revealed significant differences in OS, dependent on age, sex, TNM stage, neurological symptoms, margin status and *MYB* rearrangement (Fig. 2; Table IV). For specific groups, the median survival times were absent, as until the end of the follow-up period, the overall survival rate in these groups remained at >50%.

Therefore, the method used to determine survival analysis could not provide the hazard ratio in the case of >2 groups. In multivariate analysis, YA was indicated to be significantly associated with a shorter OS time (Table V).

## Discussion

Salivary ACC is one of the most common malignant tumors of the oral and maxillofacial region. In agreement with previous studies (5,22,23), the present study indicated that salivary ACC originates more frequently from minor rather than major glands, and predominantly affects the palate.

Although previous studies have suggested that salivary ACC affects a wide age distribution and has no sex predilection (5,24), the present results indicate that salivary ACC has a minor male predominance. Consistently, analysis using Kaplan-Meier survival curves revealed significant differences between men and women, with women having improved survival outcomes. Moreover, salivary ACC typically occurs in the fifth or sixth decade of life, although it may also present in YA patients (25,26). Certain reports suggest that older age



Table IV. Kaplan-Meier survival analysis for OS time in patients with salivary adenoid cystic carcinoma.

Variable	OS time, months	P-value
Age, years		0.001
≤40	47.518±6.708	
41-65	91.381±4.246	
>65	75.231±8.733	
Sex		0.035
Male	59.205±4.495	
Female	87.080±4.834	
Site		0.109
Major	61.076±4.629	
Minor	83.940±4.931	
TNM stage		0.001
I/II	99.599±3.026	
III/IV	67.537±5.183	
Neurological symptoms		0.014
Yes	71.842±4.594	
No	98.241±3.929	
Histopathological grade		0.082
1	83.764±4.783	
2/3	60.023±5.698	
Perineural invasion		0.880
Yes	59.356±3.719	
No	79.464±5.011	
Vascular invasion		0.207
Yes	56.333±7.342	
No	81.684±4.446	
Margin status		0.011
Positive	61.210±4.887	
Negative	88.098±4.828	
Treatment		0.143
Surgery	67.059±10.782	
Surgery and radiation	73.169±3.222	
Surgery and chemoradiation	72.810±11.052	
MYB rearrangement		0.029
Yes	55.582±3.842	
No	96.615±7.095	

TNM, Tumor-Node-Metastasis; OS, overall survival; MYB, MYB proto-oncogene transcription factor.

is a risk factor for lower survival rates in patients with salivary ACC (5,10,27,28). Accordingly, the present study revealed that the peak incidence of salivary ACC was amongst MA patients. The incidence of salivary ACC in YA patients was relatively low and represented a minority of cases. The association between YA and prognosis is a well-described phenomenon reported across multiple cancer types (29,30). For example, in head and neck squamous cell carcinoma, young cancer patients presented with a worse prognosis (31). However, the prognosis of the YA patients in the context of salivary ACC

has yet to be evaluated. The present results indicated that YA patients presented with a worse prognosis compared with MA and OA patients.

Patients with ACC frequently develop neurological symptoms in the early stages of the disease (32,33). Neural spread away from a tumor frequently results in specific symptoms, including pain, muscle weakness and atrophy, depending on the nerves involved. Occasionally, pain may occur in the early stage of the disease until there is a noticeable swelling. In certain cases, the treatment of patients is delayed due to the initial diagnosis of trigeminal or glossopharyngeal neuralgia (22). Although the most common initial presentation is unclear, almost one-third of patients present with dysaesthesia. This symptom is important in the absence of clinically visible symptoms, as it may indicate an underlying neoplastic variation and warrant further investigation. Despite these observations, the association between histopathological perineural invasion and disease prognosis remains controversial (28,34,35). Moreover, the connection between neurological symptoms and prognosis in patients with cancer is yet to be addressed. By contrast, the present results indicate that patients with neurological symptoms had a comparatively poor prognosis, but did not exhibit histopathological perineural invasion. These results suggested that patients with salivary ACC, but without neurological symptoms, had a relatively good prognosis, and were more likely to be misdiagnosed with other salivary gland tumors.

