



Survival outcomes of eye-sparing surgery for adenoid cystic carcinoma of lacrimal gland

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Abstract

Purpose To survey adenoid cystic carcinoma of lacrimal glands in Asian population and investigate the predictability in prognosis following the 8th edition American Joint Committee on Cancer (AJCC) staging guideline.

Study design Retrospective study.

Methods The clinical entities and surgical outcomes of the patients who were histologically confirmed with a diagnosis of lacrimal adenoid cystic carcinoma in National Taiwan University Hospital between January 1995 and December 2015 were retrospectively reviewed.

Results Enrolled were 11 patients. The median follow-up was 7.2 years. Eight patients (72.7%) were diagnosed as T1 or T2 disease, and three patients (27.3%) were diagnosed as T3 or T4 disease according to the AJCC 8th edition guideline. Eye-sparing surgery with radiotherapy was performed in nine patients. Local recurrence was noted in six patients (54.5%) with median disease-free interval of 23.5 months. Six patients (54.5%) developed distant metastases, including lung, bone, and cranial invasions. Overall survival rate during the study period was 54.6%. Five-year overall survival was 81.8% and ten-year overall survival was 68.2%. The Log-rank test for overall survival and disease-free survival between patients with less than T3 disease ($p=0.001$) and patients with T3 or T4 disease ($p=0.006$) revealed significant differences.

Conclusion This study highlighted the aggressive nature of adenoid cystic carcinoma of lacrimal glands. Eye-sparing surgery with adjunctive radiotherapy may achieve relatively optimal disease control in diseases staged T1 or T2, but in advanced disease metastasis and mortality are usually inevitable.

Keywords Adenoid cystic carcinoma · Lacrimal gland tumor · AJCC staging

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Introduction

Lacrimal gland tumor is one of the most common orbital masses, and adenoid cystic carcinoma is the most common malignant epithelial tumor of the lacrimal gland [1]. In Shield's study, half of the lacrimal gland tumors were of epithelial origin and 12% of these were adenoid cystic carcinoma [2]. In two studies from China, adenoid cystic carcinoma accounted for about 6% of lacrimal gland tumors [3, 4]. Clinical manifestations of adenoid cystic carcinoma include proptosis, diplopia, and S-shape ptosis. Pain is sometimes presented in aggressive lesions, but hypoesthesia may be characteristic of orbital nerve invasion [5]. Image studies, including MRI and CT, reveal space-occupying solid tumor with possible bone erosion, local invasion, or lymphatic metastasis. The most common site of distant metastasis is the lungs, followed by bones and liver [6]. A slowly progressive clinical course with poor prognosis is often observed.

Controversy remains regarding the appropriate local therapy for adenoid cystic carcinoma of the lacrimal gland. Several articles report success in eye-sparing surgery with adjunctive radiotherapy or chemotherapy [7]. Ahmad et al. investigated the efficacy of the 6th American Joint Committee on Cancer Classification (AJCC) in predicting the survival and local control in these patients. They report poorer outcomes of local recurrence in T3 or worse disease [8]. The 8th version of AJCC, published in 2016, classified tumors with or without periosteum and bone involvement as T1 to T3 stages according to tumor size, and any involvement of adjacent structures as T4 [9].

This study was aimed at surveying the clinical entity in Asian population and investigating the prognosis of lacrimal adenoid cystic carcinoma as staged by the newer 8th edition AJCC guideline.

Methods

A retrospective chart review was conducted in National Taiwan University Hospital between January 1995 and December 2015. The study enrolled patients who were histologically confirmed with a diagnosis of lacrimal adenoid cystic carcinoma, and the protocol was approved by the Ethics Committee of the National Taiwan University Hospital and followed the Declaration of Helsinki Guidelines. Information analyzed included sex and age at diagnosis, symptoms at presentation, laterality, histological characteristics, extent of disease at diagnosis, the presence of perineural invasion, the presence of adequate free margin in specimen, staging by the AJCC 8th edition guideline

Table 1 American Joint committee on cancer classification 8th edition for lacrimal tumor staging. *Adapted from American Joint Committee on Cancer (AJCC) classification 8th edition manual [9]

Stage	Description
T1	Tumor size < or = 2 cm
T2	Tumor size between 2 cm and 4 cm
T3	Tumor size > 4 cm
For stage T1 to T3	a No periosteum or bone involvement b Periosteum involvement only c Bone involvement
T4	Invasion into adjacent structure a Tumor size < or = 2 cm b Tumor size between 2 cm and 4 cm c Tumor size > 4 cm
N	Presence of lymph node metastasis
M	Presence of distant metastasis

(Table 1) with image study at presentation, forms of surgical and adjuvant local therapies [9].

