• Clinical Research •

Clinical analysis of 109 cases of lacrimal gland pleomorphic adenoma

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Abstract

● **AIM:** To monitor the prognosis of patients with lacrimal gland pleomorphic adenoma (LGPA) following surgical resection within the past 10y. The factors affecting patient prognosis are analyzed and the experience of surgical treatment is summarized.

● **METHODS:** In this retrospective, comparative case series, clinical records from 109 cases of LGPA treated chiefly at the same institution between November 2009 and May 2019 were reviewed. All 109 patients underwent surgery, histopathological examination, and imaging examination. For patients who underwent surgery for the first time, LGPA could be resected completely, including tumor and capsule tissues, using a surgical approach *via* the eyebrow arch or double eyelid crease.

● **RESULTS:** The ratio of males to females was 1:1.60, the ages ranged from 19 to 74 years old with a mean age of 43.64±13.07 years old, and the ratio of left to right eyes was 1:1.37. A total of 109 patients underwent surgical excision and five of these received radiotherapy after malignant transformation. Of these patients, 15 were lost to follow up within the April 1, 2020 deadline and 1 was diagnosed as a recurring pathology. The 5-year recurrence rate for 86 patients who underwent initial surgery was 7.27%. Single factor analysis revealed that the course of disease, bone destruction, invasion of surrounding tissues, tumor size, capsule integrity, and expression of Ki-67 were statistically significant (P<0.05). Binomial Logistic regression analysis showed that capsule integrity was a risk factor influencing recurrence (P=0.008).

● **CONCLUSION:** LGPA has a risk of recurrence and potential for malignant transformation. Complete removal of the tumor and capsule in the initial surgery is a key factor in preventing recurrence.

● **KEYWORDS:** pleomorphic adenoma; lacrimal gland; malignant transformation; treatment; prognosis

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INTRODUCTION

Lacrimal gland pleomorphic adenoma (LGPA), also known as lacrimal gland mixed tumor, is the most common benign epithelial tumor of the lacrimal gland, accounting for about 50% of epithelial tumors[1-2]. Its microscopic structure shows glandular epithelium, myoepithelium, myxoid or chondroid matrix, and other components. LGPA has a risk of recurrence and malignant transformation. With improvement of diagnosis and treatment in recent years, the recurrence rate of LGPA has declined. In this article, the treatment and prognosis of 109 cases of LGPA occurring within the past 10y have been analyzed to assess the recurrence rate and prognostic factors.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Ethics Committee of Beijing Tongren Hospital and conducted according to the Helsinki principles. Written informed consents were obtained from all patients.

Study Design and Procedure A total of 109 patients with LGPA, who were diagnosed between November 2009 and May 2019 by histopathologic examination, were observed in the Department of Ophthalmology at Beijing Tongren Hospital, Capital Medical University.

The analysis of clinical data included age, gender, clinical manifestation, physical examination, tumor size, imaging findings and histopathological manifestations, and treatment and prognosis. The period between the first appearance of symptoms and the last treatment was regarded as the course of disease and divided into four parts as follows: ≤5y, 5-10y, 10-15y, and 10-20y. Tumor size was classified into

the following four groups: ≤1.0 cm, 1.0-2.0 cm, 2.0-3.0 cm, and >3.0 cm. Ki-67 expression was grouped into three groups according to the following percentages: ≤5%, 5%-10%, and >10%.

Treatment All 109 patients underwent surgery, histopathological examination, and imaging examination. For patients who underwent surgery for the first time, LGPA could be resected completely, including tumor and capsule tissues, using a surgical approach *via* the eyebrow arch or double eyelid crease. For patients with recurring tumors, based on preoperative imaging findings and intraoperative conditions, an extended total lacrimal tumor resection, including removal of surrounding tissues and involved bone, margin assessment, and frozen section, was performed for the following conditions: multiple lesions and a maximum diameter for single tumors ≥4 cm; tumor capsule ruptures, with extensive involvement of surrounding tissues, including fat, skin, and nerves; and bone destruction or bone wall defect. For LGPA patients suspected of malignant transformation before surgery, the eyebrow arch approach was adopted for tumor removal due to complete exposure of the tumor and radiotherapy was adopted for cases of extensive malignancy following diagnosis by histopathology.