The present study confirmed previous studies indicating that TNM stage at diagnosis is the primary factor for survival prediction in patients with cancer (5,7,8,36). Owing to the slow-growing nature and protracted clinical presentation of salivary ACC, patients are not always aware of the cancer until the rapid growth or metastasis stage. In the present study, there were 8 patients who presented with pulmonary metastasis during the time of diagnosis of the primary lesion. Moreover, lymph node involvement in the salivary ACC is uncommon. In the study by Min *et al* (24), 62 out of 616 (10.1%) cases of lymph node metastasis were identified, with the most common primary site originating from the base of the tongue, mobile tongue and floor of the mouth. In the present study, metastases to the regional lymph nodes were determined in only 5 cases, which all occurred in T3 and T4 tumors, with 4 cases originating from the floor of the mouth and 1 case from the buccal mucosa.

Salivary ACC has notable heterogeneous morphology and contains tubular, cribriform, solid or mixed patterns. However, these histopathological features are not specific to salivary ACC and may also be present in other salivary gland tumors, including pleomorphic adenoma, basal cell adenoma, basal cell adenocarcinoma and polymorphous low-grade adenocarcinoma. Therefore, novel molecular biomarkers may encourage more accurate prediction of clinical outcome in patients with salivary ACC. Genetic alterations detected in tumors may be associated with the oncogenic process and potentially serve as diagnostic biomarkers. *MYB-NFIB* gene fusion and *MYB* activation have frequently been utilized as molecular biomarkers in clinical and differential diagnoses (13-15). However, studies investigating the expression of *MYB* in pleomorphic adenoma suggest that alterations in the *MYB* gene are not a definitive diagnostic biomarker (37). Moreover, as a potential diagnostic biomarker for ACC, the

Table V. Univariate and Multivariate Cox analysis of variables considered for overall survival of salivary adenoid cystic carcinoma patients.

Variables	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Age ( $\leq 40$ vs. $>40$ )	3.884	1.676-9.003	0.002 <sup>a</sup>	2.921	1.191-7.142	0.019 <sup>a</sup>
Margin status (positive vs. negative)	3.014	1.228-7.396	0.016 <sup>a</sup>	2.677	1.049-6.830	0.039 <sup>a</sup>
Neurological symptoms (yes vs. no)	5.137	1.202-21.966	0.027 <sup>a</sup>	3.357	0.757-14.895	0.111
TNM stage (III/IV vs. I/II)	8.904	2.087-37.994	0.003 <sup>a</sup>	3.947	0.854-18.248	0.079
Histopathology grade (2/3 vs. 1)	2.585	1.053-6.347	0.038 <sup>a</sup>	2.483	0.925-6.661	0.071
Sex (male vs. female)	0.676	0.274-1.688	0.395			
Site (major vs. minor)	0.968	0.545-1.720	0.912			
Perineural invasion (yes vs. no)	1.056	0.429-2.956	0.906			
Vascular invasion (yes vs. no)	1.880	0.692-5.180	0.215			
<i>MYB</i> rearrangement (yes vs. no)	0.035	0.000-4.223	0.170			

<sup>a</sup>P<0.05. HR, hazard ratio; CI, confidence interval; TNM, Tumor-Node-Metastasis; *MYB*, *MYB* proto-oncogene transcription factor.

