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Prognostic factors for lacrimal gland adenoid cystic carcinoma: a retrospective study in Chinese patients

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Abstract

● **AIM:** To explore the prognostic factors for lacrimal gland adenoid cystic carcinoma (LGACC) in Chinese patients.

● **METHODS:** Clinical and histopathological data were reviewed in patients with pathologically confirmed LGACC. Local recurrence, metastasis, and disease-specific death were the main outcome measures. Univariate and multivariate analyses were performed by the Kaplan-Meier method and a Cox proportional hazard model.

● **RESULTS:** This retrospective cohort study included 45 patients with pathologically confirmed LGACC between January 2008 and June 2022. Tumor (T) classification (P=0.005), nodal metastasis (N) classification (P=0.018) and positive margin (P=0.008) were independent risk factors of recurrence; T (P=0.013) and N (P=0.003) classification and the basaloid tumor type (P=0.032) were independent risk factors for metastasis; T classification (P<0.001) was an independent factor of death of disease. In the further analysis, the durations from first surgery to radiotherapy is correlated with metastatic risk in LGACC patients with basaloid component (P=0.022).

● **CONCLUSION:** Histological subtype should be emphasized when evaluating prognosis and guiding treatment. Timely radiotherapy may reduce the risk of metastasis in patients with basaloid component.

● **KEYWORDS:** lacrimal gland adenoid cystic carcinoma; risk factors; prognostic analysis; histological subtypes
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INTRODUCTION

Lacrimal gland adenoid cystic carcinoma (LGACC) is the most common malignancy in the lacrimal area, accounting for about 25% to 30% of lacrimal gland epithelial tumors, and 60% to 75% of lacrimal gland malignant tumors[1-5]. The disease is more common in middle-aged and elderly women[6-7]. Patients usually visit the clinic after presenting with periorbital pain, exophthalmos and mass lesion[8-10]. LGACC is prone to invade surrounding bones, nerves and soft tissues, and may also develop distant metastasis[11-14]. Although surgical removal of the tumor supplemented by postoperative radiotherapy/chemotherapy is widely used, the disease still exhibits a poor prognosis[15-22]. Reported rates range from 9.1% to 50% for local recurrence[23-28], from 8% to 40% for metastasis[11,13,18], and more than half of the patients will succumb to disease[1,20,24,29].

The risk factors were rarely reported in LGACC, however, in adenoid cystic carcinoma (ACC) of other sites, positive margins have been documented as a risk factor for local recurrence[30]. Neural invasion[31], lymphovascular invasion, tumor size, T categories[32] were found to be correlated with metastasis and disease-specific death. Moreover, pathologically, ACC is mainly divided into four histological subtypes, namely basaloid, cribriform, tubular and mixed, and different histological types may have different prognosis[33-34]. It has been reported that among ACCs in breast and salivary glands, basaloid tumors were usually poorly differentiated and highly malignant, which were associated with higher metastatic rates and shorter disease-specific survival (DSS)[35-37]. Identifying the risk factors helps clinicians to stratify the risk of poor prognosis and guide the management of patients with LGACC.

In the present study, we undertook a retrospective analysis of the clinical and histopathological data of 45 patients with LGACC. Statistical analysis to determine prognostic factors for local recurrence, metastasis and disease-specific death was performed.

SUBJECTS AND METHODS

Ethical Approval This research was performed in accordance with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all patients. The study was approved by the Ethics Committee of Shanghai Jiao Tong University (SH9H-2019-T185-2).

Patient Selection This was a retrospective chart review of all consecutive patients diagnosed as LGACC treated at Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine from January 2008 to June 2022. Patients were excluded if they did not have sufficient follow-up information.

Clinical and Histological Data A retrospective review of medical records, pathology reports and photographic images was performed. The following data were evaluated and carefully documented: 1) demographic characteristics; 2) tumor features (tumor diameter, lesion location, number of lesions); 3) American Joint Committee on Cancer (AJCC) classification (8^{th} edition) at the time of sample collection; 4) imaging data [characteristics of orbit shown on magnetic resonance imaging (MRI), computed tomography (CT)]; 5) Follow-up data (date of local recurrence, distant metastasis or death). Tumors were routinely evaluated by pathologists in Shanghai Ninth People's Hospital. The growth pattern [predominantly basaloid (solid); predominantly cribriform and tubular] was determined according to the type and arrangement of tumor cells. The histopathological subtypes were defined as the predominantly growth pattern[38]. Based on the results of orbital imaging scans, intraoperative findings and histopathological examination results, comprehensively judgment whether the tumor has damaged the surrounding bony and/or nerve invasion. Tumor size, by greatest dimension, was measured on preoperative CT or MRI. Perineural invasion (PNI) was diagnosed histologically based on biopsy specimen tissues. Bony involvement was diagnosed based on the preoperative imaging, intraoperative findings, and the histological results.