For radiotherapy, ^{125}I seed radiation is a locally precise radiotherapy method with few complications and is considered to be effective for treating recurrent or malignant, lacrimal, epithelial tumors. ^{125}I seeds were implanted at the inner and outer margins of the superior rectus muscle, the superior and lower margins of the superior temporal muscle, and the superior and lower margins of the external rectus muscle, with a spacing of 1 cm and a distance of 0.8 cm from the skin. The average number of implanted seeds was 18, each with a unit activity of 0.7-0.8 mCi. External radiotherapy was also recommended. Recurrence was judged on the basis of histopathological examination. The deadline for follow-up was April 1st, 2020. By the time of follow-up, patients without recurrence, loss of follow-up, or without previous history of recurrence were designated as primary patients and those with a relapse or a history of recurrence were designated as recurrent patients.

Statistics In this study, SPSS 19.0 statistical software was used to process and analyze the data. Analysis of variance, Chi-square test, or Fisher's exact test were used to evaluate correlations between variables. Modulating factors were analyzed by binomial Logistic regression analysis in combination with the values obtained from the univariate clinical analysis. P<0.05 was considered statistically significant.

RESULTS

General Clinical Characteristics There were 109 cases of LGPA, of which 42 were male and 67 were female, with an overall age range from 19 to 74y and a mean of 43.64±13.07y. Forty six cases occurred in the left eye, 63 cases in the right eye, with a cumulative ratio of left to right eye of 1:1.37. The age, gender, and eye onset were not significantly different between primary and recurrent patients in Table 1 (P>0.05). A significant difference in the course of the disease was observed between primary and recurrent patients (P<0.05). The postoperative follow-up time was 10-124mo, with an average interval of 44.51±24.92mo.

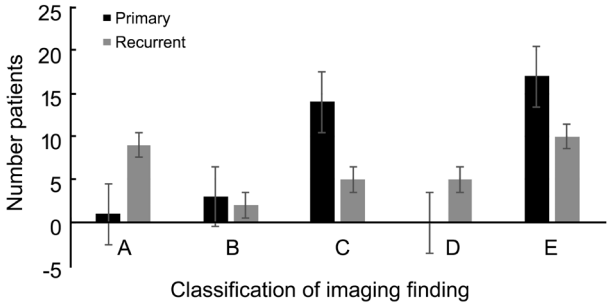

Figure 1 The imaging finding distribution graph of primary and recurrent patients A: Periosteal and bone involvement; B: Periosteal involvement only; C: Bone resorption; D: Involvement of surrounding structures (include fat, skin, nerves); E: Compression of the extraocular muscle.

The common clinical manifestations were exophthalmos (65.1%), eyelid mass (29.4%), eye movement disorder (22.9%), strabismus (21.1%), and decreased visual acuity (11.0%). Unusual symptoms included tearing (8.3%), diplopia (3.7%), ocular discomfort (0.9%), and esotropia (0.9%).

Imaging Observations of Bone Destruction (included periosteal involvement) and Involvement of Surrounding Tissues were Prone to Recurrence Combined computer tomography (CT) and magnetic resonance imaging (MRI) revealed that recurrent tumors were prone to bone destruction with involvement of the surrounding tissues and compression of extraocular muscles, while primary tumors exhibited more bone absorption and compression of extraocular tissue, as shown in Figure 1. Patients with bone destruction (included periosteal involvement) and the involvement of surrounding tissues displayed statistically significant likelihood of recurrence (P<0.05; Table 1).

Recurrent Patients with More Incomplete Capsules and Higher Expression of Ki-67 Most of the neoplasms were solid pale masses with clear boundaries and a thin capsule. In our study, sizes of primary tumors differed significantly from those of recurrent patients (Table 1; P=0.028). Eighty-four primary patients had complete capsules and five had incomplete capsules. Sixteen recurrent patients had incomplete capsules and three patients were complete. Hence, primary and recurrent patients (P=0.000) statistically differed in complete and incomplete capsule numbers.