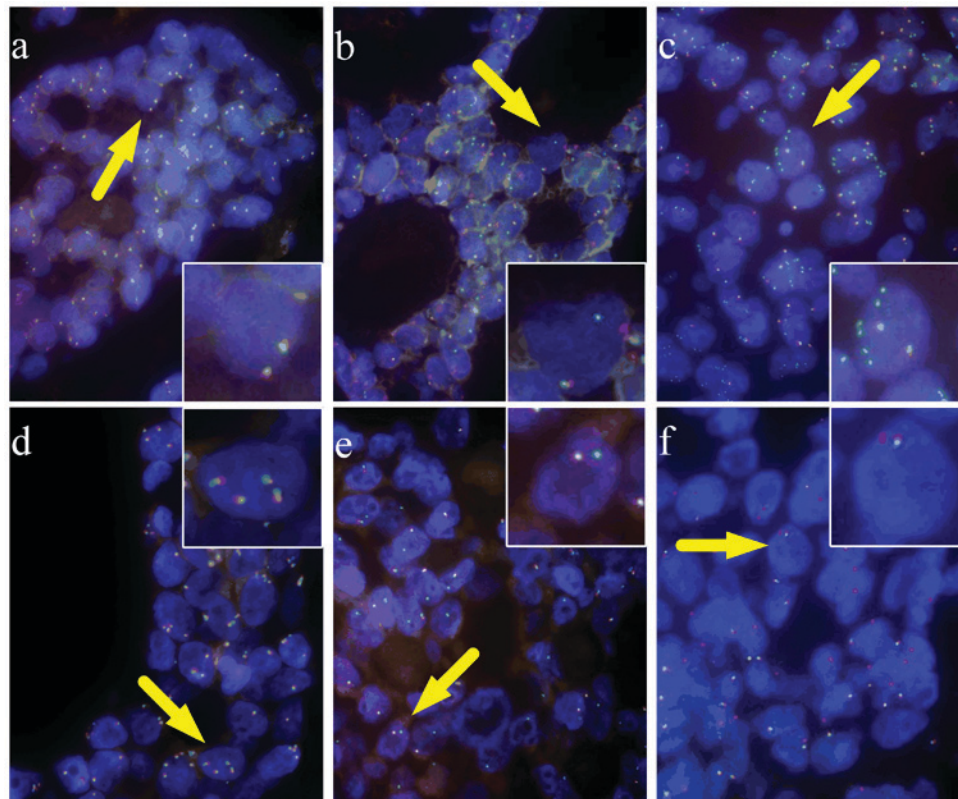


Figure 1. Rearrangements of *MYB* detected by fluorescence *in situ* hybridization. (A) Normal (x1,000, oil mirror), (B) split (x1,000, oil mirror), (C) 5'-part amplification (x1,000, oil mirror), (D) copy number amplification (x1,000, oil mirror), (E) loss of 3'-part and (F) loss of 5'-part (x1,000, oil mirror). Cells with a normal pattern present as two fusion signals. *MYB* abnormalities present either with typical rearrangement (one fusion and another separate orange and green signal), deletion (one fusion and only one other orange or green signal) or amplification (more than two orange and/or green signals). *MYB*, *MYB* proto-oncogene transcription factor.

specific association of *MYB* rearrangement with clinical features and the prognosis of salivary ACC have not been completely elucidated (11,21).

FISH studies by Perrson *et al* (38) indicated that *MYB-NFIB* gene fusion occurred in 86% of tumors, and that gene rearrangement due to chromatin instability frequently led

to a loss of 6q24.1-6q27, more commonly in high histological grade cancer. Roden *et al* (20) detected 35 cases of lung ACC with the *MYB* break-apart probe, showing 100% specificity of *MYB* rearrangement in 41% of cases; however, there was no correlation between *MYB* rearrangement and clinical features or prognosis. Broz *et al* (2) detected 23 cases of salivary ACC,

