**Title:** Lymphoma of the lacrimal gland - An International Multicenter Retrospective Study

**Authors:**

Stine Dahl Vest, MD1; Lauge Hjorth Mikkelsen, MD1,2; Frederik Holm, MD1; Peter Kristian Rasmussen, MD, PhD2; Tine Gadegaard Olsen, MD1; Marina M. Kirkegaard, MD1; Sarah E. Coupland, MBBS, PhD, FRCPath3; Bita Esmaeli, MD4; Paul T. Finger, MD5; Gerardo F. Graue, MD5; Hans E. Grossniklaus, MD, MBA6; Santosh G. Honavar, MD7,8; Kaustubh Mulay, DNB9; Lene D. Sjö, MD, PhD1; E. Ralfkiaer, MD, DMSc1; Matthew E. Sniegowski, MD4; Geeta K. Vemuganti, MD10,11; Bradley A. Thuro, MD4; Steffen Heegaard, MD, DMSc1,2.

**Affiliations:**

1: Eye Pathology Section, Department of Pathology, Rigshospitalet, University of Copenhagen, Denmark;

2: Department of Ophthalmology, Rigshospitalet, University of Copenhagen, Denmark;

3: Department of Cellular and Molecular Pathology, University of Liverpool, England;

4: Orbital Oncology and Ophthalmic Plastic Surgery, Department of Plastic Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA;

5: The New York Eye Cancer Center, New York, New York, USA;

6: Section of Ocular Oncology, Emory Eye Center, Atlanta, Georgia, USA;

7: Department of Ophthalmic and Facial Plastic Surgery, Orbit and Ocular Oncology, Centre for Sight, Hyderabad, India;

8: Department of Ocular Oncology and Oculoplastics, LV Prasad Eye Institute, Hyderabad, India;

9: National Reporting Centre for Ophthalmic Pathology, Centre for Sight, Hyderabad, India;

10: Visiting Faculty, Ophthalmic Pathology Services, LV Prasad Eye Institute, Hyderabad, India;

11: Kallam Anji Reddy Campus, School of Medical Sciences, University of Hyderabad, Hyderabad, India.

**Author Contributions:**

**Vest, Mikkelsen, Holm** had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* **Vest**, Mikkelsen, Rasmussen, Coupland, Esmaeli, Heegaard.

*Acqusition, analysis, or interpretation of data*: **Vest**, Mikkelsen, Holm, Rasmussen, Olsen, Kirkegaard, Coupland, Esmaeli, Finger, Graue, Grossniklaus, Honavar, Mulay, Ralfkiaer, Sniegowski, Sjö, Vemuganto, Thuro, Heegaard.

*Drafting of manuscript:* **Vest**, Mikkelsen, Coupland, Heegaard.

*Critical revision of the manuscript for important intellectual content:* **Vest**, Mikkelsen, Holm, Rasmussen, Olsen, Kirkegaard, Coupland, Esmaeli, Graue, Finger, Grossniklaus, Honavar, Mulay, Sjö, Ralfkiaer, Sniegowski, Vemuganti, Thuro, Heegaard.

*Statistical analysis:* **Vest**, Holm.

*Obtained funding:* Heegaard.

*Administrative, technical, or material support:* Holm, Mikkelsen, Coupland, Esmaeli, Finger, Graue, Grossniklaus, Mulay, Sjö, Thuro.

*Study supervision:* Mikkelsen, Holm, Honavar, Vemuganti, Heegaard.

**Corresponding author:**

Professor, MD, DMSc Steffen Heegaard

Department of Pathology, Rigshospitalet, University of Copenhagen

Frederik V’s Vej, 11, 1. Sal

DK-2100 Copenhagen Ø, Denmark

Telephone: +45 35326075, Fax: +45 35326080, Email: sthe@sund.ku.dk

**Disclosures:** The authors declare no proprietary or commercial interest in any product mentioned or any concept discussed in this article.

**Word count:** 3,792 words

**Abstract**

**Purpose:** To characterize the clinical features of subtype-specific lacrimal gland lymphoma and their effect on patient survival

**Design:** Multi-center retrospective observational case series.

**Methods:** Patient data were collected from 6 international eye cancer centers from January 1, 1980 through December 31, 2017. All patients with histologically verified primary or secondary lymphoma of the lacrimal gland were included. Primary endpoints were overall survival (OS) and disease-specific survival (DSS).

**Results:** 261 patients with lacrimal gland lymphoma were identified. The median age was 58 years and 52% of patients were men. Non-Hodgkin B-cell lymphomas constituted 99% (n=259) and T-cell lymphomas constituted 1% (n=2). The most frequent lymphoma subtypes were extranodal marginal zone lymphoma (EMZL) (n=178, 68%), follicular lymphoma (FL) (n=26, 10%), diffuse large B-cell lymphoma (DLBCL) (n=26, 10%), and mantle cell lymphoma (MCL) (n=17, 7%). Low-grade lymphomas (EMZL and FL) were most commonly treated with external beam radiotherapy (EBRT), whereas high-grade lymphomas (DLBCL and MCL) were treated with chemotherapy in combination with Rituximab and/or EBRT. The prognosis was relatively good with a 5-year OS and DSS of 73.8% and 87.5%, respectively. Lymphoma subtype was a statistically significant predictor for DSS with EMZL (5-year DSS: 93%) having the best prognosis, and DLBCL (5-year DSS: 54.2%) having the poorest.

**Conclusions and Relevance:** This is the largest reported collection of data of subtype-specific lacrimal gland lymphoma. The subtype distribution of lacrimal gland lymphoma resembles that of the other ocular adnexa. Prognosis is good and the histologic subtype is a significant predictor for disease-specific survival.

# Introduction

Lymphomas comprise a heterogeneous group of malignant neoplasms derived from clonal expansion of B-lymphocytes, T-lymphocytes, or NK-cells. Lymphomas are commonly divided into Hodgkin- and non-Hodgkin lymphomas (NHL), and the latter may be further subclassified according to presumed cell of origin (1).

The lacrimal gland is anatomically considered a part of the ocular adnexa (OA), and neoplastic lesions of the lacrimal gland are relatively rare with an annual incidence rate of 0.7 per million (2). NHL of B-cell type have been found to constitute between 37-58% of malignant lacrimal gland neoplasms (2,3). Hodgkin lymphoma involving the OA is extremely rare (4), and the most common malignant lymphomas found in the lacrimal gland are NHL with extranodal marginal zone lymphoma (EMZL), follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL) being the most frequent, whereas mantle cell lymphoma (MCL) and small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) are less common (5). Patients affected are primarily elderly and with a female predominance (5).

To date the largest clinicopathologic study of lacrimal gland lymphomas includes 27 patients from a single eye-cancer center (6). The present study will therefore seek to describe epidemiologic trends, clinical features, and prognosis of patients with malignant lacrimal gland non-Hodgkin lymphoma in a large cohort of patients from six different eye cancer centers.

# Methods

### Study design

This study is a retrospective observational case series based on data from 6 international eye cancer centers: Copenhagen, Denmark; Liverpool, United Kingdom; Atlanta, Georgia, USA; New York, USA; Hyderabad, India; and Houston, Texas, USA. All patients with lymphoma of the lacrimal gland were included. The patients were collected from January 1, 1980 through December 31, 2017. The study followed the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability act of 1996 in the United States. Institutional review board and health information privacy agency approvals for this retrospective study were obtained from the Danish Data Protection Agency and the Local Ethics Committee (J no. H-B-2009-054). 27 patients from the Danish cohort have been published earlier (6).

### Biopsy specimens

Histopathologic examination of tumor specimens included staining with hematoxylin-eosin and immunohistochemical analysis. Currently, the following panel for B-cell lymphomas is recommended: CD3, CD5, CD10, CD20, CD23, CD79α, cyclin D-1, BCL2, BCL6, MUM-1/IRF4, MIB-1, and κ and λ light chains, including CD30, c-MYC, and EBER (Epstein-Barr virus encoded RNA) for large-cell lymphomas (1). Patients from 6 different eye cancer centers were included in this study spanning 38 years; hence, not all samples were analyzed in this uniform way. However, all specimens were reviewed and reclassified by the respective cancer centers according to the World Health Organization (WHO) Classification of Tumours of Hematopoietic and Lymphoid Tissues 4th edition(1).