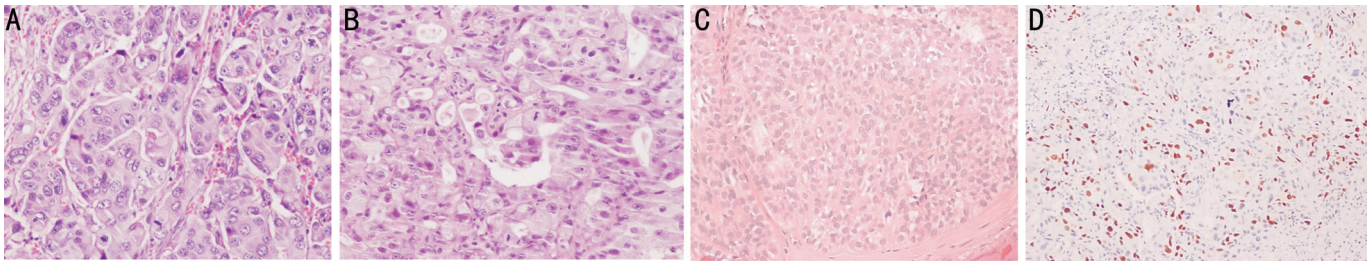

Figure 2 Histopathological findings in malignant patients (HE staining, the amplification factor ×200) A: The pathologic features showed large tumor cells, and cell nucleus were hyperchromatic and pleomorphic, which led to the diagnosis of adenocarcinoma. B: The pathologic features of carcinoma in LGPA showed that the morphology of tumor cells was quite different, and the cell nucleus were pleomorphic and heteromorphic. C: The pathological manifestations were nests or sheets of cancer cells and the cytoplasm was opaque. A large number of cells were round or elliptic, which was diagnosed as myoepithelial carcinoma. D: The Ki-67 was positively expressed in adenocarcinoma (brown).

Table 1 Clinical analysis of risk factors affecting or predicting LGPA recurrence

Characteristic	Total	Primary	Recurrent	Test value	*P*
Gender (male/total)	42/109	36	6	0.753	0.386[a]
Mean age (y)	43.64±13.066	44.27±13.173	40.85±12.516	0.161	0.689[b]
Position (left/right)	46/63	39/50	7/13	0.521	0.470[a]
The medical center of initial operation				-	0.000[c]
Beijing Tongren Hospital	96	89	7		
Local hospital	13	0	13		
Course of disease				40.538	0.000[c]
≤5y	87	82	5		
5-10y	10	5	5		
10-15y	12	2	10		
Imaging findings				-	0.000[c]
Periosteal and bone involvement	10	1	9		
Involvement of surrounding structures (include fat, skin, nerves)	5	0	5		
Tumor size				8.193	0.028[c]
≤1 cm	8	5	3		
1-2 cm	36	33	3		
2-3 cm	56	46	10		
>3 cm	9	5	4		
Complete capsules	87	84	3	-	0.000[c]
Incomplete capsules	21	5	16		
Ki-67 index				13.737	0.001[c]
≤5%	92	78	14		
5%-10%	7	7	0		
>10%	4	0	4		

[a]Chi-square test; [b]Analysis of variance; [c]Fisher's exact test and $P<0.05$.

Five cases of LGPA exhibited malignant transformations, with pathologies involving two cases of adenocarcinoma, one of myoepithelial carcinoma, one of mucoepidermoid carcinoma, and one of carcinoma in pleomorphic adenoma (PA; Figure 2). Ki-67 expression was significantly different between primary and recurrent patients (P=0.001). The expression of Ki-67 in four malignant patients was 10%, 15%, 60%, and 90% respectively, with the remainder of the cases unknown. In our group, 57 patients exhibited positive P63 expression, 1 patient with a benign tumor showed negative expression, 4 patients with negative P63 expression, and 1 patient with positive expression in malignant tumor. There was a statistically significant difference in the expression of P63 between benign and malignant tumors (P<0.05).