The timing of local recurrence and distant metastasis, treatment associated complications, disease-free and overall survival times were also analyzed. Disease-related mortality was defined as the percentage of patients who died as a direct result of their disease, including peri-operative death. Disease-free survival time was measured from the completion of treatment to the date of recurrence or the most recent follow-up examination. Overall survival time was measured from the date of initial diagnosis. According to previous literature of outcome analysis, the Kaplan–Meier method was used to simulate overall and disease-free survival distributions and log rank test was performed to compare overall and disease-free survival between tumors \geq T3 stage and $<$ T3 stage [8].

Results

Patient characteristics and modality of treatment

There were 11 cases enrolled in this retrospective study. Patient and treatment characteristics are summarized in Table 2. The mean age at diagnosis was 43.6 ± 18.6 years (range 20 to 86 years). The median follow-up was 7.2 years (rang 1.8 to 16.3 years). The study included seven men (63.6%) and four women (36.4%). The tumor was located on the left side in five patients and on the right side in six patients. The clinical manifestations included proptosis in seven patients (7/11, 63.6%), orbital pain in three patients (3/11, 27.3%), decreased visual acuity in three patients (3/11, 27.3%) and lid swelling in two patients (2/11, 19.2%). Two patients (2/11, 19.2%) were diagnosed as T1 disease,

Table 2 Patient characteristics, treatment, pattern of recurrence and outcomes

Case	Age	Sex	Side	AJCC Stage	Treatment	RT dose (cGy) & Model	Histology	Perineural invasion	Free margin	Time and status at last follow-up (months)	Time of local recurrence (months)	Time and site of metastasis (months)
1	40	M	R	T1aN0M0	Resection Exenteration	60, IMRT	Cribriform	+	+	86; alive with D	43	No metastasis
2	39	M	L	T2aN0M0	Resection	60, 3DRT	Cribriform	+	-	156; Died of D	No LR	114; lung metastasis
3	28	M	R	T2aN0M0	Resection	70, 3DRT	Cribriform	+	-	163; Alive, no D	No LR	No metastasis
4	29	F	L	T1aN0M0	Resection	60, 3DRT	Cribriform	-	+	196; Alive, no D	No LR	No metastasis
5	50	F	R	T2cN0M0	Resection	70, 3DRT	Cribriform	+	-	129; Alive with D	77	105; lung metastasis
6	86	F	L	T4cN0M0	Craniotomy + Resection	70, 3DRT	Tubular	+	-	28; Died of D	4	Initial intra-cranial bone invasion
7	23	M	L	T2cN0M0	Resection x III*	No RT	Tubular	-	-	144; Died of D	12	120; bone metastasis
8	50	F	R	T4bN0M0	Resection Exenteration	60, 3DRT	Cribriform	+	-	38; Died of D	27	27; intra-cranial invasion
9	35	M	R	T4?N0M0#	Resection +CT Exenteration	60, 3DRT	Basaloid	+	-	114; Died of D	15	15; bone metastasis
10	40	M	L	T2cN0M0	Resection	60, IMRT	Cribriform	-	-	64; Alive, no D	No LR	No metastasis
11	20	M	R	T2aN0M0	Resection	60, IMRT	Cribriform	+	-	65; Alive, no D	No LR	No metastasis

AJCC American Joint Committee on Cancer Classification, *M* male, *F* female, *R* right, *L* left, *RT* radiation therapy, *IMRT* intensity-modulated radiation therapy, *3DRT* 3D radiation therapy, *CT* chemotherapy, *D* disease, *LR* local recurrence

*Three consecutive surgeries as tumor resection were done due to local recurrence in Patient No. 7

#Resection was done in case No 9 in other hospital, and the documentation of size was not available. Cranial fossa involvement documented by image report

six patients (6/11, 54.5%) as T2 disease, and three patients (3/11, 27.3%) as T4 disease following to the AJCC 8th edition guideline. None of these patients had lymph node or distant metastases upon diagnosis.