For treatment, all patients in our cohort underwent the surgery. There are two types of surgery, local tumor resection and orbital content resection. Orbital content resection was performed in patients with invasion of the eyeball or extraocular muscles, and local tumor resection is performed in other patients. Radiation therapy is mainly performed on patients with bone invasion or tumor capsule invasion. The mean interval time between surgery and radiotherapy was 30d (range, 6-546d). Radiotherapy was administered twice daily at 1.2 Gy per fraction to 16 patients and once daily at 1.8 Gy per fraction to 6 patients. All patients received continuous course radiotherapy, without unscheduled breaks in treatment. Chemotherapy is mainly given to patients with extraconal invasion. The intra-arterial chemotherapy regimen is cisplatin, and the intravenous chemotherapy regimen is doxorubicin combined with cyclophosphamide or vinorelbine combined with cisplatin.

For outcome measures, DSS were defined as time from date of definitive surgery to date of death related to LGACC, respectively. Patients who were alive at the end of follow-up or who died of other causes were considered censored. The recurrence/metastasis-free survival was defined as time from surgery to recurrence/metastasis and was censored at last follow-up date or date of death, whichever occurred first, for patients who did not experience the event. In order to assure sufficient follow-up, we excluded individuals with less than 8mo follow-up.

Statistical Analysis Categorical variables were divided into absolute and relative frequencies, while quantitative variables were presented as means and medians with standard deviation (SD). Survival curves were estimated using the Kaplan-Meier method. The log-rank test and Manny-White test were used to determine whether there was statistical significance. The odds ratio (OR) and 95% confidence intervals (95%CI) were calculated in logistic regression models. Cox regression models were used to identify risk factors for clinical outcomes. Variables with a *P*-value of <0.10 in the univariate analyses were included in the multivariate analysis. Hazard ratios (HRs) with corresponding 95%CIs were used to describe the impact of risk factors. A *P*-value less than 0.05 indicated statistical significance. All analyses were performed using SPSS software (V.22.0, IBM, Armonk, New York, USA) and R packages in R V 3.4.1.

RESULTS

Patients' Characteristics Baseline characteristics of the study population are shown in Table 1. Forty-five patients with a mean age at diagnosis of 51.9y (median: 54y) were eventually included. Totally 57.8% were men (*n*=26) and 44.4% had right eye involvement (*n*=20). The lesions of patients were all unilateral. Common symptoms included exophthalmos (*n*=26, 57.8%), periorbital pain (*n*=20, 44.4%), decreased vision (*n*=11, 24.4%), orbital and periocular masses (*n*=6, 13.3%). Other less frequent symptoms mentioned were epiphora and periorbital itching. The median duration of symptoms was 6mo (range: 0.25-120.0mo). The largest tumor diameter measured a median of 26 mm (range: 11.0-76.0 mm) in one dimension. Characteristic CT image findings are multiple hypodense have cribriform changes (Figure 1). Abnormal findings on CT scans included invasion to bone in 67.5% of cases, and soft tissue calcification in 17.5% of cases. Furthermore, patients presenting with advanced T stages tended to have higher proportions of bony invasion (OR=4.18; 95%CI, 1.162-15.046;

Table 1 Baseline demographic and clinical characteristics of the patients

Characteristics	*n* (%)
Age, y	
<60	34 (75.6)
≥60	11 (24.4)
Gender	
Male	26 (57.8)
Female	19 (42.2)
Affected side	
Left	25 (55.6)
Right	20 (44.4)
Duration of symptom (mo)	6 (0.25-120)
Perineural invasion	
Positive	24 (54.5)
Negative	20 (45.5)
Bone invasion	
Positive	27 (67.5)
Negative	13 (32.5)
Predominant histologic subtype	
Basaloid	13 (31.7)
Cribriform	13 (31.7)
Tubular	15 (36.6)
T classification	
T1	12 (26.7)
T2	25 (55.6)
T3	5 (11.1)
T4	3 (6.7)
N classification	
N0	43 (95.6)
N1	2 (4.4)
M classification	
M0	44 (97.8)
M1	1 (2.2)
Free margin	
Positive	10 (24.4)
Negative	31 (75.6)
Surgery	
Local excision	40 (88.9)
Orbital content excision	5 (11.1)
Treatment	
Excision	8 (17.8)
Excision+radiotherapy	22 (48.9)
Excision+radiotherapy+chemotherapy	15 (33.3)
Duration from first surgery to radiotherapy (d)	30 (6-546)

