Published in final edited form as:

Otolaryngol Head Neck Surg. 2015 February ; 152(2): 279–283. doi:10.1177/0194599814556624.

Epidemiological Trends in Malignant Lacrimal Gland Tumors

Michael T. Andreoli, M.D.¹, Vinay Aakalu, M.D., M.P.H.¹, and Pete Setabutr, M.D.¹

¹Illinois Eye and Ear Infirmary, UIC Department of Ophthalmology and Visual Sciences, University of Illinois, Chicago, IL, USA

Abstract

Objective—To describe epidemiological trends in lacrimal gland malignancies in the United States.

Study Design—Retrospective database review

Setting—Multicenter registry

Subjects and Methods—A total of 702 malignant tumors of the lacrimal gland from the Surveillance, Epidemiology, and End Results (SEER) database were included in the study. Disease-specific and overall survival were the primary outcome measures. Kaplan-Meier survival curves were generated for multiple patient and tumor characteristics, including race, histology, TNM tumor stage, age at diagnosis, radiotherapy, gender, and tumor grade. Cox proportional hazards regression was performed to assess the impact of patient and tumor characteristics on survival.

Results—Lymphoma (58.0%), adenoid cystic carcinoma (13.4%), adenocarcinoma (3.8%), and mucoepidermoid carcinoma (3.6%) accounted for the majority of tumors. Lymphoma was associated with more favorable survival rates, while adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma were associated with worse prognosis. There was a steady increase in the proportion of lymphoma diagnosed since 1973. In a multivariate Cox proportional hazards regression model, tumor histology remained as the only covariate correlated with disease-specific survival.

Conclusion—Patient characteristics and survival rates differ between lymphoma, adenoid cystic carcinoma, adenocarcinoma, and mucoepidermoid carcinoma. The proportion of lacrimal gland cancer diagnosed as lymphoma has steadily increased over time. Cox proportional hazards regression analysis demonstrated tumor histology as one of the most important factors in patient survival. These results augment our understanding of the expected disease course of lacrimal gland malignancies.

Keywords

Lacrimal malignancy; lacrimal gland; lacrimal tumor; lacrimal cancer; lacrimal lymphoma; adenoid cystic carcinoma; mucoepidermoid carcinoma

Corresponding Author: Michael Andreoli, M.D., Address: 1855 W. Taylor St., Chicago, IL 60612, Phone: 312-996-6562, michaelandreoli@gmail.com.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Introduction

Lacrimal gland lesions are relatively rare, with an estimated incidence of 1.3/1,000,000/year.¹ Shields et al. demonstrated that at least half of lacrimal lesions are inflammatory.² Similarly, existing studies have described a Chinese population in which pleomorphic adenoma and inflammatory pseudotumor accounted for over half of the space-occupying lesions.³ Malignant lacrimal gland tumors are even more rare, accounting for approximately one quarter of all lacrimal gland lesions.¹ In a Danish population, the most common lacrimal gland cancer was malignant epithelial tumor, namely adenoid cystic carcinoma, carcinoma ex pleomorphic adenoma, and mucoepidermoid carcinoma. The next most common malignancies were lymphoid tumors, secondary invading lesions, and metastases.¹ In terms of treatment, eye-sparing surgery has been shown to yield similar survival outcomes to orbital exenteration in carefully selected malignancies of the lacrimal apparatus.⁴

An epidemiological survey of Japanese lacrimal fossa lesions demonstrated a difference in gender predisposition for pleomorphic adenoma and malignant epithelial tumors.⁵ However, there is currently a paucity of epidemiological studies of lacrimal gland malignancies in large, diverse populations. This study aims to describe the trends in malignant tumors of the lacrimal gland in the United States for the last 37 years by utilizing the Surveillance, Epidemiology, and End Results (SEER) program database.

Methods

All cases of malignant orbital tumors between 1973 and 2009 were selected from the SEER database, including all 18 registries. The SEER database is a population-based cancer registry that captures 18 distinct population groups in 198 counties in the United States. It represents approximately 26% of the overall United States population and contains information on 7,262,696 cases of cancer diagnosed since 1973.⁶ Permission to use this data for analysis was obtained from the National Cancer Institute SEER program. Institutional Review Board permission was not required for this study, as the data is anonymized and publicly available.