Eye-sparing surgery (orbitotomy with wide excision of lacrimal gland tumor) without radiotherapy was performed in one patient (case 7), and eye-sparing surgery with radiation was performed in six patients (cases 2-5, 10, 11). One patient (case 9) had local tumor excision with post-operative adjuvant radiation and chemotherapy as the first management; however, after local recurrence with rib metastasis, exenteration and bone removal with adjuvant radiation were done subsequently. Two patients (case 1, 8) received local tumor excision with adjuvant radiation as the initial treatment and exenteration without bone removal combined with adjuvant radiation following recurrence. One patient (case 6) underwent tumor excision and craniotomy with adjuvant radiation due to skull invasion. Ten out of 11 patients received adjuvant radiation after initial operation. The dose of radiation ranged from 60 to 70 Gy in 30 to 35 separate sessions. The radiation modality involved 3D radiotherapy (3DRT) or intensity-modulated radiotherapy (IMRT). The radiation field covered the skull base in addition to the orbit due to the high prevalence of perineural invasion in most patients.

Tissue blocks and histological sections were available for all 11 patients in this study. All tumors showed a mixture of tubular, cribriform, and basaloid (solid) patterns. Predominantly cribriform patterns were found in eight specimens (72.7%), predominantly tubular pattern in two (18.2%), and predominantly basaloid pattern in one (9.1%). Eight of 11 patients had histological evidence of perineural invasion (72.7%). Among the patients with histological evidence of perineural invasion, 5 (62.5%) had local recurrence, 3 of them eventually developed distant metastasis (cases 5, 6, 9), and two had intracranial invasion. One patient (case 2) with histological evidence of perineural invasion and no local recurrence developed lung metastasis. Only two specimens (18.2%) had adequate free margin. Between these two patients, one patient with perineural invasion had local recurrence (case 1). The other patient without perineural invasion remained without local recurrence for 196 months after operation (case 4).

Treatment complications

The common complications are listed in Table 3. Radiation related problems accounted for most complications. Dry eye occurred in all patients with radiation (100%). Three patients (27.3 %) developed radiation retinopathy and neuropathy, with visual acuity that deteriorated to hand motion or worse. Secondary glaucoma due to tumor burden occurred in three patients (27.3%) with poor visual acuity

(no light perception). Other complications included diplopia (2, 18.2%), cataract (1, 9.1%), and eyelid erythema (1, 9.1%).

Patterns of recurrence and survival

The patterns of recurrence and survival are listed in Table 2. Local recurrence was noted in six patients (54.5%) with mean and median disease-free intervals of 30.5 months and 23.5 months, respectively. Three of them (cases 1, 8, 9) received exenteration due to extensive local recurrence (50%) and one (case 9) received rescue chemotherapy. Adjuvant radiation was done in two patients (case 1, 5). Four patients (36.4%) developed distant metastasis and two patients (18.2%, cases 6, 8) had direct intracranial invasion during the study period. Lung metastasis was found in two patients (18.2%, cases 2, 5), while bone metastasis (spine, rib) was noted in other two patients (18.2%, cases 7, 9). Six of eleven patients were alive at the time of chart review and overall survival rate was 54.6%. One patient (case 5) with lung metastasis undergone wedge resection and was alive during the follow-up period.

There were eight patients with T1 and T2 diseases, and four of them were disease free at the time of this review (50%, cases 3, 4, 10, 11). One had local recurrence at 43 months after diagnosis and received exenteration (case 1). One case had lung metastasis at 114 months after diagnosis, resulting in mortality (case 2). One case had lung metastasis at 105 months and was alive after treatment (case 5). The last case died of disease at 144 months, the patient had received surgery only, without radiotherapy (case 7). Three patients had T4 disease, and all of them died with disease during the follow-up period (case 6, 8, 9), with mean survival of 60 months.