PNI: Perineural invasion; T: Tumor; N: Nodal metastasis; M: Distant metastasis.

P=0.028). In this cohort, 24 patients were detected PNI based on their histological findings.

Treatments The main treatment of ACC was the surgical removal of the tumor. Forty patients in our cohort underwent local tumor excision, whereas five patients underwent orbital content resection. Postoperative pathological reports revealed that one (2.2%) patient had lymph node invasion according to the histological results of the lymph node specimens, 10 (24%) patients had positive resection margins and 24 patients had PNIs. Fourteen patients underwent osteotomy during the surgery. We performed a logistic regression analysis to evaluate whether osteotomy resulted in a lower possibility of positive margins as the available space in the surgical field was significantly larger compared to cases without osteotomy. The results showed that the osteotomy did not correlate with positive margins in LGACC patients (OR=1.40; 95%CI, 0.32-6.10; *P*=0.654). There was no significant difference between PNI and TNM stages, histologic subtypes and patients' age, which was consistent with the results of Woo *et al*[15]. Tumor histological subtypes were available for 41 patients. The histological tumor subtype was basaloid in 13 patients, cribriform in 13, tubular in 15 (Figure 2). As for the adjuvant therapy, 22 patients received radiotherapy, and all of them had different degrees of radiotherapy-related skin and mucosal reactions, which could be improved by symptomatic treatment after the radiotherapy was completed. The median duration from first surgery to radiotherapy was 30d (range: 6-546d). Statistical analysis was performed using the Manny-Whitney test and results demonstrated that receiving radiotherapy within 2wk after surgery was correlated with

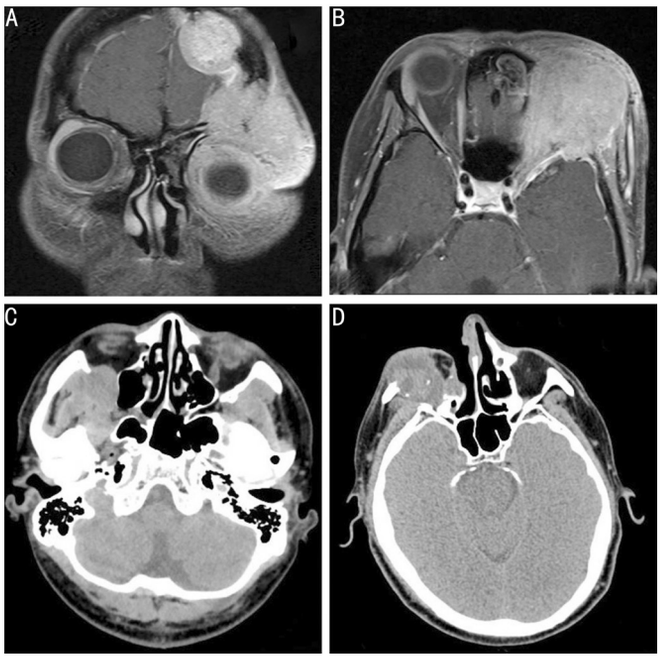

Figure 1 MRI and CT scans of patients who had adenoid cystic carcinoma of the lacrimal gland A, B: The MRI images of the same patient showed the tumor directly invades the brain parenchyma with bony invasions; C: Characteristic CT image findings were multiple hypodense with cribriform changes; D: CT scan showed calcification spots within the tumor. MRI: Magnetic resonance imaging; CT: Computed tomography.