### Clinical data

The clinical data collected included age, sex, symptoms, clinical findings, systemic involvement according to the Ann Arbor staging classification (7) and to the American Joint Committee on Cancer (AJCC) TNM classification system (8), data about treatment modalities and response to therapy, survival duration, and cause of death. All clinical parameters were not available in all patients. Systemic involvement and laterality were determined using clinical information and diagnostic tools available at the time of diagnosis. Currently, a complete diagnostic work-up for lymphoma includes the following: a tumor biopsy; computed tomography (CT), full-body positron emission tomography (PET-CT), or magnetic resonance imaging (MRI); and a bone-marrow biopsy.

Primary lacrimal gland lymphoma was defined as follows: a biopsy-verified stage IE (E = extranodal) lacrimal gland lymphoma or stage IIE lacrimal gland lymphoma (involvement of unilateral preauricular or submandibular lymph nodes or adjacent structures); and no history of prior lymphoma. Secondary lymphoma was defined as a systemic lymphoma with secondary lacrimal gland manifestation of disease or lymphoma relapse affecting the lacrimal gland on the background of clinically known systemic lymphoma. As defined by the AJCC/TNM system, only primary lymphomas were classified according to AJCC/TNM (8).

### Statistical analysis

Overall survival (OS) and disease-specific survival (DSS) were considered primary endpoints. OS was defined as the time from the date of diagnosis of lacrimal gland lymphoma to death by any cause or to last follow-up, with the latter being a censored event. DSS was defined as the time from the date of diagnosis to the date of death by lymphoma or the date of last follow-up, with the latter being a censored event. Survival outcomes were calculated and visualized using life-tables and Kaplan-Meier plots, and median survival was calculated if survival reached 0.5 during the follow-up period. Different risk groups were compared using the log-rank test. Risk factors were compared using the Fisher’s exact test. *P*<0.05 was considered statistically significant. Statistical analysis and calculation were made using IBM SPSS Package, version 25 (IBM Corporation, Armonk, New York, USA).

# Results

### Lymphoma subtype classification

261 patients with malignant lymphoma of the lacrimal gland were identified (Tables 1 and 2). The majority of lacrimal gland lymphomas were of B-cell origin (99%, n=259). Eight B-cell lymphoma subtypes were identified according to the WHO lymphoma classification (1): EMZL (n=178, 68%), FL (n=26, 10%), DLBCL (n=26, 10%), MCL (n=17, 7%), SLL/CLL (n=3, 1%), Burkitt lymphoma (BL) (n=2, 1%), plasmacytoma (PL) (n=2, 1%), and lymphoplasmacytic lymphoma (LPL) (n=1, 0.4%). Four lymphomas (2%) were of B-cell origin but could not be further classified: BCL, not otherwise specified (BCL-NOS). Only one T-cell lymphoma subtype was identified: Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) (n=2, 1%).

The distribution of lymphoma subtypes differed between eye cancer centers (Table 1). Hyderabad, Houston, Copenhagen, and Liverpool contributed with most cases to the study, and when comparing these eye cancer centers, Hyderabad had a higher proportion of patients with EMZL (84%) than the remaining eye cancer centers (44-61%). Consequently, a lower proportion of patients with FL and DLBCL, and no patients with MCL, were found in Hyderabad (Table 1). Furthermore, a high proportion of the patients from Copenhagen had MCL (22%) (Table 1).

### Clinical features

Of the 261 patients, 137 (52%) were men and 124 (48%) were women (Tables 1 and 2). The median age was 58 years (range 12-100 years) (Tables 1 and 2). Median age and male-to-female ratio differed between eye cancer centers and lymphoma subtypes (Table 1). Men predominated in EMZL (56%), whereas women predominated in FL (62%), DLBCL (58%), and an almost equal distribution was seen in MCL (53% females) (Tables 1 and 2). 183 patients (71%) were diagnosed as having primary lymphoma, 31 patients (12%) had systemic lymphoma with secondary lacrimal gland manifestation, and 45 patients (17%) had relapse of lymphoma in the lacrimal gland (Table 2).

199 patients (79%) were classified as having Ann Arbor stage IE disease, 16 patients (6%) had stage IIE disease, 6 patients (2%) had stage IIIE disease, and 32 patients (13%) had stage IVE disease (Table 2). All but one patient with primary lacrimal gland lymphoma were classified as having TNM stage T2 (n=182, 99%) and one patient had TNM stage T4 (Table 2). TNM stage T1 is per definition not possible in lymphomas of the lacrimal gland (8). In 87% of patients (n=228) the lacrimal gland lymphoma was unilateral, whereas 13% of patients (n=33) had bilateral affection of the lacrimal gland (Table 2). The most common site of local invasion was the orbit (n=191, 73%) (Table 3).

The most common symptoms reported from the ocular adnexal region were a visible or palpable mass of the lacrimal gland (n=126, 53%), periorbital swelling (n=118, 50%), and/or proptosis (n=112, 47%) (Table 3). The median symptom duration was 4 months (range 0-96 months). B-symptoms (i.e. fever, night sweats, and weight loss) were reported by 6 patients (3%) of whom two were diagnosed as having advanced stage disease (Ann Arbor stage III or IV). The most common clinical signs were an objective mass of the lacrimal gland (n=178, 75%), proptosis (n=128, 54%), displacement of the eyeball (127, 54%), and/or objectively restricted eye movement (n=94, 40%) (Table 3).

### Treatment outcome and survival

Treatment regimens of all lymphoma subtypes are listed in Table 4. Disease status at last follow-up was available for 99% of patients (n=260), and the median follow-up period was 18 months (range 0-372 months). 5- and 10-year OS for the entire group was 73.8% and 57.2%, respectively (median OS, 147 months; 95% confidence interval [CI] 111-183 months). 5- and 10-year, DSS for the entire group was 87.5% and 71.1%, respectively.

Overall survival and disease specific survival were significantly different between lymphoma subtypes (OS: *P*<0.001, pooled log rank test; DSS: *P*<0.001, pooled log rank test). Of the four major lymphoma subtypes EMZL had the highest DSS, and the DSS of DLBCL was significantly lower compared to EMZL (*P*<0.001, pairwise log rank test). However, no significant difference in DSS for DLBCL was seen compared to MCL (*P*=0.38, pairwise log rank test) and FL (*P*=0.09, pairwise log rank test). Furthermore, DSS for EMZL was not significantly different compared to MCL (*P*=0.051, pairwise log rank test) and FL (*P*=0.23, pairwise log rank test).

EMZL and DLBCL patients with progression/relapse had a significantly lower DSS compared to patients with no progression/relapse (EMZL: *P*=0.002; DLBCL: 0.007; log rank test). When examining risk factors for progression/relapse, a high Ann Arbor stage (stage III/IVE) (*P*<0.05, Fisher’s exact test) or secondary lymphoma (*P*<0.05, Fisher’s exact test) was significantly associated with an increased frequency of progression/relapse for the entire group of patients and patients with the DLBCL subtype. No other clinical characteristics showed a significant difference in DSS between risk groups within the four major lymphoma subtypes EMZL, FL, DLBCL, and MCL (*P*>0.05, log rank test). There was no significant difference in subtype-specific DSS between eye cancer centers (*P*>0.05, log rank test)

## Major non-Hodgkin B-cell lymphoma subtypes

### Extranodal marginal zone B-cell lymphoma

#### Clinical features

EMZL was the most frequent lymphoma of the lacrimal gland in this study constituting 68% of all cases (n=178). 83% of patients had primary lymphoma of the lacrimal gland while 17% presented with a secondary lymphoma of the lacrimal gland (Table 2). The median age was 55 years (range 13-100 years) and 56% of patients were men (n=100) (Tables 1 and 2). The vast majority of patients were classified as Ann Arbor stage IE (n=155, 89%) and TNM T2 lymphoma (n=146, 99%), whereas one patient had TNM T4 lymphoma (1%) (Table 2).