The Kaplan Meier Survival Plot for overall survival and disease free survival are presented in Figures 1 and 2. The mean overall survival time for the entire group was 107.5 months (ranged 28 to 196 months). The mean disease-free survival time for the entire group was 74.7 months (ranged 0 to 196 months). Five-year overall survival was 81.8% and 10-year overall survival was 68.2%. 5-year disease-free survival was 54.5% and 10-year disease-free survival was 27.3%. The Log-rank test was performed to compare the overall survival and disease free survival between patients with less than T3 disease and patients with T3 or T4 disease, both of which revealed statistically significant differences between both groups ($p=0.001$ and $p=0.006$, respectively). (Figs. 3, 4) Moreover, overall survival was better when the pathology revealed predominant cribriform pattern followed by tubular or basaloid pattern, which were 75% and 0%, respectively ($p=0.027$, Log Rank test for Kaplan Meier Survival Plot, Fig. 5).

The archived tissue blocks were available for all 11 patients. One patient (case 9) with basaloid histological

Table 3 Extent of adenoidal cystic carcinoma and treatment complications

Case	AJCC Stage	Treatment	Extent of disease	Treatment complications
1	T1aN0M0	Resection + RT Exenteration	Tumor size : 1.8x0.5x0.5 cm Tumor size : 1.8x0.5x0.5 cm	Diplopia, Dry eye
2	T2aN0M0	Resection + RT	Tumor size: 2.5 x1x1 cm	Dry eye, cataract
3	T2aN0M0	Resection + RT	Tumor size: 3.5x2x1.5 cm Muscle, Globe involvement	Dry eye, radiation retinopathy, radiation neuropathy, NVG, globe atrophy, NLP
4	T1aN0M0	Resection + RT	Tumor size: 1.8x1.7x1.2 cm	Dry eye, radiation retinopathy, radiation neuropathy, LP
5	T2cN0M0	Resection + RT	Tumor size: 3.0x2.0x0.8 cm Bone involvement	Dry eye
6	T4cN0M0	Craniotomy Resection+ RT	Tumor size:7x7x10 cm Bone involvement & Intracranial invasion	Local eyelid erythema Dry eye
7	T2cN0M0	Resection x III*	Tumor size: 2.3x1.5x0.5 cm Bone involvement	Secondary glaucoma, NLP
8	T4bN0M0	Resection + RT Exenteration	Tumor size: 3.0x3.0x2.5 cm Cranial fossa involvement	Diplopia, Dry eye Secondary glaucoma, NLP
9	T4?N0M0 #	Resection + RT + CT Exenteration + Craniotomy	Tumor size: N/A, Cranial fossa involvement Tumor size: 7.5x3.0x3.0 cm Bone, Eyelid and Muscle involvement	Dry eye, Radiation retinopathy, HM10 cm
10	T2cN0M0	Resection +RT	Tumor size: 3.0x2.5x1.8 cm Bone involvement	Dry eye
11	T2aN0M0	Resection +RT	Tumor size: 3.0x2.5x2.0 cm	Dry eye

AJCC American Joint Committee on Cancer Classification, RT radiation therapy, CT chemotherapy, LR local recurrence, N/A not available, NLP no light perception, LP only light perception, HM10 cm visual acuity only hand motion 10 cm

*Three consecutive surgeries as tumor resection were done due to local recurrence in case No. 7

#Resection was done in case No 9 in other hospital, and the documentation of size was not available. Cranial fossa involvement documented by image report

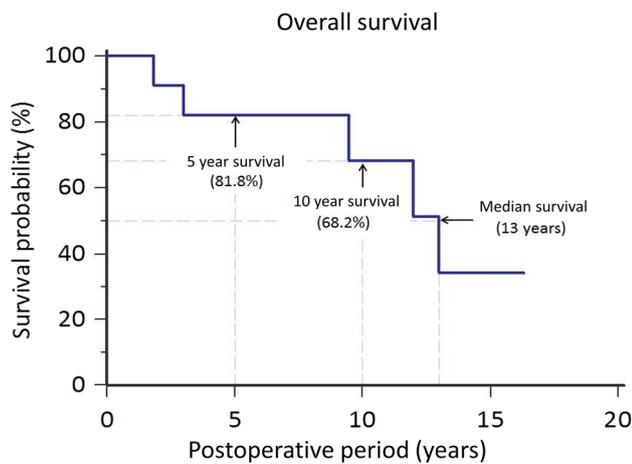


Fig. 1 Kaplan–Meier overall survival curve of 11 cases after surgery and intervention for lacrimal gland adenoid cystic carcinoma. 5-year-survival rate was 81.8% and 10-year-survival rate was 68.2%