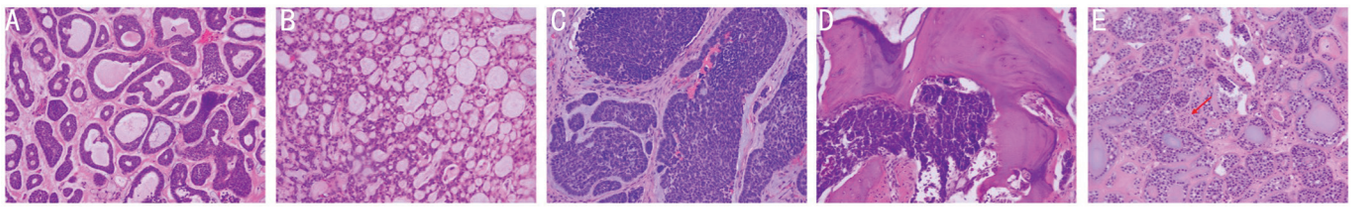

Figure 2 Histopathological findings of adenoid cystic carcinoma of lacrimal gland A: Glandular tube type: tumor cells are arranged into the duct; B: Cribriform type: there are various pore-like cavities in tumor nests; C: Solid type: tumor cells are closely arranged in clusters, forming round or oval solid tumor nests; D: Tumor cells invade the bone tissue and cause bony invasion; E: Tumor cells grow around the nerve and partially invade the nerve.

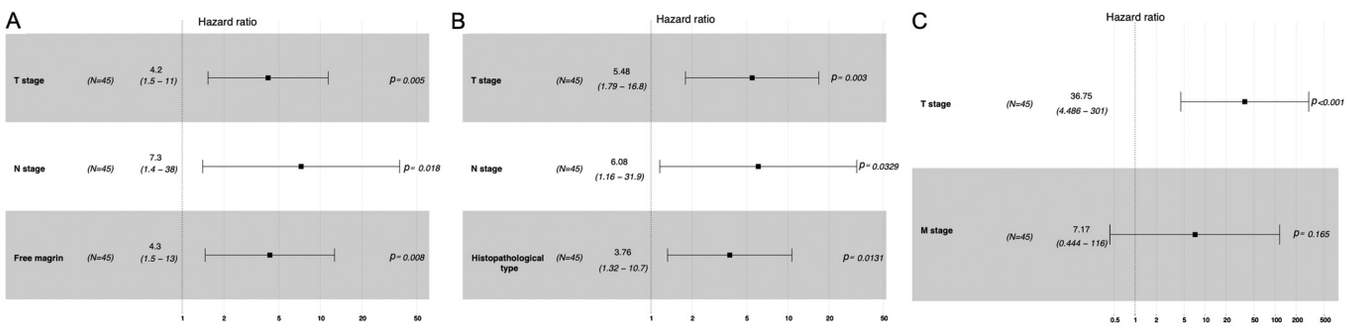

Figure 3 Multivariate Cox regression forest plot for recurrence (A), distant metastasis (B), and disease-specific survival (C).

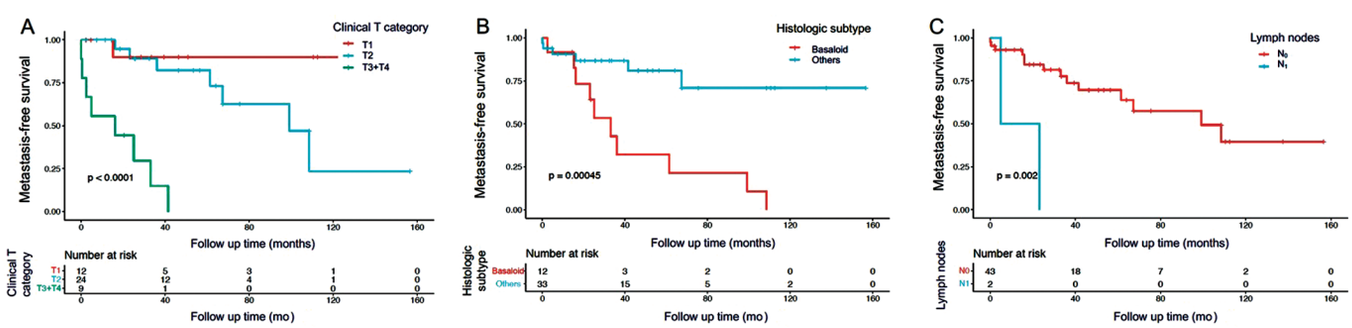

Figure 4 Metastasis-free survival rate of different LGACC patients Significant different metastasis-free survival rates were observed in patients with <T3a and ≥T3a tumors according to the 8th AJCC classification (A), histological subtype (B), and N stage (C). AJCC: The American Joint Committee on Cancer; N: Nodal metastasis.

metastatic risk in LGACC patients with basaloid component (P=0.022). However, in the Kaplan-Meier analysis, there is no significance observed due to the limited sample size. Fifteen patients received chemotherapy. Two of them underwent intra-arterial chemotherapy after biopsy surgery. Thirteen patients underwent intravenous chemotherapy.