#### Treatment

Treatment information was available in 174 of 178 patients (98%). Stage IE patients were primarily treated with external beam radiation therapy (EBRT) as monotherapy (n=133, 88%) (Table 4). Stage IVE patients were most frequently treated with chemotherapy in combination with rituximab (n=5, 45%) (Table 4). The median radiation dose was 24 Gy (range 4-100 Gy, registered in 21 patients) most commonly given as 12-20 fractions of 1.5-2 Gy, but regimens of 2 fractions of 2 Gy was also seen.

#### Treatment outcome and survival

144 of 178 EMZL patients (81%) had complete remission of disease with a median follow-up period of 16 months (range 1-372 months) (Table 2). 27 patients (16%) had progression or relapse of disease (Table 2) with a median duration before relapse of 36 months (range 5-187 months) (time to relapse/progression accessible in 15 out of 27 patients). 5-, 10-, and 20-year OS were 77.8%, 71.3%, and 48.9%, respectively (median OS, 158 months; 95% CI 53-263 months). 5-, 10-, and 20-year DSS were 93.4%, 89.9%, and 77.1%, respectively (Figure 2).

For stage I-IIE EMZL no significant difference was seen in DSS between patients treated with EBRT as monotherapy and EBRT in combination with chemotherapy (*P*=0.52, log rank test). Furthermore, there was no significant difference in OS and DSS between patients receiving EBRT given as 12-20 fractions of 1.5-2 Gy compared to 2 fractions of 2 Gy (*P*>0.05, log rank test).

### Follicular lymphoma

#### Clinical features

26 cases (10%) of FL of the lacrimal gland were identified with 42% of cases being primary lymphoma of the lacrimal gland (Table 2). The median age was 63 years (range 29-88 years) and 62% of patients were women (n=16) (Tables 1 and 2). 61% of patients were staged as Ann Arbor stage IE, 22% as IIE, 9% as IIIE, and 9% as stage IVE (Table 2).

#### Treatment

Treatment information was available in 24 out of 26 patients (92%). Patients with Ann Arbor stage IE were primarily treated with EBRT as monotherapy (46%) or EBRT in combination with chemotherapy (38%)(Table 4). The median radiation dose was 26 Gy (range 4-30 Gy, registered in 5 patients) most commonly delivered in 13 fractions of 2 Gy. For patients receiving chemotherapy, combination regimens, such as CHOP (cyclophosphamide, hydroxydaunorubicin, vincristin, prednisone), were commonly used.

#### Treatment outcome and survival

42% (n= ?) of FL patients had complete remission while 19% (n= ?) of patients died of lymphoma (Table 2). The median follow-up period was 67 months (range 0-223 months). 13 patients (54%) had either relapse or progression of their disease (Table 2) with a median duration before relapse/progression of 43 months (range 7-218 months) (time to relapse/progression accessible in 8 out of 13 patients). 5- and 10-year OS were 86.5%, and 69.5%, respectively (median OS, 177 months, 95% CI 42-312 months). 5- and 10-year DSS were 86.5% and 69.5% (Figure 2).

For localized FL stage IE there was no significant difference in DSS between patients treated with a combination regimen of EBRT and chemotherapy compared to patients treated with EBRT as monotherapy (*P*=0.80, log rank test).

### Diffuse Large B-cell lymphoma

#### Clinical findings

Twenty-six cases (10%) of DLBCL of the lacrimal gland were identified with 58% of cases being primary lymphoma of the lacrimal gland (Table 2). The median age was 68 years (range 28-85 years) and 58% of patients were women (n=15) (Tables 1 and 2). 65% of patients were staged as Ann Arbor stage IE, 15% as IIE, and 19% as stage IVE (Table 2).

#### Treatment

Treatment information was available for all patients. Stage IE patients were primarily treated with chemotherapy in combination with EBRT (n=10, 59%). Patients with stage IIE and IVE were primarily treated with chemotherapy in combination with rituximab with the most common regimen being R-CHOP (IIE: n=3, 75%; IVE: n=3, 60%) (Table 4).

#### Treatment outcome and survival

36% of DLBCL patients (n=9) had complete remission of disease, 28% (n=7) died of lymphoma, and 28% (n=7) were dead from other causes (Table 2). The median follow-up period was 15 months (range 0-135 months). 11 patients (46%) had progression or relapse of disease (Table 2) with a median duration before relapse/progression of 17 months (range 15-19 months) (time to relapse/progression accessible in 2 out of 11 patients). 3- and 5-year OS were 51.8 and 31.1%, respectively (median OS, 39 months, 95% CI 16-62 months). 3- and 5-year DSS were 67.7% and 54.2%, respectively (Figure 2).

### Mantle Cell Lymphoma

#### Clinical findings

17 cases (7%) of lacrimal gland MCL were identified. One patient (6%) had primary lymphoma of the lacrimal gland, whereas 10 (63%) had systemic lymphoma with secondary lacrimal gland manifestation and 5 (31%) had lacrimal gland lymphoma relapse (Table 2). The median age was 70 years (range 43-81 years) and 53% of patients were women (n=9) (Tables 1 and 2). The vast majority had stage IVE disease (n=12, 75) (Table 2).

#### Treatment

Treatment information was available for all patients. 75% of patients (n=9) with stage IVE were treated with a rituximab-based chemotherapy regimen with or without an addition of EBRT. Furthermore, 2 patients (12%) with stage IVE had a bone marrow transplantation as an addition to their rituximab-based chemotherapy regimen (Table 4).

#### Treatment outcome and survival

53% (n=9) had complete remission of disease, 24% (n=4) were alive with disease, and 18% (n=3) were dead from lymphoma (Table 2). Median follow-up time was 25 months (range 4-232 months). 11 patients (65%) had progression or relapse of disease (Table 2) with a median duration before relapse/progression of 15 months (range 0-59 months) (time to relapse/progression accessible in 8 out of 11 patients). 3- and 5-year OS were both 79.9% and 10-year OS were 53.2%. 3- and 5-year DSS were both 87.8% and 10-year DSS was 58.6% (Figure 2).

### Rare B-cell and T-cell lymphoma subtypes

See Tables 2, 3, and 4. Patients with BL were young (median age: 16.5 years; range: 12-21 years) and the same applied for PTCL-NOS (median age: 34 years; range: 30-38 years). Patients with SLL/CLL were adults or elderly (median age: 68 years; range: 45-75 years). PL was found both in a young (14 years) and an elderly patient (69 years), and the one patient with LPL was 66 years old (Tables 1 and 2).

# Discussion

The present study identified 261 patients with malignant lacrimal gland lymphoma from six international eye cancer centers. This is the largest reported collection of clinical and pathological data including subtype distribution in patients with lacrimal gland lymphoma to date.

The four major subtypes of lymphoma identified in this study were EMZL (n=178, 68%), FL (n=26, 10%), DLBCL (n=26, 10%), and MCL (n=17, 7%), which is in line with previous studies of the lacrimal gland and also similar to the distribution of ocular adnexal lymphoma (4,6,9,10). The present study had a different distribution of the major subtypes than previously recorded in the lacrimal gland, where EMZL was less frequent (37%), and FL (19%) and DLBCL (15%) were more frequent (11). Thus, in the study by Rasmussen et al., which included 27 patients, it was proposed that the distribution of lymphoma subtypes in the lacrimal gland resembled that of the salivary glands more than that of the OA. However, with the large number of cases in this present study, the distribution of lymphoma subtypes resembles the distributions reported in the orbit and OA rather than that of the salivary glands (4,9,10,12–14).