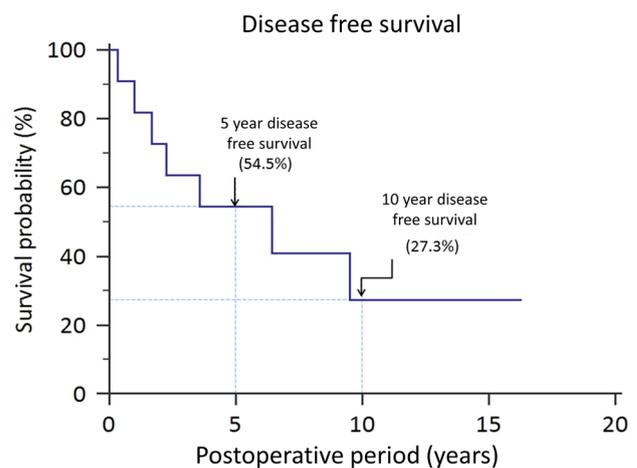


Fig. 2 Kaplan–Meier disease-free survival curve of 11 cases after surgery and intervention for lacrimal gland adenoid cystic carcinomas. 5-year-survival rate was 54.5% and 10-year-survival rate was 27.3%

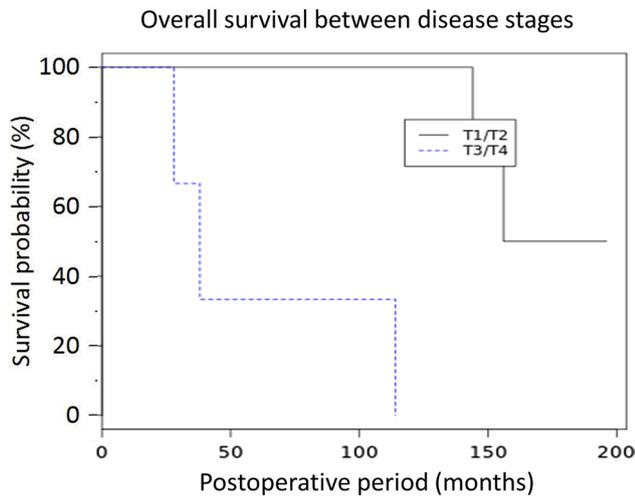


Fig. 3 Kaplan–Meier overall survival curve of 11 cases after surgery and intervention for lacrimal gland adenoid cystic carcinoma, between T1 / T2 and T3 / T4 groups. $p = 0.001$ (Log-rank test)

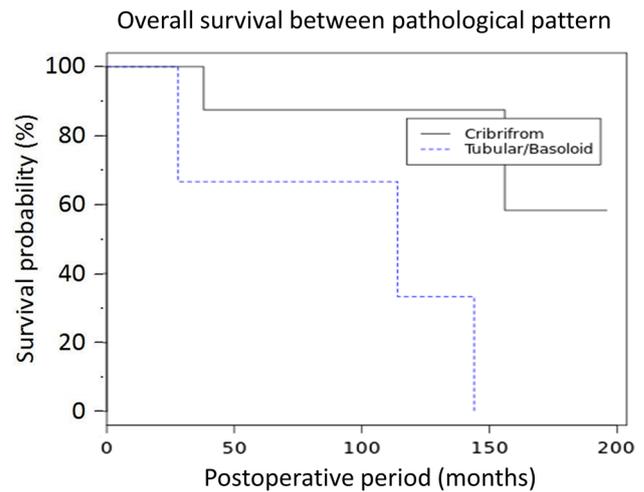


Fig. 5 Kaplan–Meier overall survival curve of 11 cases after surgery and intervention for lacrimal gland adenoid cystic carcinoma, between cribriform and tubular/basoloid pattern in pathology. $p = 0.027$ (Log-rank test)