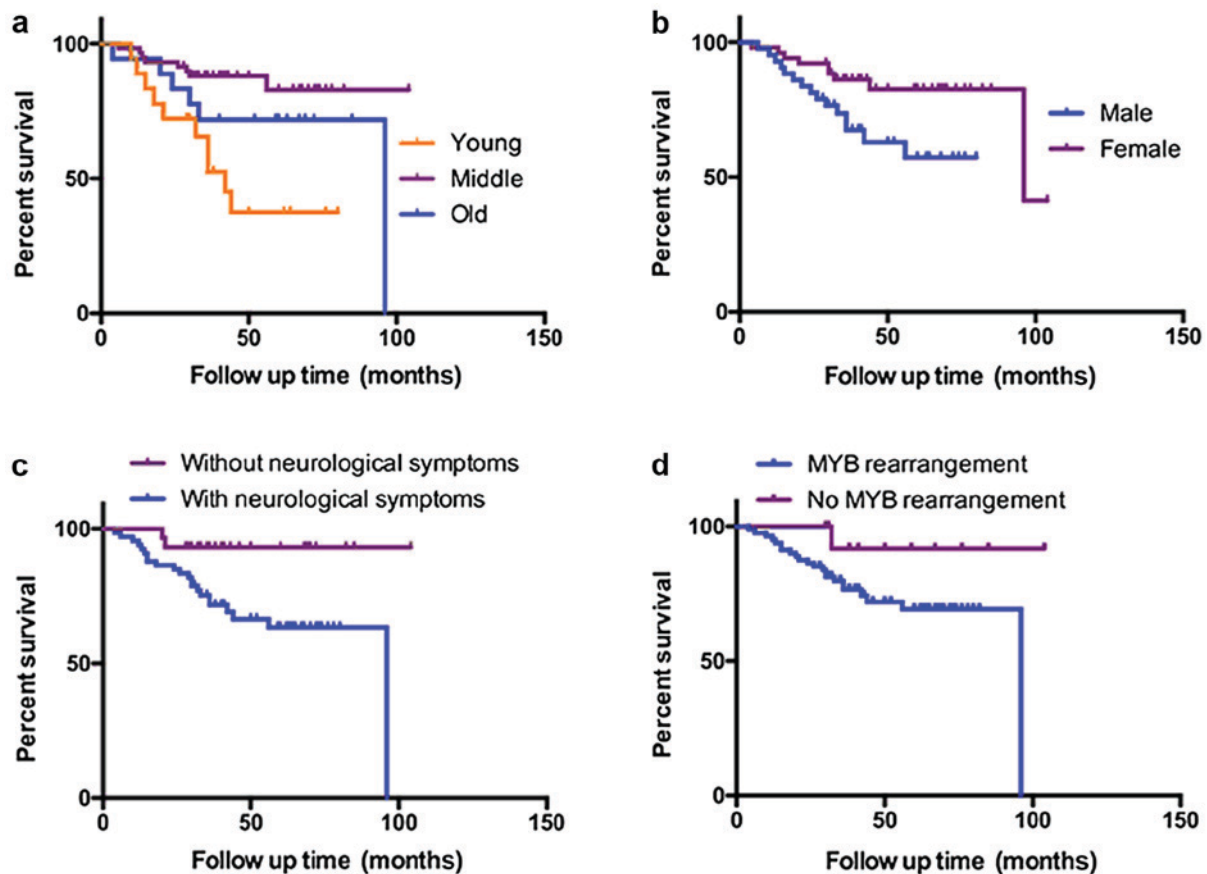


Figure 2. (A-D) Kaplan-Meier survival curves for salivary adenoid cystic carcinoma patients with different clinical characteristics and *MYB* rearrangement. *MYB*, *MYB* proto-oncogene transcription factor.

with 15 cases positive for rearrangement and 8 cases with no rearrangement (2). There were no significant differences in age, sex, perineural invasion, the presence of hematogenic and nodal metastases, or degree of histopathological grading between patients with and without *MYB* rearrangement. Survival analysis revealed no statistically significant differences in survival between patients with and without *MYB* rearrangement; however, a lack of *MYB* alteration was associated with a better prognosis (2). In the present study, the vast majority of cases exhibited *MYB* isolation, and few cases displayed deletion or amplification of *MYB*; there was no significant association between the different gene alterations and the histological phenotype of ACC. Survival analysis indicated significantly improved OS times in patients with no alterations in *MYB* compared with those in patients with *MYB* rearrangements, which is in agreement with the conclusions of Broz *et al* (2), despite their findings not being statistically significant.

Moreover, the present results suggested that YA patients with salivary ACC have a worse prognosis, which is significantly different from the majority of patients presenting with salivary ACC. Detection of *MYB* alterations by FISH could achieve a high positive detection rate in salivary ACC, which would facilitate clinical diagnosis, and the lack of *MYB* rearrangement may be associated with a better prognosis. Therefore, establishing the association between *MYB* rearrangement and prognosis may be beneficial for a greater understanding and the improved treatment of salivary ACC.

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## Availability of data and material

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

## Authors' contributions

JH and CYZ were responsible for the study conception and design. TG and XY conducted experimental testing and follow-up. LWH and ZT collected the data and revised the manuscript. Data analysis and interpretation was conducted by JL and CPZ. All authors contributed to writing the manuscript and provided final approval.

## Ethics approval and consent to participate

The present study was approved by the Review Board of the Ninth People's Hospital and informed consent was obtained from all participants.



## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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