Table 2 Binomial Logistic regression analysis of factors affecting LGPA recurrence

Influencing factor	Wals	df	*P*	Exp (B)
Single medical center	0.000	1	0.998	2.811
Periosteal and bone involvement	0.000	1	0.999	1.638
Involvement of surrounding structures	0.000	1	0.999	0.000
Tumor size	0.000	1	1.000	0.005
Complete capsules	6.938	1	0.008	44.475
Ki-67 index	0.000	1	0.999	0.000
Constant	0.000	1	1.000	4.874

Treatment and Prognosis Five patients with malignant transformation had a history of multiple recurrences. Two patients underwent extensive surgical resection and postoperative ^{125}I seed implantation radiotherapy and three patients underwent extensive surgical resection and external radiotherapy. As shown in Table 1, 89 primary patients and 7 recurrent patients received their first complete surgery (including tumor and capsules) in our hospital. The first postoperative recurrence interval for 7 patients was 1.5-11y, or an average of about 6.5y. These patients underwent a second or third operation, which included removal of the surrounding tissues and bone malignancy. Thirteen recurrent patients did not receive their first surgery in our hospital and so the scope of this initial surgical resection was not known. These latter patients underwent their second or third operations in our hospital, which included removal of the malignant tissues and bone. The first postoperative recurrence time of these 13 recurrent patients was 2-17y, with an average of about 5y.

By the follow-up date, 10 primary and 5 recurrent patients had been lost to follow up. Excluding these cases, the 5-year recurrence rate for the 86 patients who had undergone the initial surgery in our hospital was 7.27%. Common complications included dry eyes (9 cases), ptosis (5 cases), eyelid swelling (5 cases), decreased vision (3 cases), eyelid numbness (3 cases), sunken eye sockets (2 cases), pain (1 case), and strabismus (1 case). More complications occurred in recurrent than in primary patients.

Capsule Integrity is the Main Factor Affecting Recurrence Single factor clinical analysis (Table 1) revealed that the course of disease, medical center of initial surgery, bone destruction, invasion of surrounding tissues, tumor size, capsule integrity, and expression of Ki-67 were factors affecting or predictive of tumor recurrence (P<0.05). Binomial Logistic regression analysis on these related factors (Table 2) showed that capsule integrity was an independent risk factor affecting tumor recurrence (P=0.008).

DISCUSSION

Pleomorphic adenoma (PA) is the most common, benign, epithelial neoplasm in the lacrimal and salivary glands. Many studies have reported that lacrimal and salivary glands have similar histological characteristics, suggesting that they are similar in the disease characteristics and clinical manifestations of PA[3-4]. LGPA occurs mainly in middle-aged people, ranging in age from 30 to 50 years old, and is more common in women[5]. The pathophysiology is mainly due to abnormal differentiation of ectoderm and mesoderm tissues.

PA is a benign tumor that displays recurrence and malignancy. Previous studies have reported that the recurrence rate of PA is 30%[6]. In recent years, with continued medical improvement, clinical ophthalmologists now pay great attention to the complete resection of the tumor and capsule as far as possible during the initial operation. Therefore, therapeutic outcome is constantly improving, and the rate of recurrence and malignancy are limited to some extent. With complete excision, recurrence rates of 3% after 5y have been reported[7]. In our study, the 5-year recurrence rate of 86 patients who underwent initial surgery in our hospital was 7.27%.

Significant differences were observed between recurrent and primary PA in imaging studies. Recurrent PAs were more likely to present with uneven density, unclear boundaries, adjacent bone destruction, and adherence to surrounding tissues than primary tumors, suggesting that recurrent tumors may display malignant features in imaging data. According to the statistical analyses, bone destruction (included periosteal involvement) and invasion of surrounding tissues were significant factors affecting tumor recurrence. These results suggest that tissue imaging is useful for determining tumor characteristics and prognosis. Preoperative imaging examination is especially helpful for guiding the surgical operation.