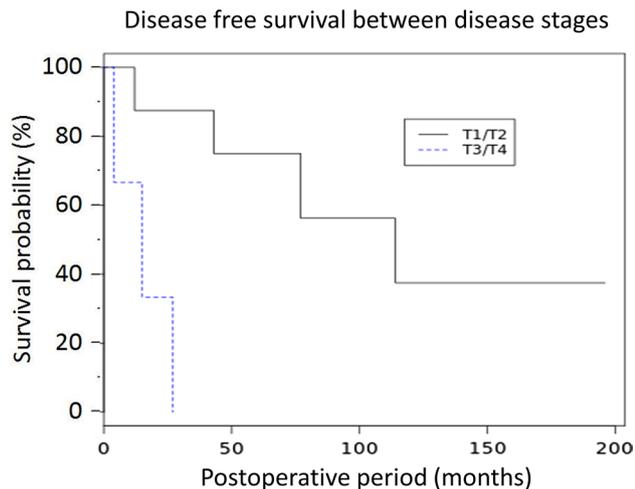


Fig. 4 Kaplan–Meier disease-free survival curve of 11 cases after surgery and intervention for lacrimal gland adenoid cystic carcinoma, between by T1 / T2 and T3 / T4 groups. $p = 0.006$ (Log-rank test)

subtype had local recurrence and died of rib and spinal metastases. Among the two patients (case 6, 7) with tubular subtype, both had local recurrence and one patient had spinal metastasis during follow-up. The patients died at 28 and 144 months respectively after the final treatment. Eight patients with cribriform subtype had diseases with more indolent behavior and two of them (cases 2, 5) had lung metastasis at 114 and 105 months after diagnosis respectively. Two patients with cribriform subtype (2/8, 25%) died at 38 and 156 months respectively after the final treatment.

Discussion

In this case series, we report the prognoses of 11 patients with adenoid cystic carcinoma of lacrimal gland from 1995 to 2015. All patients received eye-sparing surgery for tumor resection as initial therapy. Adjunctive radiotherapy was done in most patients. The 5-year and 10-year survival rates were 81.8% and 68.2%, comparable with previous studies and better than stated in some reports [6, 10]. The adenoid cystic carcinoma of lacrimal gland had relatively slow progression compared with other solid tumors, including adenoid cystic carcinoma of salivary gland, which resulted in relatively higher survival [11].

The histological subtype of adenoid cystic carcinoma was proposed as an important prognostic factor for survival in previous reports [6, 12, 13]. In Gamel et al.'s study, patients with basaloid predominant subtype were found to have poorer outcome compared to cribriform predominant subtype for both lacrimal and salivary gland tumors, with a 5-year overall survival as low as 21% [13, 14]. In our study, patients with cribriform predominant subtype had longer local recurrence intervals, slower distant metastasis, and better overall survival ($p = 0.0260$). On the other hand, patients with basaloid or tubular predominant subtype developed frequent local recurrence with shorter disease-free intervals and multiple distant metastases (Table 2).

Perineural invasion and the failure to obtain free margin in specimen also indicated higher risk of recurrence and mortality [8, 15, 16]. Ahmad et al. report that 93% of local recurrence had histological evidence of perineural invasion and 53% of local recurrence had failure to obtain free margin. The authors also emphasize that the decision to undergo

adjunctive radiation was based on the presence of perineural invasion [8]. In our study, the patient with the longest follow-up without any clinically observable recurrence (196 months) had cribriform predominant subtype with histological tumor-cell-free margin and absence of perineural invasion (case 4). Cases 1 and 2 did have perineural invasion, and both local recurrence and distant metastasis were found, despite the relative earlier stage of T1 and T2 disease. In the patients without perineural invasion, mortality rate was 33.3% (1/3), lower than those with perineural invasion (4/8, 50%). However, due to the limitation in sample size and different disease severities, it was difficult to derive statistically significant conclusions from this study.