Clinical Outcome Follow-up data were available for all patients with a mean of 69.0mo (median 60.5, range 8.3-167.5mo). Generally, local recurrences were found in 21 cases, with 1-, 3-, and 5-year recurrence rates of 15.6%, 33.3% and 44.4%, respectively. Sixteen patients developed distant metastases (35.6%), which were located in the brain (n=11), lung (n=7), liver (n=1), among them, 3 (6.7%) presented with metastases involving multiple sites. The median duration between the initial diagnosis and first metastasis was 33.4mo (mean: 44.4mo; range: 0-108.4mo) with 1-, 3-, and 5-year metastasis rates of 8.9%, 22.2%, and 26.7%, respectively. A total of 10 patients died during follow-up, including 9 died from tumor-related causes, 1 from intracranial infection. At the end of follow-up, the mortality rate in the overall cohort was 22.2% (10/45), with 1-, 3-, and 5-year disease-specific mortality of 4.4%, 13.3%, and 17.8%, respectively.

Outcome Analysis Distant metastasis was the primary endpoint for this study, while the secondary endpoint including local recurrence and tumor-related survival. We evaluated several potential predictive factors for the endpoints, as shown in Table 2. Univariate and multivariate analysis revealed that distant metastasis was correlated with the T (HR=5.48; 95%CI, 1.79, 16.8) and N (HR=6.08; 95%CI, 1.16, 31.9) classification, and histological subtypes (HR=3.76; 95%CI, 1.32, 10.7; Figure 3). Kaplan-Meier survival curves showed that patients a higher T stage (P<0.0001), nodal metastasis at presentation (P=0.0013), and histological subtype of basaloid (P<0.0001) were associated with a worse distant metastasis-free survival (Figure 4). As presented in Table 2, T (HR=4.18; 95%CI, 1.54, 11.40), N (HR=7.26; 95%CI, 1.40, 37.51)

Table 2 Univariate and multivariate analyses of clinical characteristics for local recurrence, metastasis, and tumor-related death in lacrimal gland adenoid cystic carcinoma patients

Variable	Local recurrence				Distant metastasis				Tumor-related death			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	P	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)
Age	0.569	0.99 (0.95, 1.03)			0.677	0.99 (0.95, 1.03)			0.282	0.97 (0.92, 1.02)		
Gender	0.287	1.63 (0.66, 4.02)			0.617	1.29 (0.47, 3.55)			0.571	1.45 (0.40, 5.25)		
Affected side	0.621	1.25 (0.52, 3.03)			0.935	0.96 (0.36, 2.58)			0.246	0.47 (0.13, 1.68)		
Duration of symptom (mo)	0.675	1.00 (0.99, 1.02)			0.921	1.00 (0.98, 1.02)			0.615	1.00 (0.99, 1.02)		
PNI	0.142	1.94 (0.80, 4.72)			0.600	1.31 (0.48, 3.56)			0.490	1.57 (0.44, 5.65)		
Bone invasion	0.481	1.45 (0.52, 4.05)			0.889	1.09 (0.34, 3.50)			0.693	1.38 (0.28, 6.93)		
Histologic subtypes	0.353	1.55 (0.62, 3.90)			<0.001[a]	6.24 (2.25, 17.32)	0.013[a]	3.76 (1.32, 10.72)	0.083	3.01 (0.87, 10.47)		
T classification	0.003[a]	3.41 (1.51, 7.66)	0.005[a]	4.18 (1.54, 11.40)	<0.001[a]	7.15 (2.60, 19.64)	0.003[a]	5.48 (1.78, 16.84)	<0.001[a]	39.85 (4.95, 321.18)	<0.001[a]	36.75 (4.49, 301.10)
N classification	0.023[a]	5.84 (1.27, 26.84)	0.018[a]	7.26 (1.40, 37.51)	0.010[a]	8.81 (1.76, 44.11)	0.032[a]	6.08 (1.12, 31.94)	0.146	4.94 (0.57, 42.64)		
M classification	NA	NA			NA	NA			0.007[a]	43.50 (2.72, 695.44)	0.165	7.17 (0.44, 115.70)
Free margin	0.024[a]	3.21 (1.17, 8.86)	0.008[a]	4.31 (1.47, 12.67)	0.953	1.04 (0.29, 3.74)			0.764	1.28 (0.26, 6.36)		
Surgery types	0.110	2.74 (0.80, 9.40)			0.110	2.84 (0.79, 10.23)			0.193	2.85 (0.59, 13.74)		
Osteotomy	0.153	1.91 (0.79, 4.64)			0.723	1.21 (0.42, 3.52)			0.702	1.30 (0.33, 5.09)		
Treatment	0.461	0.79 (0.41, 1.49)			0.743	1.13 (0.54, 2.36)			0.816	0.90 (0.37, 2.21)		