The data in this study were standardized according to schema-published second and third editions of the *International Classification of Disease for Oncology*. For the current study, primary site was restricted to the lacrimal gland, defined as site code C69.5, which excludes the lacrimal sac and lacrimal duct by the SEER coding scheme. Specific details regarding radiation dose, fractionation schedules, and adjuvant chemotherapy were not available in the SEER database. Data were analyzed using the SEER*Stat Limited Use software (National Cancer Institute, Bethesda, MD), GraphPad Prism (GraphPad Software, Inc., La Jolla, CA), and SPSS version 17.0 software (SPSS, Inc.; Chicago, IL). Pathological tumor grade was reported for biopsy or resection specimen when available. Overall survival and disease-specific survival were the primary outcome measures. Survival curves were generated using the Kaplan-Meier method and compared using the Mantel-Cox log-rank test. Cox proportional hazards regression was performed to assess the impact of patient and tumor characteristics on survival. Significance was defined as $P < 0.05$.

Results

A total of 702 patients comprising 702 distinct lacrimal gland malignancies were included in the study. Median follow-up time was 55.0 months (standard deviation 67.5 months). Table 1 summarizes the baseline patient demographics. The patients were 42.6% male and 57.4% female. The overall median patient age at diagnosis was 62 years (range 4 to 101 years). The disease-specific and overall patient survival rates at 10 year follow-up were 71.5% and 50.1%, respectively. Radiation therapy was utilized in 53.5% of cases. For malignancies with adequate tumor staging data, the tumor stage was stage I in 26%, stage II in 22%, stage III in 3%, and stage IV in 49%. For cases with provided histological tumor grade, the tumor grade was grade 1 in 11%, grade 2 in 32%, grade 3 in 46%, and grade 4 in 10%. The lacrimal gland malignancy was the first documented cancer in 87.3% of patients.

The most common tumor histology was lymphoma (58.0%). Of the 407 tumors diagnosed as lymphoma, the median age was 63 years (range 11 to 96 years). The patients were more commonly female (66.1%). The patients were typically Caucasian (85.0%). The median follow-up time was 62 months. The disease-specific and overall survival rates at 10 year follow-up were 79.1% and 55.1%, respectively. A longitudinal analysis reveals that the proportion of lacrimal gland tumors diagnosed as lymphoma is steadily increasing over time, with a most pronounced change from 1973 to 1990 (Figure 3).

The second most common malignant tumor was adenoid cystic carcinoma (13.4%). The median age at diagnosis was 50.5 years (range 8 to 90 years). The patients were more often female (54.3%). The patients were predominantly Caucasian (70.2%). There was a small population of African American (18.1%) and Asian or Pacific Islander (11.7%) patients. The median follow-up time was 55 months. The disease-specific and overall survival rates at 10 year follow-up were 51.4% and 38.7%, respectively.

Adenocarcinoma accounted for 3.8% of malignant lacrimal tumors. The median age at diagnosis was 63 years (range 26 to 101). The majority of patients (81%) were male. The vast majority of patients were Caucasian (85%). The median follow-up time was 47 months. The disease-specific and overall survival rates at 10 year follow-up were 51.4% and 27.7%, respectively.

Mucoepidermoid carcinoma accounted for 3.6% of malignant lacrimal tumors. The median age at diagnosis was 61 years (range 24 to 89). The patients were evenly distributed between males (48%) and females (52%). The patients were 64% Caucasian, 20% Asian or Pacific Islander, and 12% African American. The median follow-up time was 32 months. The disease-specific and overall survival rates at 10 year follow-up were 78.6% and 40.3%, respectively.

Cox proportional hazards regression analysis was performed for all malignant lacrimal tumors with disease-specific survival as the primary outcome. The following variables were entered into the analysis: race, histology, T stage (TNM staging), age at diagnosis, radiotherapy, gender, and tumor grade. The resulting model is presented in Table 2. In summary, tumor histology was the only variable associated with disease-specific survival in

this model. Notably, race, T stage, age at diagnosis, radiotherapy, gender, and tumor grade were not associated with disease-specific survival in this analysis.

Figure 1 and Figure 2 depict patient overall and disease-specific survival curves by tumor histology, respectively. Table 3 summarizes the 10 year survival rates for the most common histological diagnoses. There was a significant difference in overall survival between histological diagnoses ($P = 0.0005$). Lymphoma demonstrated superior overall survival to adenoid cystic carcinoma ($P = 0.0268$; hazard ratio = 1.520; 95% CI [1.049 – 2.201]) and adenocarcinoma ($P < 0.0001$; hazard ratio = 3.787; 95% CI [1.951 – 7.350]). There was no difference in overall survival among adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma ($P = 0.1451$). There was also no difference in overall survival between lymphoma and mucoepidermoid carcinoma ($P = 0.2422$; hazard ratio = 1.540; 95% CI [0.7470 – 3.173]).