The treatment protocol for adenoid cystic carcinoma remains controversial. Uncertainties exist in deciding between eye-sparing surgery for tumor resection and exenteration, as well as between adjunctive radiotherapy and systemic chemotherapy. Esmaeli et al. report seven cases with T4 disease that received exenteration and bone removal, and although local control was achieved in all cases five died from distant metastasis [17]. The same authors also report the efficacy of eye-sparing surgery and adjunctive radiotherapy, with disease-free survival up to 64 months [18]. Chen et al. demonstrate the benefits of post-operative radiotherapy in patients with head and neck adenoid cystic carcinoma, associated with lower local recurrence rates within 5 and 10 years, although these had no significant effect on distant metastases. They advocate post-operative radiotherapy as standard treatment for these patients [10].

In our study, the decision to perform an orbital exenteration was based on the gross radiographic presence of tumor in the orbital apex or extension beyond the orbit into paranasal sinuses and the brain parenchyma. The decision to remove bone depended on either obvious radiographic evidence of bony involvement or intra-operative findings of abnormal bony orbit. Three patients received exenteration and postoperative radiation and two of them died from the disease. The mortality rate was 66.6% among these three patients.

All patients but one underwent postoperative radiation therapy in this study. All patients received photon external beam radiation with 60 to 70 Gy radiation dose. One patient without perineural invasion and negative free section margin refused to receive radiotherapy and had a repeated local recurrence later. It seems that lack of treatment with postoperative radiation may lead to local recurrence, even without the evidence of histological perineural invasion. The patient developed secondary glaucoma and visual acuity was only light perception due to repeated local recurrence.

Previous studies report complications related to radiotherapy, such as dry eye, dermatitis, ocular pain, cataract, vision threatening keratitis and radiation retinopathy or neuropathy [19, 20]. While minor complications, such as

cataract and eyelid erythema, occurred in limited number of cases, retinopathy and neuropathy were noted in three patients in our study and impaired the vision to hand motion or worse. The occurrence of complications seems to be correlated with the therapeutic dosage. Doses exceeding 50 Gy may result in corneal damage and further conjunctival metaplasia. More than 60 Gy of radiation exposure may raise the risk of developing optic neuropathy, which was required for adequate cancer control [21]. Newer radiation techniques, such as three-dimensional conformal radiation therapy or intensity-modulated radiation therapy, were tried in order to increase local control and decrease ocular side effects [7].

Other potential local therapies for lacrimal gland adenoid cystic carcinoma have been introduced. Tse et al. advocate intra-arterial cytoreductive chemotherapy for lacrimal gland adenoid cystic carcinoma. They report that neoadjuvant intra-arterial cytoreductive chemotherapy seemed to improve overall survival and decrease disease recurrence [21]. This potential treatment modality can be beneficial for patients with large, inoperable tumors by shrinking mass to a more surgically amenable size.

According to the literature, 5-year survival rate of lacrimal gland adenoid cystic carcinoma is about 50% despite various conventional treatment modalities [1, 6]. Our series with surgical excision and adjunctive radiotherapy had obtained the higher 5-year survival rate of 81.8%. Esmaeli et al. report that the patients in their cohort with < T3 tumors had 5-year survival rates of about 100% and with \geq T3 tumors 55% [6]. Our series had comparable results with 5-year survival rates of about 100% and 63%, respectively. The AJCC 8th edition emphasizes the importance of the involvement of adjacent structure, which is identified as T4 disease. The involvement of periosteum or bone was categorized in to T1 to T3 according to tumor size. Based on our results, the prognosis is still poorer in patients staged with T3 and T4 disease. Larger tumor size was considered to be more unfavorable than bone involvement on survival in the case series by Williams et al. [22].

The rare prevalence of the disease, the small sample size and retrospective nature pose limitations on the attempt to represent Asian populations and to identify other prognostic factors besides tumor grading. There was also lack of sufficient evidence related to the decision between exenteration and eye-sparing surgery, hence a larger sample size for comparative study is still needed in the future.

In summary, this study describes the aggressive nature, the high risk of systemic metastases and the high mortality of adenoid cystic carcinoma in lacrimal gland. Eye-sparing surgery with adjunctive radiotherapy may achieve relatively optimal disease control in less severe disease, those staged as T1 or T2 according to the newest AJCC system, but metastasis and mortality are usually inevitable in more advanced cases.

Conflicts of interest J.-Y. Hung, None; Y.-H. Wei, None; C.-H. Huang, None; L.-W. Chen, None; C.-S. Fuh, None; S.-L. Liao, None.

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