The distribution of lymphoma subtypes differed between eye cancer centers and Hyderabad had a noticeably higher proportion of patients with EMZL (84 %) than the remaining eye cancer (44-61 %) (Table 1). There was a slight male predominance for the entire group (52 % males) and a significant male predominance in the group of patients with EMZL, while females predominated in FL and DLBCL. Interestingly, there was no male predominance in MCL patients as seen in previous studies of ocular adnexal lymphoma, which is probably due to the low number of cases (4,9). Male-to-female ratio varied between eye cancer centers and in the EMZL group approximately 60 % of patients came from Hyderabad where males predominated the patient group in contrast to the remaining eye cancer centers. A male predominance in lacrimal gland and ocular adnexal EMZL patients has previously been recorded in Asian countries (15,16), in contrast to national studies from Denmark, Canada and United states (4,11,17). Most patients in this study were adults with a median age of 58 years (range 12-100) at diagnosis. Patients with MCL, SLL/CLL, and DLBCL tended to be older than patients with FL and EMZL, and median age also varied between eye cancer centers (table 1). EMZL patients in Hyderabad were markedly younger than EMZL patients from the remaining eye cancer centers. Previously lymphoma of the lacrimal gland has been characterized by a predominance of female, elderly patients (median age 69 years) (11), which is in contrast to this study. Part of this difference might be due to the large proportion of EMZL patients from Hyderabad.

The prognosis for patients with lacrimal gland lymphoma found in this study is relatively good with a 5 year OS of 73.8% and a 5 year DSS of 87.5%, which is similar to previous studies (11). Overall survival and disease specific survival was significantly different between subtypes (OS: *P*<0.001, pooled log rank test; DSS: *P*<0.001, pooled log rank test), which has previously been shown in other anatomic sites of the OA (9,18,19).

Patients with EMZL and FL were found to have a good prognosis with a 5-year DSS of 93.4 % and 86.5 %, respectively, which is similar to previous studies of the OA (20,21). The current recommendation for treating localized stage I-IIE EMZL and FL of the OA is EBRT applying 24-36 Gy in conventional daily fractions (22). In line with this, the present study found no significant difference in DSS between low stage EMZL and FL patients treated with EBRT as monotherapy and patients treated with combination regimens of chemotherapy and EBRT. An addition of chemotherapy to an EBRT regimen for EMZL and FL patients with localized low stage disease is thus not found to improve DSS in this study.

Patients with DLBCL of the lacrimal gland were found to carry the poorest prognosis with a 3- and 5-year DSS of 67.7% and 54.2%, which is in line with previous survival data of DLBCL of the OA (23). Relapse or progression of disease was found to worsen the prognosis in respect to DSS within the EMZL and DLBCL subtypes. Risk factors for progression/relapse of disease was found to be a high Ann Arbor stage (III/IVE) and secondary lymphoma in both the entire group of patients and patients with the DLBCL subtype, which is in line with previous studies of orbital lymphoma (9).

Patients with MCL had a 3- and 5-year DSS of 87.8%, where it should be noted that the number of patients left in the cohort at the 5-year follow-up is quite small. These survival rates are surprisingly high compared to previous data of ocular adnexal MCL where 3- and 5-year DSS have been reported as low as 72% and 38%, respectively (24). 65% of the MCL patients in the present study had relapse or progression of disease, but this percentage has previously been recorded as high as 84% in the OA (24). In conclusion, lacrimal gland MCL in the present study shows a better prognosis than previously recorded ocular adnexal MCL. R-CHOP has previously been shown to improve MCL prognosis and is currently recommended for the treatment of MCL (22). 75% of patients with stage IVE MCL in this study were treated with a rituximab-based chemotherapy regimen, which is a higher number than in the study of ocular adnexal MCL (24), and this could thus be a possible explanation for the higher survival rates in the present study.

The retrospective design of this study poses some limitations. Data was collected from 6 different eye cancer centers over a 38-year period. Thus, not all medical records were complete and heterogeneous diagnostic methods were used. The median time to follow-up was 18 months (range 0-372), which might not have been enough time to detect outcome variables.

In summary, this international multi-center study of 261 patients with malignant lymphoma of the lacrimal gland confirms that the major NHL subtypes of lacrimal gland are EMZL (68%), FL (10%), DLBCL (10%), and MCL (7%), which resembles the distribution of lymphoma subtypes in the ocular adnexa rather than that of the salivary glands as previously assumed. The prognosis of lacrimal gland lymphoma was good with a 5 year OS of 73.8% and a 5 year DSS of 87.5%. Lymphoma subtype was a significant predictor in explaining the difference in disease-specific mortality with EMZL having the best prognosis and DLBCL having the worst.

**Acknowledgements**

LHM was supported by Candys Foundation. The funding sources played no role in study design; collection, analysis, and interpretation of data; in writing of the report; or in the decision to submit the article for publication.

# References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H TJ. WHO classification of tumours of haematopoietic and lymphoid tissues. Revised 4th ed. Lyon, France: International Agency for Research in Cancer (IARC). 2017. 585 p.

2. von Holstein SL, Therkildsen MH, Prause JU, Stenman G, Siersma VD, Heegaard S. Lacrimal gland lesions in Denmark between 1974 and 2007. Acta Ophthalmol. 2013 Jun;91(4):349–54.

3. Andreoli MT, Aakalu V, Setabutr P. Epidemiological trends in malignant lacrimal gland tumors. Otolaryngol Head Neck Surg. 2015 Feb;152(2):279–83.

4. Ferry JA, Fung CY, Zukerberg L, Lucarelli MJ, Hasserjian RP, Preffer FI, et al. Lymphoma of the Ocular Adnexa: A Study of 353 Cases. Am J Surg Pathol. 2007 Feb;31(2):170–84.

5. Andreasen S, Esmaeli B, Holstein SL von, Mikkelsen LH, Rasmussen PK, Heegaard S. An Update on Tumors of the Lacrimal Gland. Asia-Pacific J Ophthalmol. 2017 Mar;6(2):159–72.

6. Rasmussen P, Ralfkiaer E, Prause JU, Sjo LD, Siersma VD, Heegaard S. Malignant lymphoma of the lacrimal gland: a nation-based study. Arch Ophthalmol (Chicago, Ill 1960). 2011 Oct;129(10):1275–80.

7. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin’s Disease Staging Classification. Cancer Res. 1971 Nov;31(11):1860–1.

8. Amin MB, Edge SB, American Joint Committee on Cancer. AJCC cancer staging manual. 1024 p.

9. Olsen TG, Holm F, Mikkelsen LH, Rasmussen PK, Coupland SE, Esmaeli B, et al. Orbital Lymphoma—An International Multicenter Retrospective Study. Am J Ophthalmol. 2019 Mar 1;199:44–57.

10. Sjo LD. Ophthalmic lymphoma: epidemiology and pathogenesis. Acta Ophthalmol. 2009 Feb;87 Thesis:1–20.

11. Rasmussen P, Ralfkiaer E, Prause JU, Sjö LD, Siersma VD, Heegaard S. Malignant Lymphoma of the Lacrimal Gland. Arch Ophthalmol. 2011 Oct 1;129(10):1275.

12. Weber AL, Rahemtullah A, Ferry JA. Hodgkin and non-Hodgkin lymphoma of the head and neck: clinical, pathologic, and imaging evaluation. Neuroimaging Clin N Am. 2003 Aug;13(3):371–92.

13. Jamal B. Treatment of Parotid Non-Hodgkin Lymphoma: A Meta-Analysis. J Glob Oncol. 2018 Nov;4(4):1–6.

14. Kojima M, Shimizu K, Nishikawa M, Tamaki Y, Ito H, Tsukamoto N, et al. Primary salivary gland lymphoma among Japanese: A clinicopathological study of 30 cases. Leuk Lymphoma. 2007 Jan;48(9):1793–8.

15. Asadi-Amoli F, Nozarian Z, Bonaki HN, Mehrtash V, Entezari S. Clinicopathologic Assessment of Ocular Adnexal Lymphoproliferative Lesions at a Tertiary Eye Hospital in Iran. Asian Pac J Cancer Prev. 2016;17(8):3727–31.

16. Kao S-C, Kau H-C, Tsai C-C, Tsay S-H, Yang C-F, Wu J-S, et al. Lacrimal gland extranodal marginal zone B-cell lymphoma of MALT-type. Am J Ophthalmol. 2007 Feb;143(2):311–6.