In PA, both myoepithelial and glandular epithelial components can become malignant. Pathologic types of malignancies are diverse and include adenocarcinoma, ductal carcinoma, myoepithelial carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, and squamous cell carcinoma, and 75% of the malignant lesions were adenocarcinoma[8-10]. The most common types of malignancy reported for salivary gland PA are duct and myoepithelial carcinomas[11]. The studies reported that approximately less than 10% of PA underwent malignant change within 20y after the first treatment and 20% by the end of 30y[2,12]. Some malignant PAs could metastasize to the

lungs, bone, abdomen, and central nervous system[12-13]. In this study, four patients were admitted due to tumor recurrence. Pathological examination after surgical resection showed malignant tumors, with one patient having a primary carcinoma in PA. The pathological types of malignancy included two cases of adenocarcinoma, one case of myoepithelial carcinoma, one case of mucoepidermoid carcinoma, and one case of carcinoma in PA. The malignancy intervals of the four patients were 3, 8, 8, and 11y, respectively. One patient was observed to have a primary carcinoma in PA in the first operation. The interval of malignancy transformation was undetermined.

One recurrent case notably developed a myoepithelial carcinoma of the right lacrimal gland *in situ* and a non-specific adenocarcinoma of the right temporal fossa. It had been previously reported that one or two components were capable of malignant transformation *in situ* PA[14]. In this case, it was unclear whether the non-specific adenocarcinoma of the temporal fossa was malignant due to LGPA or was a primary tumor. This finding shows that malignant LGPA also has a risk of developing simultaneous ectopic tumors.

Recurrence and transformation to malignancy have been shown to be closely related to surgical operation and tumor characteristics. If the tumor is not completely removed during the initial operation, risk of tumor recurrence increases. Literature reports indicate that when tumors are not completely removed, the recurrence rates are 20%-45% and the malignant transformation rate is 20%[15-16]. When the capsule is incomplete, the risk of recurrence and malignancy is also significantly increased. It has been reported that the incidence of malignant transformation increases with the duration of disease[2]. According to our statistical analysis (Tables 1 and 2), capsule integrity significantly differs between primary and recurrent patients and is an independent risk factor for patient prognosis.

Although the mechanism of malignant transformation is unknown, many studies have found that malignancy mechanisms may be related to gene aberrations. Mendoza *et al*[17] found, for example, that *PLAG1* gene translocation t (5; 8; p13; Q12) may be a strong diagnostic marker. Genome array comparisons of LGPA and precancerous PA, using gene chip technology (Harrison *et al*[2]), found that the *NFIB* and *PDGFB* genes may also play important roles, as a result of copy number gains involving 9p and 22q. These results suggest fruitful avenues for further exploration of the malignant mechanism of PA.

Ki-67 is a marker of tumor proliferation and malignant tumors are usually highly expressed[18]. In this group, positive expression of Ki-67 in benign patients was usually less than 5%, while that of malignant patients was typically more than 10%. The expression level of Ki-67 could indicate the degree of malignancy and future prognosis. In addition, it has been reported that P63 is mostly positively expressed in benign PA, and negatively expressed in malignant PA[19-20]. In our study, most benign patients had positive P63 expression. Four malignant patients, however, had negative P63 expression with one malignant patient having positive P63 expression. In this latter case, it is worth noting that the pathological type was myoepithelial carcinoma. This may be related to the fact that P63 is a biomarker of myoepithelial components. Recent studies have reported that CD44 can act as a surface marker for PA and that inhibiting the expression of CD44 can inhibit the growth of PA. This finding suggests a potential site for therapeutically treating PA[21].

In conclusion, LGPA is a benign tumor with a recurrence risk and potential for malignant transformation. Preoperative imaging evaluation is important for guiding treatment. Complete removal of the tumor and capsule in the initial surgical resection is essential to reduce the frequency of recurrence, and patients with complete tumor and capsule resection generally have better prognosis. An incomplete capsule is an independent risk factor influencing the recurrence of LGPA.

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