Discussion

This study analyzes a vast population of lacrimal gland malignancies. The histological categorization correlates with previous studies describing a predominance of nonepithelial tumors of the lacrimal gland, contrary to traditional teaching.^{2,7} The median age at diagnosis was near 60 years old for lymphoma, adenocarcinoma, and mucoepidermoid carcinoma. Adenoid cystic carcinoma was diagnosed slightly earlier, at approximately 50 years old. Lymphoma and adenoid cystic carcinoma were diagnosed in all age groups, while the other histologies were typically diagnosed in adults. Patient ages at diagnosis were generally older than described in early studies.⁸ The gender distribution was fairly equal between men and women for adenoid cystic carcinoma and mucoepidermoid carcinoma, while two-thirds of the lymphoma patients were female and the majority of adenocarcinoma patients were male. Adenoid cystic carcinoma and mucoepidermoid carcinoma were diagnosed in a more racially diverse population than adenocarcinoma and lymphoma, which was predominantly found in Caucasian patients. Over time, there appears to be an increase in the proportion of malignant lacrimal tumors diagnosed as lymphoma. This observation may represent a local phenomenon in the orbit as previously described in the Florida cancer registry by Margo et al.⁹, or may reflect an upward trend in systemic lymphoma. Alternatively, other factors such as increased utilization or diagnostic capability of imaging modalities may play a role. Additionally, lacrimal gland lymphoma may account for a greater fraction of malignant lacrimal gland tumors than previously suspected.¹⁰ The proportions of lymphoma and mucoepidermoid carcinoma were comparable to a large series by Shields et al.¹¹, but adenoid cystic carcinoma was much less common than lymphoma in our cohort. This discrepancy may be explained by referral patterns to tertiary care centers.

The overall patient survival rates for malignant lacrimal tumors in the SEER database closely paralleled those reported by Skinner et al.⁴, out to several decades of follow-up. Cox proportional hazards regression demonstrated that tumor histology was the only variable associated with disease-specific survival in this dataset. Interestingly, characteristics such as age at diagnosis, tumor TNM T stage, and tumor grade were not associated with survival. Similarly, race, radiotherapy, and gender were not associated with survival. Of the histologies studied, adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid

carcinoma were associated with the worst disease-specific survival rates. The prognosis was better for lymphoma.

The SEER database provides useful, well-validated cancer data. However, there are limitations to the available data, such as lack of specifics of radiotherapy or chemotherapy treatment protocols. Additionally, while the intended coding scheme records tumors by primary site and not extension or metastasis, one cannot guarantee that some of the listed tumors were not extensions from surrounding tissues of the orbit or sinus, particularly for tumors such as squamous cell carcinoma. Since squamous cell carcinoma of the lacrimal gland is quite rare, many of these cases likely represent spread of sinus, orbit, or skin cancers and were thus excluded from the main survival analysis. Also, the histological diagnoses provided by the SEER database do not capture every histological variant and lymphoma subtype.

The current study offers longitudinal data on a vast, diverse population of malignant lacrimal tumors. This epidemiological data regarding patient demographics improves our knowledge of predisposed populations for these diagnoses. Differences in patient survival by tumor histology assist in patient counseling and treatment planning. Longitudinal statistics imply that there may be a gradual evolution in tumor histology, with a steady increase in the relative percentage of lymphoma over the last four decades. Cox proportional hazard regression suggests that patient age, T stage, and tumor grade, which are commonly associated with survival outcomes, may be less important than tumor histology for predicting disease-specific survival in lacrimal gland malignancies. These findings further our understanding of lacrimal gland cancer and the expected clinical course.