17. Farmer JP, Lamba M, Lamba WR, Jordan DR, Gilberg S, Sengar DPS, et al. Lymphoproliferative lesions of the lacrimal gland: clinicopathological, immunohistochemical and molecular genetic analysis. Can J Ophthalmol. 2005 Apr;40(2):151–60.

18. Svendsen FH, Rasmussen PK, Coupland SE, Esmaeli B, Finger PT, Graue GF, et al. Lymphoma of the Eyelid - An International Multicenter Retrospective Study. Am J Ophthalmol. 2017 May;177:58–68.

19. Kirkegaard MM, Rasmussen PK, Coupland SE, Esmaeli B, Finger PT, Graue GF, et al. Conjunctival Lymphoma—An International Multicenter Retrospective Study. JAMA Ophthalmol. 2016 Apr 1;134(4):406.

20. Hindsø TG, Esmaeli B, Holm F, Mikkelsen LH, Rasmussen PK, Coupland SE, et al. International multicentre retrospective cohort study of ocular adnexal marginal zone B-cell lymphoma. Br J Ophthalmol. 2019 Jun 8;bjophthalmol-2019-314008.

21. Rasmussen PK, Coupland SE, Finger PT, Graue GF, Grossniklaus HE, Honavar SG, et al. Ocular adnexal follicular lymphoma: a multicenter international study. JAMA Ophthalmol. 2014 Jul;132(7):851–8.

22. Mikkelsen LH, Würtz NS, Heegaard S. Recent advances in treating extra-ocular lymphomas. Expert Rev Ophthalmol. 2018 Jul 4;13(4):205–17.

23. Munch-Petersen HD, Rasmussen PK, Coupland SE, Esmaeli B, Finger PT, Graue GF, et al. Ocular Adnexal Diffuse Large B-cell Lymphoma. JAMA Ophthalmol. 2015 Feb 1;133(2):165.

24. Knudsen MKH, Rasmussen PK, Coupland SE, Esmaeli B, Finger PT, Graue GF, et al. Clinicopathological Features of Ocular Adnexal Mantle-Cell Lymphoma in an International Multicenter Cohort. JAMA Ophthalmol. 2017 Dec 1;135(12):1367.