[a]Statistically significant. PNI: Perineural invasion; T: Tumor; N: Nodal metastasis; M: Distant metastasis; HR: Hazard ratio; CI: Confidence intervals.

classification and positive resection margins (HR=4.31; 95%CI, 1.47, 12.67) were significantly associated with the local recurrence. T stage was evaluated as an important factor for survival time (HR=36.75; 95%CI, 4.49, 301.10; Figure 3). Seven (87.5%) patients with ≥T3 tumors had local recurrence, distant metastasis and tumor-related death. Only 14 (37.84%) of the 37 patients with ≤T3 tumors had a local recurrence, 9 (24.32%) of them had distant metastasis and 3 (8.11%) of them had disease-specific death.

DISCUSSION

Data on LGACC are mostly limited to small case series and there are few studies providing insights into histopathology review, which might be a validated, strong and independent prognostic factor of survival. In this study, we sought to identify the prognostic factors, especially histopathological factors in 45 LGACC patients. To our knowledge, this is the largest series of LGACCs to correlate pathologic parameters with outcome. We revealed the risk factors for recurrence, distant metastasis and disease-specific death. More importantly, we demonstrated that the LGACC with basaloid component portend a more aggressive behavior out of these four histological patterns. And we first revealed that the durations from first surgery to radiotherapy is correlated with metastatic risk in LGACC patients with basaloid component.

The 5-year recurrence-free survival rate, metastasis-free survival rate and DSS rate of our center were similar to those of other specialty centers. Previous studies demonstrated that the prognosis of ACC is poor. Lesueur *et al*[18] reported a 5-year progression-free survival (PFS), local PFS and overall survival (OS) rate of 38%, 60% and 78%, respectively, in 15 patients with LGACC. Wolkow *et al*[11] reported a 5-year PFS and OS rate of 75% and 85%, with local recurrence rate of 22%. However, the recurrence rate of our cohort is relatively high, which might be caused by the serious condition of patient at the time of presentation or different surgical procedures. The findings indicated that the probabilities of recurrence, metastasis and disease-specific death vary among different institutions, and the discrepancies may have resulted from various management methods, surgical conditions, and multiple tumor characteristics.

In our cohort, most LGACC patients presented with exophthalmos and pain, which keep in line with previous studies[11,32]. Among 45 LGACC patients, the median difference of exophthalmometry between normal and affected eye is 5 mm (0-18 mm). Seventeen patients in this cohort had vision deterioration and 20 patients had eye movement disturbances. The median duration of symptoms is 6mo, which was very close to the report of 4mo[39].

The imaging manifestation of LGACC often presents as an oval-shaped lacrimal fossa soft tissue lesion on CT[40-41]. However, this

imaging manifestation lacks specificity. Soft tissue calcification on CT scans was found in 18% of cases. Calcification has little diagnostic value as it can also be encountered in pleomorphic adenoma[11,42]. Tumor-infiltrated condition can be evaluated through MRI with the mass enhancement is not uniformly visualized. The invasion of nerves in ACC patients is shown on MRI as the enlarged and irregular abnormal enhancement of the involved nerves, absence of perineuronal space and the atrophy or edema modifications of muscles adjacent.