References

1. von Holstein SL, Therkildsen MH, Prause JU, et al. Lacrimal gland lesions in Denmark between 1974 and 2007. *Acta Ophthalmol.* 2013; 91:349–354. [PubMed: 22471375]
2. Shields CL, Shields JA, Eagle RC, et al. Clinicopathologic review of 142 cases of lacrimal gland lesions. *Ophthalmology.* 1989; 96:431–5. [PubMed: 2726173]
3. Wang XN, Qian J, Yuan YF, et al. Space-occupying lesions of the lacrimal gland at one tertiary eye center in China: a retrospective clinical study of 95 patients. *Int J Ophthalmol.* 2012; 5:208–11. [PubMed: 22762051]
4. Skinner HD, Garden AS, Rosenthal DI, et al. Outcomes of malignant tumors of the lacrimal apparatus: the University of Texas M. D. Anderson Cancer Center experience. *Cancer.* 2011; 117:2801–10. [PubMed: 21656758]
5. Lacrimal Gland Tumor Study Group. An epidemiological survey of lacrimal fossa lesions in Japan: number of patients and their sex ratio by pathological diagnosis. *Jpn J Ophthalmol.* 2005; 49:343–8. [PubMed: 16187032]
6. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2011 Sub (1973-2009) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2010 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2012 based on the November 2011 submission.
7. Shields JA, Shields CL, Epstein JA, et al. Review: primary epithelial malignancies of the lacrimal gland: the 2003 Ramon L. Font lecture. *Ophthal Plast Reconstr Surg.* 2004; 20:10–21.
8. Wright JE, Rose GE, Garner A. Primary malignant neoplasms of the lacrimal gland. *Br J Ophthalmol.* 1992; 76:401–7. [PubMed: 1320924]

9. Margo CE, Mulla ZD. Malignant tumors of the orbit. Analysis of the Florida Cancer Registry. *Ophthalmology*. 1998; 105:185–90. [PubMed: 9442797]
10. Rasmussen P, Ralfkiaer E, Prause JU, et al. Malignant lymphoma of the lacrimal gland: a nation-based study. *Arch Ophthalmol*. 2011; 129:1275–80. [PubMed: 21987669]
11. Shields JA, Shields CL, Scartozzi R. Survey of 1264 patients with orbital tumors and simulating lesions: The 2002 Montgomery Lecture, part 1. *Ophthalmology*. 2004; 111:997–1008. [PubMed: 15121380]

Figure 1. Kaplan-Meier Overall Survival by Tumor Histology

Lymphoma yielded superior overall survival to adenocarcinoma and adenoid cystic carcinoma. There were no survival differences among mucoepidermoid carcinoma, adenocarcinoma, and adenoid cystic carcinoma.

Figure 2. Kaplan-Meier Disease-Specific Survival by Tumor Histology

Lymphoma demonstrated superior disease-specific survival to adenoid cystic carcinoma and adenocarcinoma. There were no survival differences among mucoepidermoid carcinoma, adenocarcinoma, and adenoid cystic carcinoma.

Figure 3. Proportion of Lacrimal Tumors Diagnosed as Lymphoma over Time
 Plot of proportion of lacrimal tumors diagnosed as lymphoma by year.

Table 1

Baseline characteristics of 702 malignant lacrimal gland tumors

<i>Total Patients</i>	702
<i>Gender</i>	
Male	299 (42.6%)
Female	403 (57.5%)
<i>Race</i>	
Caucasian	570 (82.1%)
African American	57 (8.2%)
Asian or Pacific Islander	65 (9.4%)
Native American or Alaska Native	2 (0.3%)
<i>Histology</i>	
Lymphoma	407 (58.0%)
Adenoid cystic carcinoma	94 (13.4%)
Squamous cell carcinoma	81 (11.5%)
Adenocarcinoma	27 (3.8%)
Mucoepidermoid carcinoma	25 (3.6%)
Other carcinoma	41 (5.8%)
Mixed tumor	6 (0.9%)
Unspecified malignancy	3 (0.4%)
Other	19 (2.7%)

Table 2

Cox Proportional Hazards Regression Analysis of Patient Disease-Specific Survival

Variable	Beta Coefficient	Standard Error	P value	Hazard Ratio (95% CI)
Tumor histology	0.470	0.219	0.032	1.600 (1.042 – 2.457)
Race	0.408	0.359	0.256	1.504 (0.744 – 3.040)
Radiotherapy	1.105	0.977	0.258	3.019 (0.445 – 20.471)
T stage	−0.199	0.289	0.492	0.820 (0.465 – 1.444)
Tumor grade	0.263	0.565	0.642	1.301 (0.429 – 3.941)
Gender	−0.307	0.735	0.676	0.735 (0.174 – 3.104)
Age at diagnosis	−0.003	0.023	0.900	0.997 (0.953 – 1.044)

CI, Confidence Interval

Table 3

Survival Rates for Common Histological Diagnoses

Histology	Median age	10 year overall survival	10 year disease-specific survival
Lymphoma	63 years	55.1%	79.1%
Adenoid cystic carcinoma	50.5 years	38.7%	51.4%
Adenocarcinoma	63 years	27.7%	51.4%
Mucoepidermoid carcinoma	61 years	40.3%	78.6%