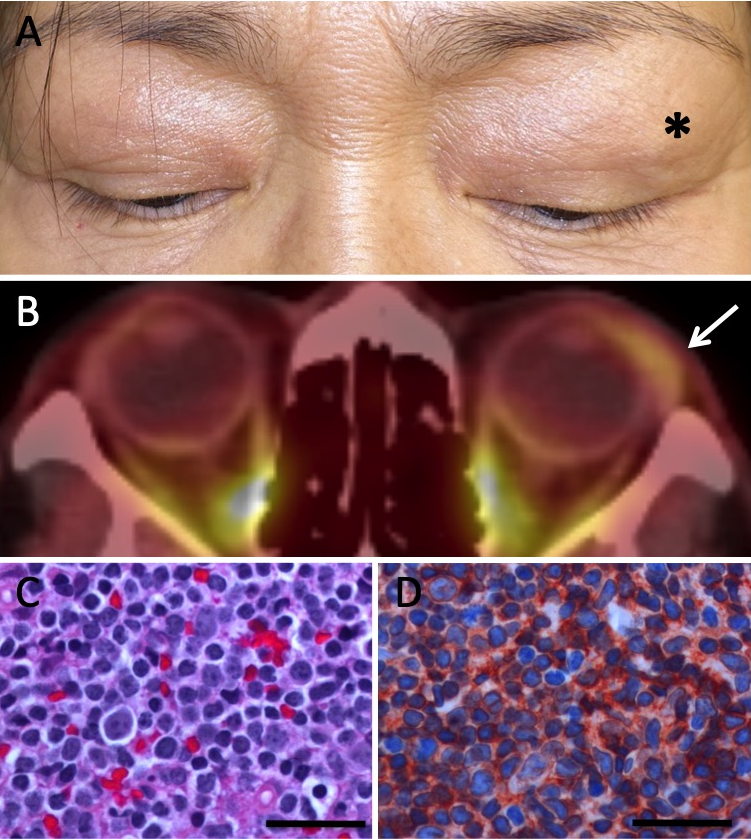
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Table 1. Eye Cancer Center Distribution of Patients by Subtype of Lacrimal Gland Lymphoma | | | | | | | |
|  | **Eye Cancer Center** | | | | | | |
| **CPH** | **LIV** | **HOU** | **HYD** | **NY** | **ATL** | **Total** |
| All lymphomas (%a) | 45 (17) | 19 (7) | 51 (20) | 130 (50) | 14 (5) | 2 (1) | 261 (100) |
| B-Cell Lymphomas |  |  |  |  |  |  |  |
| EMZL |  |  |  |  |  |  |  |
| No. of patients (% within centerb) | 20 (44) | 9 (47) | 31 (61) | 109 (84) | 8 (57) | 1 (50) | 178 (68) |
| Median age, years | 70 | 65 | 64 | 51 | 58 | 59 | 55 |
| Male-to-female ratio | 6:14 | 2:7 | 10:21 | 79:30 | 2:6 | 1:0 | 100:78 |
| FL |  |  |  |  |  |  |  |
| No. of patients (% within centerb) | 5 (11) | 3 (16) | 5 (10) | 8 (6) | 4 (29) | 1 (50) | 26 (10) |
| Median age, years | 63 | 57 | 66 | 58 | 66 | 71 | 63 |
| Male-to-female ratio | 2:3 | 0:3 | 2:3 | 5:3 | 1:3 | 0:1 | 10:16 |
| DLBCL |  |  |  |  |  |  |  |
| No. of patients (% within centerb) | 4 (9) | 4 (21) | 9 (18) | 9 (7) | 0 | 0 | 26 (10) |
| Median age, years | 75 | 80 | 68 | 65 | NA | NA | 68 |
| Male-to-female ratio | 1:3 | 1:3 | 2:7 | 7:2 | NA | NA | 11:15 |
| MCL |  |  |  |  |  |  |  |
| No. of patients (% within centerb) | 10 (22) | 0 | 6 (12) | 0 | 1 (7) | 0 | 17 (7) |
| Median age, years | 70 | NA | 70 | NA | 77 | NA | 70 |
| Male-to-female ratio | 6:4 | NA | 2:4 | NA | 0:1 | NA | 8:9 |
| SLL/CLL |  |  |  |  |  |  |  |
| No. of patients (% within centerb) | 3 (7) | 0 | 0 | 0 | 0 | 0 | 3 (1) |
| Median age, years | 68 | NA | NA | NA | NA | NA | 68 |
| Male-to-female ratio | 1:2 | NA | NA | NA | NA | NA | 1:2 |
| BL |  |  |  |  |  |  |  |
| No. of patients (% within centerb) | 0 | 0 | 0 | 1 (7) | 1 (1) | 0 | 2 (1) |
| Median age, years | NA | NA | NA | 12 | 21 | NA | 16,5 |
| Male-to-female ratio | NA | NA | NA | 1:0 | 0:1 | NA | 1:1 |
| PL |  |  |  |  |  |  |  |
| No. of patients (% within centerb) | 0 | 2 (11) | 0 | 0 | 0 | 0 | 2 (1) |
| Median age, years | NA | 42 | NA | NA | NA | NA | 42 |
| Male-to-female ratio | NA | 2:0 | NA | NA | NA | NA | 2:0 |
| LPL |  |  |  |  |  |  |  |
| No. of patients (% within centerb) | 1 (2) | 0 | 0 | 0 | 0 | 0 | 1 (0.5) |
| Median age, years | 66 | NA | NA | NA | NA | NA | 66 |
| Male-to-female ratio | 1:0 | NA | NA | NA | NA | NA | 1:0 |
| BCL, NOS |  |  |  |  |  |  |  |
| No. of patients (% within centerb) | 2 (4) | 1 (5) | 0 | 1 (1) | 0 | 0 | 4 (2) |
| Median age, years | 59 | 44 | NA | 27 | NA | NA | 50 |
| Male-to-female ratio | 0:2 | 1:0 | NA | 0:1 | NA | NA | 1:3 |
| T-Cell Lymphomas |  |  |  |  |  |  |  |
| PTCL, NOS |  |  |  |  |  |  |  |
| No. of patients (% within centerb) | 0 | 0 | 0 | 2 (2) | 0 | 0 | 2 (1) |
| Median age, years | NA | NA | NA | 34 | NA | NA | 34 |
| Male-to-female ratio | NA | NA | NA | 2:0 | NA | NA | 2:0 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 2. Clinical and Staging Characteristics of Patients by Subtype of Lacrimal Gland Lymphomaa | | | | | | | | | | | | |
|  |  | **B-cell lymphoma No. (%)b** | | | | | | | | | **T-cell lymphoma No. (%)** | |
| **All**  N= 261  (%) | **EMZL**  N= 178  (68) | **FL**  N= 26  (10) | **DLBCL**  N= 26  (10) | **MCL**  N= 17  (7) | **SLL/CLL**  N= 3  (1) | **BL**  N= 2  (1) | **PL**  N= 2  (1) | **LPL**  N= 1  (0.4) | **BCL-NOS**  N= 4  (2) |  | **PTCL-NOS**  N= 2  (1) |
| Sex |  |  |  |  |  |  |  |  |  |  |  |
| Men | 137 (52) | 100 (56) | 10 (38) | 11 (42) | 8 (47) | 1 (33) | 1 (50) | 2 (100) | 1 (100) | 1 (25) | 2 (100) |
| Women | 124 (48) | 78 (44) | 16 (62) | 15 (58) | 9 (53) | 2 (67) | 1 (50) | 0 | 0 | 3 (75) | 0 |
| Age at presentation |  |  |  |  |  |  |  |  |  |  |  |
| ≤ 60 | 145 (56) | 115 (65) | 10 (38) | 7 (27) | 4 (24) | 1 (33) | 2 (100) | 1 (50) | 0 | 3 (75) | 2 (100) |
| > 60 | 116 (44) | 63 (35) | 16 (62) | 19 (73) | 13 (76) | 2 (67) | 0 | 1 (50) | 1 (100) | 1 (25) | 0 |
| Disease group |  |  |  |  |  |  |  |  |  |  |  |
| Primary disease | 183/259 (71) | 147/177 (83) | 11/26 (42) | 15/26 (58) | 1/16 (6) | 1/3 (33) | 1/2 (50) | 2/2 (100) | 0 | 4/4 (100) | 1/2 (50) |
| Disseminated disease | 31/259 (12) | 13/177 (7) | 1/26 (4) | 6/26 (23) | 10/16 (63) | 1/3 (33) | 0 | 0 | 0 | 0 | 0 |
| Relapsed disease | 45/259 (17) | 17/177 (10) | 14/26 (54) | 5/26 (19) | 5/16 (31) | 1/3 (33) | 1/2 (50) | 0 | 1/1 (100) | 0 | 1/2 (50) |
| Laterality |  |  |  |  |  |  |  |  |  |  |  |
| Unilateral | 228/261 (87) | 161/178 (90) | 19/26 (73) | 24/26 (92) | 11/17 (65) | 3/3 (100) | 2/2 (100) | 2/2 (100) | 0 | 4/4 (100) | 2/2 (100) |
| Bilateral | 33/261 (13) | 17/178 (10) | 7/26 (27) | 2/26 (8) | 6/17 (35) | 0 | 0 | 0 | 1/1 (100) | 0 | 0 |
| Ann Arbor stage |  |  |  |  |  |  |  |  |  |  |  |
| IE | 199/253 (79) | 155/175 (89) | 14/23 (61) | 17/26 (65) | 2/16 (13) | 2/3 (67) | 1/2 (50) | 2/2 (100) | 0 | 4/4 (100) | 2/2 (100) |
| IIE | 16/253 (6) | 5/175 (3) | 5/23 (22) | 4/26 (15) | 2/16 (13) | 0 | 0 | 0 | 0 | 0 | 0 |
| IIIE | 6/253 (2) | 4/175 (2) | 2/23 (9) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IVE | 32/253 (13) | 11/175 (6) | 2/23 (9) | 5/26 (19) | 12/16 (75) | 1/3 (33) | 1/2 (50) | 0 | 0 | 0 | 0 |
| Unknown stage | 8/261 (3) | 3/178 (2) | 3/26 (12) | 0 | 1/17 (6) | 0 | 0 | 0 | 1/1 (100) | 0 | 0 |
| AJCC TNM stagec |  |  |  |  |  |  |  |  |  |  |  |
| T1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| T2 | 182/183 (99) | 146/147 (99) | 11/11 (100) | 15/15 (100) | 1/1 (100) | 1/1 (100) | 1/1 (100) | 2/2 (100) | 0 | 4/4 (100) | 1/1 (100) |
| T3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| T4 | 1/183 (1) | 1/147 (1) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Relapse/progression |  |  |  |  |  |  |  |  |  |  |  |
| Yes | 67/252 (27) | 27/173 (16) | 13/24 (54) | 11/24 (46) | 11/17 (65) | 0 | 2/2 (100) | 2/2 (100) | 0 | 1/4 (25) | 0 |
| No | 185/252 (73) | 146/173 (84) | 11/24 (46) | 13/24 (54) | 6/17 (35) | 3/3 (100) | 0 | 0 | 1/1 (100) | 3/4 (75) | 2/2 (100) |
| Site of recurrence at relapsed |  |  |  |  |  |  |  |  |  |  |  |
| OA | 29/52 (56) | 14/23 (61) | 5/11 (45) | 6/9 (67) | 4/6 (67) | NA | NA | 0 | NA | 0 | NA |
| Nodal and/or extranodal | 37/52 (71) | 15/23 (65) | 9/11 (82) | 6/9 (67) | 4/6 (67) | NA | NA | 2/2 (100) | NA | 1/1 (100) | NA |
| OA plus nodal and/or extranodal | 15/52 (29) | 7/23 (30) | 3/11 (27) | 3/9 (33) | 2/6 (33) | NA | NA | 0 | NA | 0 | NA |
| Bone marrow | 3/52 (6) | 1/23 (4) | 1/11 (9) | 0 | 0 | NA | NA | 0 | NA | 1/1 (100) |  | NA |
| Disease status at last follow-up |  |  |  |  |  |  |  |  |  |  |  |  |
| Complete remission | 177/260 (68) | 144/178 (81) | 11/26 (42) | 9/25 (36) | 9/17 (53) | 0 | 0 | 0 | 0 | 2/4 (50) |  | 2/2 (100) |
| Alive with disease | 34/260 (13) | 17/178 (10) | 8/26 (31) | 2/25 (8) | 4/17 (24) | 1/3 (33) | 1/2 (50) | 0 | 1/1 (100) | 0 |  | 0 |
| Dead of lymphoma | 25/260 (10) | 6/178 (3) | 5/26 (19) | 7/25 (28) | 3/17 (18) | 0 | 1/2 (50) | 2/2 (100) | 0 | 1/4 (25) |  | 0 |
| Dead from other causes | 24/260 (9) | 11/178 (6) | 2/26 (8) | 7/25 (28) | 1/17 (6) | 2/3 (67) | 0 | 0 | 0 | 1/4 (25) |  | 0 |
| Median time to last follow-up , months (range) | 18 (0-372) | 16 (1-372) | 67 (0-223) | 15 (0-135) | 25 (4-232) | 23 (21-147) | 9 (4-14) | 95 (77-113) | 0 | 52 (6-116) |  | 10 (9-11) |