Bony invasion and T stage are important factors in AJCC staging system of LGACC. Bony invasion of the lacrimal gland fossa is quite common in LGACC patients[39,43]. According to imaging, intraoperative findings and histopathological examinations, 27 cases of tumor cells infiltrated bone, causing bone destruction. There is no evidence from our cohort data that bony invasion is associated with poor patient outcomes. However, several research have demonstrated bony invasion as an important signature of prognosis. Spiro *et al*[44] have concluded that bony invasion was an ominous sign for ACC patients. In their cohort, only 5 of 75 patients (6.7%) with bony invasion were survived, while for patients without bony invasion, 32.3% of them survived without the evidence of disease. According to AJCC recommendations, staging of LGACC is mainly based on the TNM system. Our results reflected that tumor staged T3 or worse at presentation were associated with a poorer outcome. Certain studies also confirmed that T stage was correlated with ACC prognosis. The results of Ueda *et al*[26] showed that LGACC patients with progression of more than T3 in TNM classification suggested poor outcome. In their cohort, 2 of 4 patients (50%) with ≥T3 tumors were dead while 6 patients with ≤T3 tumors were alive and well.

ACC has neurophilic invasive properties and tends to spread along nerves[45]. There is no evidence from our cohort data that tumor perineural invasion is associated with poor patient outcomes. However, several publications have demonstrated PNI as an important signature of prognosis. In a cohort of 495 patients with ACC, PNI was described as an independent prognostic marker for both OS and DSS, but not of distant metastases[46]. A study of salivary ACC showed that PNI not only correlated with site, histological grade or other clinicopathological variables, but can also serve as a prognostic factor[47]. Garden *et al*[30] retrospectively analyzed 198 patients with ACC. Eighty-three patients (42%) had microscopic positive margins and an additional 55 (28%) had close (≤5 mm) or uncertain margins. They found that microscopic positive margins was an adverse prognostic factor, but even when present, local control was achieved in over 80% of ACC patients with positive margins. Our results show that T, N classification and positive resection margins are significantly associated with an increased risk of local recurrence, which was also observed in other kinds of ACC. Garden *et al*[30] evaluated the influence of positive margins in ACC of the head and neck treated with surgery and radiation, among which microscopic positive margin was an adverse prognostic factor. Therefore, they recommended a dose of 60 Gy to the tumor bed and 66 Gy for patients with positive margins to reduce the recurrence rate. However, in a study of salivary gland ACC, positive margin was found to be an independent prognostic factor for both OS and disease-free survival[48].

Our results suggested that basaloid tumors usually indicate poor prognosis. In this study, rates of metastasis in basaloid tumors are higher compared to the other types. Nearly 80% (10/13) of patients with basaloid tumors developed metastasis, while the percentage was only about 20% (6/28) in patients with other types of tumors. Similar trend was also observed in other cohorts, not only in LGACC but also in other kinds of ACC. Slodkowska *et al*[38] have previously found that basaloid mammary ACC were associated with more aggressive pathologic features as well as more frequent lymph node metastases, distant metastases and faster progression. Lee *et al*[48] found that the survival period of solid LGACC was shorter than other histopathological types. A study in Japan showed that higher histological grade was associated with a lower OS in patients with salivary gland adenoid cystic carcinoma. We further analyzed the effect of different treatment modalities on the prognosis of patients with basaloid component. We performed Manny-Whitney test and found that the durations longer than 2wk from first surgery to radiotherapy is correlated with metastatic risk in LGACC patients with basaloid component. However, there was no significant difference by Kaplan-Meier analysis, which may because of the small size of the samples in this cohort. We need to expand the size of the samples to make more rigorous verification of this conclusion.

In a study of Lesueur *et al*[18] in 2020, the durations from first surgery to radiotherapy was not independently related to LGACC patients' prognosis. However, there were few research focus on the durations from first surgery to radiotherapy.

There are several limitations in our study. The retrospective study design resulted in problems with a potential information bias. In addition, all the patients were recruited from a single ocular oncology center, and limited sample size might produce large confidence intervals for hazard ratios in Cox analysis. In addition, surgical techniques and adjuvant treatment strategies continue to evolve as knowledge and technology advance. Therefore, it would be difficult to compare the treatment outcomes with other reports.

In this study, we analyzed the association between clinical and histopathological characteristics and prognosis in LGACC. The results confirmed prognostic value of the AJCC TNM

staging system of LGACC. Moreover, considering the association between basaloid type and worse prognosis in LGACC, histological grade should be emphasized in future risk stratification and treatment planning for patients with AJCC. The significant association between positive of the surgery margin and local recurrence highlights the importance of definite the extent of the lesion before surgery and apply the surgical technique of complete resection. Moreover, timely radiotherapy may reduce the risk of metastasis in patients with basaloid component.

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