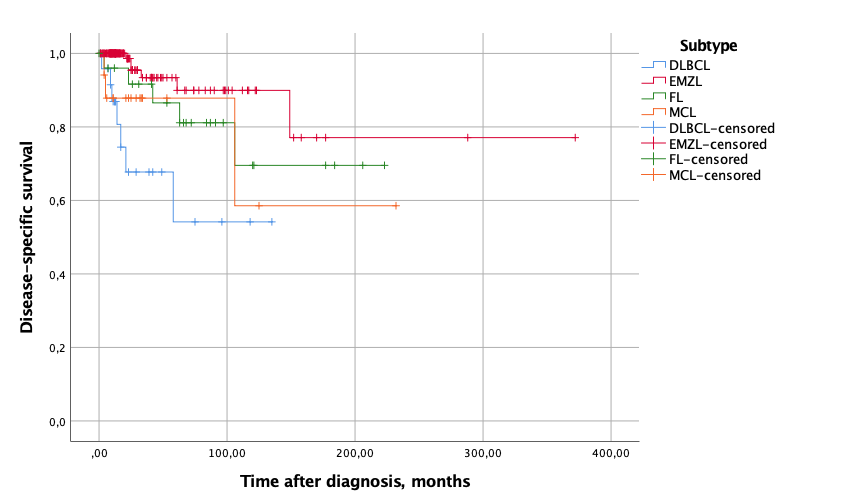
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 3. Frequency of Symptoms, Clinical Signs, and Local Spread at Presentation of Lacrimal Gland Lymphoma | | | | | | | | | | | | | |
|  |  | | **B-cell lymphoma No. (%)** | | | | | | | | |  | **T-cell lymphoma No. (%)** |
| **All**  261 | EMZL  178 (68) | | FL  26(10) | DLBCL  26 (10) | MCL  17 (7) | SLL/CLL  3 (1) | BL  2 (1) | PL  2 (1) | LPL  1 (0.4) | BCL-NOS  4 (2) |  | PTL-NOS  2 (1) |
| Symptomsb |  |  | |  |  |  |  |  |  |  |  |  |
| First presenting symptom in OAR | 214 (90) | 160 (95) | | 19 (86) | 15 (68) | 10 (71) | 3 (100) | 2 (100) | NA | 1 (100) | 3 (100) | 1 (50) |
| Mass | 126 (53) | 87 (52) | | 10 (45) | 15 (68) | 9 (64) | 1 (33) | 1 (50) | NA | 0 (0) | 2 (67) |  | 1 (50) |
| Swelling | 118 (50) | 81 (48) | | 9 (41) | 15 (68) | 8 (57) | 1 (33) | 1 (50) | NA | 0 (0) | 2 (67) | 1 (50) |
| Dry eye | 15 (6) | 3 (2) | | 5 (23) | 1 (5) | 3 (21) | 2 (67) | 0 (0) | NA | 1 (100) | 0 (0) |  | 0 (0) |
| Epiphora | 19 (8) | 13 (8) | | 1 (5) | 0 (0) | 3 (21) | 0 (0) | 0 (0) | NA | 0 (0) | 1 (33) | 1 (50) |
| Irritation/pain | 56 (24) | 29 (17) | | 8 (36) | 6 (27) | 7 (50) | 3 (100) | 2 (100) | NA | 1 (100) | 0 (0) |  | 0 (0) |
| Proptosis | 112 (47) | 83 (49) | | 10 (45) | 9 (41) | 4 (29) | 2 (67) | 0 (0) | NA | 1 (100) | 2 (67) | 1 (50) |
| Diplopia | 26 (11) | 6 (4) | | 8 (36) | 4 (18) | 5 (36) | 2 (67) | 0 (0) | NA | 1 (100) | 0 (0) |  | 0 (0) |
| Ptosis | 23 (10) | 16 (10) | | 2 (9) | 2 (9) | 3 (21) | 0 (0) | 0 (0) | NA | 0 (0) | 0 (0) | 0 (0) |
| Decreased VA | 23 (10) | 8 (5) | | 7 (32) | 2 (9) | 3 (21) | 2 (67) | 0 (0) | NA | 1 (100) | 0 (0) |  | 0 (0) |
| B-symptoms | 6 (3) | 1 (1) | | 0 (0) | 2 (9) | 2 (14) | 0 (0) | 0 (0) | NA | 0 (0) | 1 (33) | 0 (0) |
| Not stated | 24 | 10 | | 4 | 4 | 3 | 0 | 0 | 2 | 0 | 1 |  | 0 |
| Median symptom duration, months (range)c | 4 (0-96) | 4 (0-96) | | 6 (1-36) | 3 (0.5-6) | 6 (0.3-12) | 4 (2-5) | 6 (NA) | NA | 6 (NA) | 4 (2-6) | 3 (1-5) |
| Signsb |  |  | |  |  |  |  |  |  |  |  |  |  |
| Mass | 178 (75) | 132 (79) | | 16 (76) | 13 (59) | 11 (79) | 2 (67) | 1 (50) | NA | 0 (0) | 1(33) | 2 (100) |
| Proptosis | 128 (54) | 102 (61) | | 6 (29) | 10 (45) | 4 (29) | 3 (100) | 1 (50) | NA | 0 (0) | 2 (67) |  | 0 (0) |
| Displacement | 127 (54) | 100 (60) | | 7 (33) | 10 (45) | 4 (29) | 3 (100) | 1 (50) | NA | 0 (0) | 2 (67) | 0 (0) |
| Restricted eye movement | 94 (40) | 75 (45) | | 5 (24) | 9 (41) | 2 (14) | 0 (0) | 0 (0) | NA | 0 (0) | 1 (33) |  | 2 (100) |
| Diplopia | 8 (3) | 2 (1) | | 2 (10) | 1 (5) | 3 (21) | 0 (0) | 0 (0) | NA | 0 (0) | 0 (0) | 0 (0) |
| Ptosis | 22 (9) | 13 (8) | | 3 (14) | 1 (5) | 2 (14) | 2 (67) | 0 (0) | NA | 1 (100) | 0 (0) |  | 0 (0) |
| Chemosis | 20 (8) | 11 (7) | | 0 (0) | 4 (18) | 3 (21) | 0 (0) | 2 (100) | NA | 0 (0) | 0 (0) | 0 (0) |
| Epiphora | 14 (6) | 7 (4) | | 3 (14) | 0 (0) | 1 (7) | 2 (67) | 0 (0) | NA | 0 (0) | 1 (33) |  | 0 (0) |
| Edema | 11 (5) | 6 (4) | | 2 (10) | 0 (0) | 1 (7) | 1 (33) | 1 (50) | NA | 0 (0) | 0 (0) | 0 (0) |
| Resistance | 13 (6) | 5 (3) | | 1 (5) | 2 (9) | 2 (14) | 2 (67) | 0 | NA | 0 (0) | 1 (33) |  | 0 (0) |
| Not stated | 25 | 10 | | 5 | 4 | 3 | 0 | 0 | 2 | 0 | 1 | 0 |
| Systemic disease |  |  | |  |  |  |  |  |  |  |  |  |  |
| Autoimmune disease | 6 | 3 | | 3 | 0 | 0 | 0 | 0 | NA | 0 | 0 |  | 0 |
| Local Spreadb |  |  | |  |  |  |  |  |  |  |  |  |
| Orbit | 191 (73) | 135 (76) | | 19 (73) | 20 (77) | 7 (41) | 1 (33) | 2 (100) | 2 (100) | 0 (0) | 3 (75) |  | 2 (100) |
| Conjunctiva | 25 (10) | 19 (11) | | 4 (15) | 1 (4) | 1 (6) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |  | 0 (0) |
| Eyelid | 5 (2) | 1 (0.6) | | 1 (4) | 2 (8) | 1 (6) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |  | 0 (0) |
| Lacrimal sac | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |  | 0 (0) |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 4. Management of Patients by Subtype of Lacrimal Gland Lymphomaa | | | | |  |  |  |  |  |  |  |  |  |
| No. (%) of Patientsb | | | | | | | | | | | | | |
| Stage | **EBRT** | **EBRT and CTX** | **CTX** | **CTX plus Rituximab** | **EBRT and CTX plus Rituximab** | **Rituximab or Rituximab plus EBRT** | **Surgery** | **Surgery and EBRT** | **Zevalin® and rituximab** | **BM transplant** | **GM-CSF and Zevalin®** | **No treatment** | **Unknown** |
| B-cell lymphomas | |  |  |  |  |  |  |  |  |  |  |  |  |
| EMZL | **138 (79)** | **8 (5)** | **3 (2)** | **13 (7)** | **0** | **2 (1)** | **2 (1)** | **4 (2)** | **3 (2)** | **0** | **1 (1)** | **1 (1)** | **4 (2)** |
| IE | 133 (88) | 6 (4) | 0 | 2 (1) | 0 | 1 (1) | 2 (1) | 4 (3) | 3 (2) | 0 | 1(1) | 0 | 4 (3) |
| IIE | 1 (20) | 2 (40) | 0 | 2 (40) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IIIE | 1 (25) | 0 | 0 | 2 (50) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (25) | 0 |
| IVE | 3 (27) | 0 | 3 (27) | 5 (45) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 | 2 (67) | 0 | 1 (33) | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| FL | **9 (38)** | **6 (25)** | **2 (8)** | **1 (4)** | **0** | **2 (8)** | **1 (4)** | **0** | **1 (4)** | **0** | **0** | **2 (8)** | **2 (8)** |
| IE | 6 (46) | 5 (38) | 0 | 0 | 0 | 0 | 1 (8) | 0 | 0 | 0 | 0 | 1 (8) | 1 (7) |
| IIE | 1 (20) | 1 (20) | 1 (20) | 0 | 0 | 1 (20) | 0 | 0 | 0 | 0 | 0 | 1 (20) | 0 |
| IIIE | 1 (50) | 0 | 1 (50) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IVE | 0 | 0 | 0 | 1 (50) | 0 | 0 | 0 | 0 | 1 (50) | 0 | 0 | 0 | 0 |
| Unknown | 1 (50) | 0 | 0 | 0 | 0 | 1 (50) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (33) |
| DLBCL | **3 (12)** | **12 (46)** | **0** | **7 (27)** | **3 (12)** | **0** | **0** | **0** | **0** | **0** | **0** | **1 (4)** | **0** |
| IE | 3 (18) | 10 (59) | 0 | 1 (6) | 2 (12) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (6) | 0 |
| IIE | 0 | 1 (25) | 0 | 3 (75) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IIIE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IVE | 0 | 1 (20) | 0 | 3 (60) | 1 (20) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| MCL | **2 (12)** | **1 (6)** | **3 (18)** | **8 (47)** | **3 (18)** | **0** | **0** | **0** | **0** | **2 (12)** | **0** | **0** | **0** |
| IE | 0 | 1 (50) | 0 (0) | 1 (50) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IIE | 0 | 0 | 2 (100) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IIIE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IVE | 2 (17) | 0 | 1 (8) | 6 (50) | 3 (25) | 0 | 0 | 0 | 0 | 2 (17) | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 | 1 (100) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| SLL/CLL | **3 (100)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| IE | 2 (100) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IIE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IIIE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IVE | 1 (100) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| BL | **0** | **2 (100)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| IE | 0 | 1 (100) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IVE | 0 | 1 (100) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PL | **0** | **2 (100)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| IE | 0 | 2 (100) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| LPL | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **1 (100)** |
| Unknown | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (100) |
| BCL, NOS | **2 (50)** | **1 (25)** | **1 (25)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| IE | 2 (50) | 1 (25) | 1 (25) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| T-cell lymphomas | |  |  |  |  |  |  |  |  |  |  |  |  |
| PTCL, NOS | **1 (50)** | **1 (50)** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** | **0** |
| IE | 1 (50) | 1 (50) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Figure 1**

****

**Figure 2**



|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Subtype, interval, years | 0 | 5 | 10 | 15 | 20 | 25 | 30 |
| EMZL (N=178) |  |  |  |  |  |  |  |
| Patients at risk, No. | 105 | 19 | 6 | 2 | 1.5 | 1 | 0.5 |
| Events, No. | 4 | 1 | 1 | 0 | 0 | 0 | 0 |
| FL (N=26) |  |  |  |  |  |  |  |
| Patients at risk, No | 22.5 | 12 | 4.5 | 1.5 |  |  |  |
| Events, No. | 3 | 2 | 0 | 0 |  |  |  |
| DLBCL (N=26) |  |  |  |  |  |  |  |
| Patients at risk, No. | 18 | 2.5 | 0.5 |  |  |  |  |
| Events, No. | 7 | 0 | 0 |  |  |  |  |
| MCL (N=17) |  |  |  |  |  |  |  |
| Patients at risk, No | 11 | 3 | 1.5 | 0.5 |  |  |  |
| Events, No | 2 | 1 | 0 | 0 |  |  |  |

**Legends:**

Table 1:

A: Percentage of total number of patients contributed by each eye cancer center.

B: Percentage of patients with the specific lymphoma subtype within each eye cancer center and in total

Abbreviations: ATL = Atlanta, Georgia, USA; BCL-NOS = B-cell lymphoma not otherwise specified; BL = Burkitt lymphoma; CPH = Copenhagen, Denmark; DLBCL = diffuse large B-cell lymphoma; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; HOU = Houston, Texas; HYD = Hyderabad, India; LIV = Liverpool, England; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; NY = New York, USA; PL = plasmacytoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; SLL/CLL = small lymphocytic lymphoma

Table 2:

A: Data not specified in all cases

B: Number of patients / no of patients with data specified, (%) = Percentage of patients with data specified

C: AJCC TNM classification: Only primary lymphomas were staged according to AJCC TNM classification

D: A total of more than 100 % may occur because patients may have recurrence in more than 1 region

Abbreviations: AJCC = American Joint Committee on Cancer; BCL-NOS = B-cell lymphoma not otherwise specified; BL = Burkitt lymphoma; DLBCL = diffuse large B-cell lymphoma; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; OA = ocular adnexa; PL = plasmacytoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; SLL/CLL = small lymphocytic lymphoma;

Table 3:

A: Data not specified in all cases

B: A total of more than 100 % may occur because patients may have 1 or more symptoms or signs

C: Symptom duration not specified for all patients

Abbreviations: BCL-NOS = B-cell lymphoma not otherwise specified; BL = Burkitt lymphoma; DLBCL = diffuse large B-cell lymphoma; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; PL = plasmacytoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; SLL/CLL = small lymphocytic lymphoma;

Table 4:

A: Data not specified for all patients

B:Number of patients, (%) Percentage of patients with data specified stratified by Ann Arbor stage

Abbreviations: BCL-NOS = B-cell lymphoma not otherwise specified; BL = Burkitt lymphoma; BM transplant = bone marrow transplantation; CTX = chemotherapy; DLBCL = diffuse large B-cell lymphoma; EBRT = external beam radiation therpay; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; GM-CSF = Granulocyte-macrophage colony-stimulating factor; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; PL = plasmacytoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; SLL/CLL = small lymphocytic lymphoma; Zevalin® = ibritumomab tiuxetan

Figure 1

Clinical and histological findings of a lacrimal gland extranodal marginal zone B-cell lymphoma.

A: Left sided orbital mass (asterisk) in 68-year-old woman with an extranodal marginal zone B-cell lymphoma of the left lacrimal gland. Symptoms at presentation were a palpable mass, periobital swelling, epiphora, and irritation.

B: Coronal plane PET/CT demonstrating FDG uptake of the left enlarged lacrimal gland (arrow).

C: Diffuse infiltration of malignant lymphocytic tumor cells. The tumor cells are small to medium-sized, round, and with irregular nuclei, resembling centrocytes (Hematoxylin-eosin, bar = 50 μm).

D: The tumor cells demonstrates positive immunoreaction for the B-cell marker CD79α (anti-CD 79α, bar = 50 μm)

Figure 2

Disease-specific survival among patients with lacrimal gland lymphoma. Disease-specific survival is associated with lymphoma subtype. Life table showing patients’ risk of dying of lymphoma and number of patients with the event at each time point.

Abbreviations: DLBCL = diffuse large B-cell lymphoma; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma