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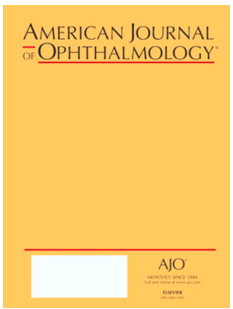

Lymphoma of the Eyelid – An International Multicenter Retrospective Study

Frederik Holm Svendsen, Peter Kristian Rasmussen, Sarah E. Coupland, Bita Esmaeli, Paul T. Finger, Gerardo F. Graue, Hans E. Grossniklaus, Santosh G. Honavar, MD, Jwu Jin Khong, Penelope A. McKelvie, Kaustubh Mulay, Elisabeth Ralfkiaer, Lene Dissing Sjö, Geeta K. Vemuganti, Bradley A. Thuro, Jeremy Curtin, Steffen Heegaard

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Purpose. To document subtype-specific clinical features of lymphoma of the eyelid, and their effect on patient outcome.

Design. Retrospective observational case series.

Methods. Patient data were collected from 7 international eye cancer centers from January 1st 1980 through December 31st 2015. The cases included primary and secondary lymphomas affecting the eyelid. Overall survival, disease-specific survival (DSS), and progression-free survival were the primary end points.

Results. Eighty-six patients were included. Mean age was 63 years and 47 (55%) were male. Non-Hodgkin B-cell lymphomas constituted 83% (n=71) and T-cell lymphomas constituted 17% (n=15). The most common subtypes were extranodal marginal-zone lymphoma (EMZL) (37% [n=32]), follicular lymphoma (FL) (23% [n=20]), diffuse large B-cell lymphoma (DLBCL) (10% [n=9]), mantle cell lymphoma (MCL) (8% [n=7]) and mycosis fungoides (MF) (9% [n=8]).

EMZL had a female predilection (69% [22 of 32]), whereas MCL (71% [5 of 7]) and MF (88% [7 of 8]) had a male predominance. MCL (57% [4 of 7]), DLBCL (56% [5 of 9]) and MF (88% [7 of 8]) were frequently secondary lymphomas. Localized EMZL and FL were mostly treated with external beam radiation therapy, whereas DLBCL, MCL and high Ann Arbor stage EMZL and FL were frequently treated with chemotherapy. DLBCL and MCL had a poor prognosis (5-year DSS, 21% and 50%, respectively), whereas EMZL, FL and MF had a good prognosis (5-year DSS, 88%, 88% and 86%, respectively).

Conclusions. Lymphoma of the eyelid consists mainly of the lymphoma subtypes: EMZL, FL, DLBCL, MCL and MF. High-grade DLBCL and MCL as well as MF are frequently secondary eyelid lymphomas. The main predictor of outcome was the histological subtype: EMZL, FL and MF had a significantly better prognosis than MCL and DLBCL.

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Title page

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Short title: Lymphoma of the Eyelid

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1. Introduction

Lymphomas are malignant neoplasms originating from clonal proliferations of lymphocytes and are a heterogeneous group with more than 40 subtypes.[1] Lymphomas can occur within nodes or extranodally and originate from B-cells, T-cells or more seldom NK-cells. Ocular adnexal lymphomas (OAL) constitute 2% of all extranodal lymphomas[2] and 5% of OAL are located in the eyelid.[3]

Lymphoma of the eyelid (LE) is defined as lymphoma involving the pre-septal tissues: the skin, subcutaneous connective tissue and orbicularis oculi muscle.[4]

LE consists of several different subtypes of B-cell, T-cell and NK-cell origin. Low-grade B-cell lymphomas include extranodal marginal-zone lymphoma (EMZL), follicular lymphoma (FL) and extramedullary plasmacytoma. High-grade B-cell lymphomas include diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL).[5] The most common T-cell lymphoma involving the eyelid is mycosis fungoides (MF).[5] The distribution of LE subtypes appears to be different from lymphomas in other ocular adnexal sites with a higher rate of eyelid T-cell lymphomas and a lower rate of eyelid EMZL.[5]

LE is a rare disease with 199 cases reported in the literature.[5] To our knowledge, no large cohort studies of specific lymphoma subtypes of the eyelid have been made and, therefore, clinical data of LE are limited. The primary predictor for prognosis of LE has been found to be the histological lymphoma subtype.[5] Overall LE are considered to have a worse prognoses than lymphomas in other ocular adnexal sites.[6] This is incorporated into the American Joint Committee on Cancer (AJCC) staging system, where involvement of the eyelid, regardless of other factors, is staged as stage T3 or higher.[4] Because of the diversity and heterogenic nature of lymphoma subtypes of the eyelid, analyses of the different subtypes are needed. The aim of this study was to describe the major subtypes of LE with their clinical features and their effect on survival in a cohort from 7 international eye cancer centers.

2. Methods

2.1. Study design

In this observational case series, patients with lymphoma of the eyelid with the main tumor bulk involving the pre-septal tissues were included. The patients were collected from January 1st 1980 to December 31st 2015. The analysis of the data was undertaken at study closure between May 20th - August 18th 2016.

Specimens were first stained with hematoxylin-eosin and analyzed immunohistochemically with a panel of antibodies for histopathological examination. Current guidelines[1] recommend the following panel for small cell lymphomas: CD3, CD5, CD10, CD20, CD23, CD79α, cyclin D-1, Bcl-2, Bcl-6, multiple myeloma oncogene 1 (MUM-1), methylation-inhibited binding protein 1 (MIB-1), and κ and λ light-chains. Guidelines for large cell lymphomas are: CD3, CD5, CD10, CD20, CD30, CD79α, Bcl-2, Bcl-6, MUM-1, and MIB-2. The data collection spans more than 30 years, and includes 7 eye cancer centers: Copenhagen, Denmark; Liverpool, England; Houston, Texas; Hyderabad, India; New York, New York, USA; Atlanta, Georgia, USA; and Melbourne, Australia, and therefore not all samples were analyzed in this uniform matter. However, the cancer centers reviewed the specimens and reclassified them according to the World Health Organization Classification of Tumours of Hematopoietic and Lymphoid tissues.[1]

This 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 were obtained from the Danish Data Protection Agency.

2.2. Clinical data

The clinical data recorded included age, gender, symptoms, clinical findings, laterality, systemic involvement and thus the Ann Arbor stage, the AJCC/TNM stage, treatment modalities, response to treatment, survival duration and cause of death. The Ann Arbor staging system stages lymphomas from stage I to stage IV. Stage I is lymphoma in a single region. Stage II is lymphoma in two separate regions on only one side of the diaphragm. Stage III is lymphoma spread to both sides of the diaphragm. Stage IV is diffusely disseminated lymphoma.

Involvement of lymph nodes, bone marrow or other extranodal sites was determined with diagnostic tools available at the time of diagnosis and clinical data. At present complete diagnostic work-up includes full-body PET-CT, CT or MRI of the eyelid and a bone marrow biopsy.

Primary LE was defined by the following: (1) Biopsy-proven lymphoma with no concurrent systemic disease at the time of diagnostic work-up, meaning lymphoma confined to the ocular adnexa (stage IE) with or without involvement of unilateral preauricular or submandibular lymph nodes or adjacent structures (stage IIE) and (2) no prior history of lymphoma. Consequently, secondary lymphoma is defined as systemic lymphoma with a secondary manifestation of the eyelid or lymphoma relapse affecting the eyelid on the background of clinically-known systemic lymphoma.

2.3. Statistical analysis

The primary end points considered were overall survival (OS), disease-specific survival (DSS) and progression-free survival (PFS). OS was defined as date of diagnosis of LE to death of any cause or last follow-up, with the latter being a censored event. DSS was defined as date of diagnosis to the date of death because of lymphoma or the date of last contact, the latter being a censored event. PFS was calculated from date of diagnosis to either the date of first relapse or progression after initial treatment, to the date of death of any cause or to the date of last contact, with the latter 2 being censored events. Life tables and Kaplan-Meier plots were made to show survival outcomes. Different risk factors were compared using the χ^2 or Fisher's Exact test depending on the number of patients. Statistical analysis and calculation were done using a software program (IBM SPSS Package, version 22; IBM Corporation).

3. Results

Eighty-six patients were identified with LE from the database of 7 eye cancer centers: Copenhagen, Denmark (n=22); Liverpool, England (n=33); Houston, Texas (n=22); Hyderabad, India (n=4); New York, New York, USA (n=3); Atlanta, Georgia, USA (n=1); and Melbourne, Australia (n=1). (Table 1) Six B-cell lymphoma subtypes were identified: EMZL (n=32); FL (n=20); DLBCL (n=9); MCL (n=7); lymphoplasmacytic lymphoma (LPL) (n=1); and small lymphocytic lymphoma (SLL/CLL) (n=1). Five T-cell lymphoma subtypes were identified: MF (n=8); peripheral T-cell lymphoma (PTCL) (n=2); lymphomatoid papulosis (LyP) (n=2); primary cutaneous anaplastic large cell

lymphoma (C-ALCL) (n=1); and anaplastic large cell lymphoma (ALCL) (n=1). One case each of a B- and a T-cell lymphoma could not be subtyped further. The median follow-up period was 53 months (range, 0-251 months).
The most common symptom for all LE subtypes was a tumor and/or swelling of the eyelid. (Table 2) Ulceration and mechanical ectropion seem to be signs of T-cell lymphomas with 27% (4 of 15) of the T-cell lymphoma patients showing ulceration, and 75% (6 of 8) of MF showing mechanical ectropion, whereas no B-cell lymphoma patient showed either sign. The AJCC/TNM staging system regards lymphoma with involvement of the pre-septal eyelid as stage T3 or higher.[4] In this study all cases of primary LE were staged as stage T3. (Table 3)

3.1. Major Non-Hodgkin B-cell Lymphoma subtypes

3.1.1. Extranodal marginal zone lymphoma

Clinical features. 32 patients (37%) were diagnosed with EMZL. The median age was 63.5 years (age range, 19-90 years). Twenty-two had primary lymphoma (69%), 24 had stage IE disease (75%) and 24 had unilateral involvement (77% [n=24 of 31]). (Table 3) The median symptom duration was 7 months (range, 2-36 months).
Treatment. The most common treatment for stage IE/IIE lymphoma was external beam radiation therapy (EBRT) (81% [n=21 of 26]) either alone or with chemotherapy (31% [n=8 of 26]). Stage IIIE/IVE lymphoma was treated with chemotherapy (67% [n=4 of 6]) with or without EBRT. (Table 4) The median radiation dose was 30.6 Gy (range, 26-40 Gy). The applied chemotherapy was CVP (cyclophosphamide, vincristine and prednisone), rituximab and unspecified chemotherapy.
Treatment outcome and survival. 21 patients experienced relapse (66%). The median duration before relapse was 35 months (range, 9-155 months). The median PFS was 61 months (range, 2-251 months). The OS and DSS rates at 5 years were 86% and 88%, respectively (median survival 5.5 years; 95% CI, 3.8-7.2 years).

3.1.2. Follicular lymphoma

Clinical features. Twenty patients (23%) were diagnosed with FL. The median age was 60 years (age range, 41-81 years). Sixteen patients (80%) had primary LE, 15 had unilateral involvement (75%) and 12 had stage IE lymphoma (60%). (Table 3) The median symptom duration was 5 months (range, 1-36 months).
Treatment. Stage IE/IIE disease were mostly treated with EBRT (67% [n=10 of 15]) with or without chemotherapy, whereas all stage IVE patients were treated with chemotherapy with or without EBRT. (Table 4) Median radiation dose was 30 Gy (range, 4-36 Gy). The chemotherapy applied consisted of CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone), CVP, rituximab, ibritumomab tiuxetan and unspecified chemotherapy.
Treatment outcome and survival. Relapse of lymphoma was observed in 12 patients (60%). (Table 3) The median duration before relapse was 23 months (range, 2-72 months). The median PFS was 49 months (range, 1-110 months). The OS rate and DSS rate at 5 years were 80% and 88%, respectively (median survival 5.0 years; 95% CI, 3.2-6.8 years).

3.1.3. Diffuse large B-cell lymphoma

Clinical features. Nine patients (10%) were diagnosed with DLBCL. The median age

was 61 years (age range, 29-93 years). DLBCL presented unilateral in all 9 cases and more than half as secondary lymphoma (56% [n=5]). (Table 3) Median symptom duration was 1 month (range, 1-4 months).
Treatment. All patients were treated with chemotherapy with or without EBRT. Radiation dose was known in one case, who was treated with 36 Gy. Applied chemotherapy was CHOP, hyper-CVAD (cyclophosphamide, vincristine, hydroxydaunorubicin and dexamethasone), rituximab, methotrexate and unspecified chemotherapy.
Treatment outcome and survival. Relapse was observed in 7 patients (78%). Median time to relapse was 1 month (range, 0-5 months). The median PFS was 5 months (range, 0-23 months). The OS at 5 years was 13%, whereas the DSS at 5 years was 21% (median survival 1.9 years, 95% CI, 0.7-3.1 years).

3.1.4. Mantle cell lymphoma
Clinical features. Seven patients (8%) were diagnosed with MCL. Five (71%) were male and the median age was 75 years (age range, 67-84 years). Five patients had unilateral involvement (71%). (Figure 1) The median symptom duration was 7 months (range, 6-8 months).
Treatment. All 7 patients were treated with chemotherapy and 5 patients (71%) were also treated with EBRT. Radiation dose was known in one case and was 24 Gy. The applied chemotherapy was CHOP, hyper-CVAD, bortezomib, methotrexate, antimetabolites and unspecified chemotherapy.
Treatment outcome and survival. Recurrence of lymphoma was observed in all 7 patients. (Table 3) The median duration before relapse was 11 months (range, 5-23 months). Both the OS rate and DSS rate at 5 years were 50%. The median survival was 2.1 years (95% CI, -0.2-4.4 years).

3.2. Rare Non-Hodgkin B-cell Lymphoma subtypes
3.2.1. Lymphoplasmacytic lymphoma
One 68-year-old female was diagnosed with primary bilateral LPL (stage IIE). She experienced nodal relapse and died of lymphoma after 32 months.

3.2.2. Small lymphocytic lymphoma
One 75-year-old man had relapsed bilateral SLL/CLL (stage IVE) through 9 months. He was treated with alkylating agents and surgery, but experienced relapse in the eyelids 11 months later and died of other causes 93 months later.

3.3. Major T-cell lymphoma subtypes
3.3.1. Mycosis fungoides
Clinical features. Eight patients (9%) had MF, 7 were male (88%) and the median age was 78 (age range, 58-88 years). Six patients (75%) had a history of prior MF and one had prior FL and all 8 patients had bilateral involvement. The most common symptom was mechanical ectropion (63% [n=5]). (Table 2)
Treatment. Stage IE/IIE was treated with EBRT with or without chemotherapy. Stage IVE disease was treated with a combination of EBRT and chemotherapy. (Table 4) The median radiation dose was 32 Gy (range, 20-37 Gy). The applied chemotherapy

included topical nitrogen mustard, methotrexate, CHOP, antimetabolites and retinoid synthetics.

Treatment outcome and survival. Three of 7 experienced relapse (43%). Relapse time was known in one patient and was 18 months. The median PFS was 31 months (range, 6-101 months). The OS and DSS rates at 5 years were 42% and 86%, respectively (median, 2.4 years; 95% CI, -0.5-5.2 years).

3.4. Rare T-cell lymphoma subtypes

3.4.1. Peripheral T-cell lymphoma

Two male patients, aged 35 and 59 years, were diagnosed with unilateral PTCL. The duration of symptoms was known in one patient and was 1 month. One patient experienced relapse on his tongue after 66 months and the other experienced nodal relapse, but achieved complete remission at 26 months after diagnosis of LE.

3.4.2. Lymphomatoid papulosis

Two male patients, aged 73 and 34 years, were diagnosed with primary unilateral LyP (stage IE). One patient had symptom duration of one month and the treatment was only surgery in the other patient. They were both in complete remission at 46 and 78 months, respectively. One patient died of non-lymphoma related disease 78 months after the diagnosis of LE.

3.4.3. Primary cutaneous anaplastic large cell lymphoma

A 61-year-old male had primary unilateral C-ALCL (stage IE) through one month. He was treated with 30 Gy and CHOP. After 6 months, the patient had relapse in the same eyelid, but was in complete remission 32 months later.

3.4.4. Anaplastic large cell lymphoma

One 54-year old male patient was diagnosed with disseminated ALCL (stage III) after 2 months of symptoms. He was treated with CHOP and was in complete remission at 78 months from the time of diagnosis.

4. Discussion

The distribution of LE subtypes had a markedly higher rate of MF, a higher rate of FL and a markedly lower rate of EMZL compared to other ocular adnexal sites.[3,7] However, the spectrum of subtypes of B-cell lymphoma subtypes was the same as for other ocular adnexal region lymphomas,[3] whereas T-cell lymphoma is very rare in other ocular adnexal structures.[3] T-cell lymphomas have a predilection for the skin, and therefore T-cell lymphomas have a higher incidence in the eyelid region compared to the rest of the eye region.

LE tends to be a disease of the elderly, with a mean age of 63 years. The median age for EMZL (64 years), FL (60 years) and MCL (75 years) seem to follow the regular age pattern for other OAL.[3,7-9] However, the median age for DLBCL is lower compared to other ocular adnexal sites (e.g. conjunctiva, 74 years[7] and OAL, 70-77 years[3,10] versus LE, 61 years). T-cell lymphomas as well as MCL had a high frequency in male patients, whereas EMZL had a predilection for female patients. (Table 3) Ulceration and mechanical ectropion seem to be signs of T-cell lymphomas. We suspect that ulceration was the cause of some cases of mechanical ectropion. The symptom

duration before diagnosis was longer in low-grade lymphomas EMZL and FL (median duration, 8 and 5 months, respectively), than the high-grade lymphoma DLBCL (median duration, 1 month). The high-grade B-cell lymphomas and the T-cell lymphoma MF are more likely secondary than FL and EMZL. (Table 3) Orbital spread is much more frequent in B-cell lymphomas than T-cell lymphomas (Table 2), which has also previously been stated.[5]

In this study, the treatment for low-grade LE without dissemination was frequently EBRT, whereas the treatment for high-grade LE and disseminated lymphomas were more frequently chemotherapy. (Table 4) Current guidelines for treatment of high-grade lymphoma subtypes MCL and DLBCL and high-stage EMZL and FL with high tumor burden, are R-CHOP or R-CHOP 'like' chemotherapy.[11-14]

The rate of recurrences of LE was higher when compared to the conjunctiva: EMZL had a recurrence rate of 66% when occurring in the eyelid, whereas only 38% recurred when occurring in the conjunctiva.[7] Likewise FL had a higher recurrence rate (conjunctiva, 43%[7] versus eyelid, 60%). DLBCL had a high recurrence at both sites (conjunctiva, 67% versus eyelid, 78%). MCL had a particularly high rate of recurrence at both sites (conjunctiva, 81% versus eyelid, 100%).

The design of this study, being a retrospective database study, has some inherent limitations. The patients in the database were collected from 7 eye cancer centers and over a 30-year period. Thus, there were incomplete medical records and heterogeneous diagnostic methods used, which we minimized by reviewing the specimens according to the WHO classification.[1] Further, the median follow-up was relatively short at 53 months, for some subtypes of lymphoma of indolent nature the duration of follow-up may not had been long enough to recognize the outcome variables. However, the multicenter database was large, which gives far greater and valuable information for a rare disease.

In a review study on LE,[5] the number of T-cell LE is much higher than the number found in this study. This could be due to several factors. Firstly, a publishing bias with a higher rate of rare T-cell lymphomas and lower rate of indolent EMZL and FL could be present in the literature review. Secondly as the eyelid contains skin a higher proportion of cutaneous T-cell lymphomas[15] like MF, LyP and C-ALCL is expected in the eyelid compared to other ocular adnexal sites. Some of the cutaneous T-cell lymphoma subtypes of the eyelid may have been examined and treated in non-ophthalmological centers and, thus, not included in our database. Further, MF often presents as a relapsed disease (Table 3) and therefore, a biopsy for histological examination from the eyelid may not have been carried out.

The ocular oncology center in Houston have a higher number of specific subtypes: MF as well as FL were more common. (Table 1) This could be due to a selection bias as some high-grade lymphoma patients are referred to specialized centers whilst low-grade lymphoma patients tend to be treated locally in non-referral centers.

The eye cancer center in Copenhagen, Denmark had access to the national database of LE and, thus, a national distribution was available. The distribution of the lymphoma subtypes in the Danish center matches the entire group of LE in the present study. (Table 1) This indicates that the present study's distribution of LE is also representative of the national distributions.

The main predictor of outcome was the histological lymphoma subtype: DLBCL and MCL had a poorer prognosis (5-year DSS, 21% and 50%, respectively) than FL and

EMZL (5-year DSS, 88% and 88%, respectively). (Figure 2) The T-cell lymphoma MF had a good prognosis with a 5-year DSS of 86%.(Figure 2) The finding that the histopathological subtype is a main predictor of outcome has also been found by Graue et al. for OAL.[16] When comparing all LE, primary lymphoma (5-year DSS, 84%) had a significant (log rank test, p=0.038) better 5-year DSS than secondary LE (5-year DSS, 64%).

The prognosis for LE has been considered worse than the prognosis of other OAL.[6,17-20] However, compared to conjunctival lymphoma the prognosis of LE seems similar: 5-year DSS for EMZL (conjunctiva 97%[7] versus eyelid 88%) and 5-year DSS for FL (conjunctiva 82%[7] versus eyelid 88%). Only in DLBCL the 5-year DSS was worse (conjunctiva 55%[7] versus eyelid 21%). In contrast the 5-year DSS for MCL of the eyelid was better than in the conjunctiva (conjunctiva 21%[7] versus eyelid 50%). This novel information regarding outcome of the different subtypes of LE could be incorporated in the future AJCC staging system.

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Figure legends

Figure 1. Clinical and histological findings of a secondary mantle cell lymphoma of the eyelid in a 51-year-old male.
(Top left) Nodular tumor (arrow) presenting in the medial portion of the right upper eyelid. (Top right) Computed tomography showing a tumor mass (arrow) of the right upper eyelid and spreading to the nasal ridge. (Center left) The tumor shows diffuse infiltration of the tissue by small to medium sized lymphoid tumor cells (hematoxylin-eosin, bar=50 µm). (Center right) The tumors cells demonstrates positivity for anti-Bcl-2 (bar=50 µm). (Bottom left) Only a few tumor cells are positive for anti-CD3 (bar=50 µm). (Bottom right) The tumor cells are reacting with anti-cyclin D-1 (bar=50 µm).

Figure 2. Disease-specific survival by subtype of lymphoma of the eyelid.
(Left) Disease-specific survival is associated with the subtype of lymphoma of the eyelid. Low-grade subtypes like extranodal marginal zone lymphoma and follicular lymphoma have a more favorable prognosis than high-grade subtypes such as diffuse large B-cell lymphoma and mantle cell lymphoma. (Right) T-cell lymphomas of the eyelid seem to have a good prognosis; this is also the case for the most common T-cell lymphoma subtype of the eyelid mycosis fungoides.
Abbreviations: ALCL, anaplastic large cell lymphoma; BCL, NOS, B-cell lymphoma, not otherwise specified; C-ALCL, primary cutaneous anaplastic large cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; LyP, lymphomatoid papulosis; MCL, mantle cell lymphoma; MF, mycosis fungoides; PTCL, peripheral T-cell lymphoma; SLL/CLL, small lymphocytic lymphoma; TCL, NOS, T-cell lymphoma, not otherwise specified.

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Table 1. Eye Cancer Center Distribution of Patients by Subtype of Lymphoma of the Eyelid							
	Eye Cancer Center						
	CPH	LIV	HOU	HYD	NY	ATL	MEL
Subtype	(n=22)	(n=33)	(n=22)	(n=4)	(n=3)	(n=1)	(n=1)
B-CELL LYMPHOMAS							
EMZL							
No. of Patients	9	18	3	0	1	0	1
Median age, y	69	62	61	NA	75	NA	55
Male to female ratio	3:6	5:13	1:2	NA	0:1	NA	1:0
FL							
No. of Patients	2	6	8	2	2	0	0
Median age, y	66	60	58	68	81	NA	NA
Male to female ratio	2:0	1:5	5:3	2:0	2:0	NA	NA
DLBCL							
No. of Patients	3	3	1	2	0	0	0
Median age, y	65	61	29	53	NA	NA	NA
Male to female ratio	2:1	2:1	0:1	1:1	NA	NA	NA
MCL							
No. of Patients	2	3	2	0	0	0	0
Median age, y	80	75	69	NA	NA	NA	NA
Male to female ratio	2:0	2:1	1:1	NA	NA	NA	NA
LPL							
No. of Patients	0	1	0	0	0	0	0
Median age, y	NA	68	NA	NA	NA	NA	NA
Male to female ratio	NA	0:1	NA	NA	NA	NA	NA
SLL/CLL							
No. of Patients	1	0	0	0	0	0	0
Median age, y	75	NA	NA	NA	NA	NA	NA
Male to female ratio	1:0	NA	NA	NA	NA	NA	NA
BCL, NOS							
No. of Patients	0	0	0	0	0	1	0
Median age, y	NA	NA	NA	NA	NA	84	NA
Male to female ratio	NA	NA	NA	NA	NA	0:1	NA
T-CELL LYMPHOMAS							
MF							
No. of Patients	1	0	7	0	0	0	0
Median age, y	77	NA	79	NA	NA	NA	NA
Male to female ratio	1:0	NA	6:1	NA	NA	NA	NA
PTCL							
No. of Patients	1	1	0	0	0	0	0
Median age, y	59	35	NA	NA	NA	NA	NA
Male to female ratio	1:0	1:0	NA	NA	NA	NA	NA
LyP							
No. of Patients	1	0	1	0	0	0	0

Median age, y	34	NA	73	NA	NA	NA	NA
Male to female ratio	1:0	NA	1:0	NA	NA	NA	NA
C-ALCL							
No. of Patients	1	0	0	0	0	0	0
Median age, y	61	NA	NA	NA	NA	NA	NA
Male to female ratio	1:0	NA	NA	NA	NA	NA	NA
ALCL							
No. of Patients	1	0	0	0	0	0	0
Median age, y	54	NA	NA	NA	NA	NA	NA
Male to female ratio	1:0	NA	NA	NA	NA	NA	NA
TCL, NOS							
No. of Patients	0	1	0	0	0	0	0
Median age, y	NA	48	NA	NA	NA	NA	NA
Male to female ratio	NA	1:0	NA	NA	NA	NA	NA

Table 1. Eye Cancer Center Distribution of Patients by Subtype of Lymphoma of the Eyelid

Abbreviations: ALCL, anaplastic large cell lymphoma; ATL, Atlanta, Georgia, USA; BCL, NOS, B-cell lymphoma, not otherwise specified; C-ALCL, primary cutaneous anaplastic large cell lymphoma; CPH, Copenhagen, Denmark; DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; HOU, Houston, Texas, USA; HYD, Hyderabad, India; LIV, Liverpool, England; LPL, lymphoplasmacytic lymphoma; LyP, lymphomatoid papulosis; MCL, mantle cell lymphoma; MEL, Melbourne, Australia; MF, mycosis fungoides; NA, not applicable; NY, New York, New York, USA; PTCL, peripheral T-cell lymphoma; SLL/CLL, small lymphocytic lymphoma; TCL, NOS, T-cell lymphoma, not otherwise specified.

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Table 2. Location, Frequency of Symptoms, and Clinical Signs at Presentation of Lymphoma of the Eyelid													
	B-cell lymphomas, No. (%) patients							T-cell lymphomas, No. (%) patients					
	EMZL	FL	DLBCL	MCL	LPL	SLL	BCL, NOS	MF	PTCL	LyP	C-ALCL	ALCL	TCL, NOS
	32 (37)	20 (23)	9 (10)	7 (8)	1 (1)	1 (1)	1 (1)	8 (9)	2 (2)	2 (2)	1 (1)	1 (1)	1 (1)
Eyelid[a, b]													
Right	14	15	5	3	1	1	1	8	2	1		1	1
Left	23	8	1	6	1	1		8			1		
Symptom[c]													
Tumor/swelling	9 (28)	13 (65)	6 (67)	4 (57)		1		1 (13)		2	1	1	
Epiphora		3 (15)						1 (13)					
Irritation/pain	1 (3)		2 (22)	1 (14)				1 (13)					
Diplopia	2 (6)	1 (5)		3 (43)								1	
Ptosis	1 (3)			1 (14)		1		1 (13)					
Erythema				1 (14)				3 (38)					
Decreased VA	2 (6)												
B symptoms	1 (3)	1 (5)		1 (14)				1 (13)					
Not stated	22 (69)	6 (30)	3 (33)	3 (43)	1		1	1 (13)	2				1
Sign[c]													
Mass	9 (28)	10 (50)	5 (56)	4 (57)		1		1 (13)	1	1	1	1	
Epiphora		2 (10)											
Diplopia	2 (6)	2 (10)		1								1	

				(14)									
Ptosis		1 (5)									1		
Ulceration								1 (13)	1	1	1		
Chemosis		2 (10)	2 (22)					1 (13)					
Edema	3 (9)		2 (22)						1				
Ectropion								6 (63)					
Not stated	20 (63)	6 (30)	3 (33)	3 (42)	1		1		1	1			1
Local spread[a]													
Orbit	6	6	4	4			1					1	
Conjunctiva	2	5				1							
Lacrimal sac	1	2											
Lacrimal gland			2										

Table 2. Location, Frequency of Symptoms, and Clinical Signs at Presentation of Lymphoma of the Eyelid

Abbreviations: ALCL, anaplastic large cell lymphoma; BCL, NOS, B-cell lymphoma, not otherwise specified; C-ALCL, primary cutaneous anaplastic large cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; LyP, lymphomatoid papulosis; MCL, mantle cell lymphoma; MF, mycosis fungoides; PTCL, peripheral T-cell lymphoma; SLL, small lymphocytic lymphoma; TCL, NOS, T-cell lymphoma, not otherwise specified; VA, visual acuity.

[a]Not specified for all cases.

[b]A total of more than 100% because patients may have bilateral affection.

[c]A total of more than 100% because patients may have 1 or more symptoms or signs.

Table 3. Clinical and Staging Characteristics of Patients by Subtype of Lymphoma of the Eyelid[a]

	B-CELL LYMPHOMAS, No. (%) patients							T-CELL LYMPHOMAS, No. (%) patients					
	EMZL	FL	DLBCL	MCL	LPL	SLL/CLL	BCL, NOS	MF	PTCL	LyP	C-ALCL	ALCL	TCL, NOS
Characteristic	(n=32)	(n=20)	(n=9)	(n=7)	(n=1)	(n=1)	(n=1)	(n=8)	(n=2)	(n=2)	(n=1)	(n=1)	(n=1)
Sex													
Male	10 (31)	12 (60)	5 (56)	5 (71)	0	1	0	7 (88)	2	2	1	1	1
Female	22 (69)	8 (40)	4 (44)	2 (29)	1	0	1	1 (13)	0	0	0	0	0
Age at presentation, y													
≤60	14 (44)	10 (50)	4 (44)	0	0	0	0	1 (13)	2	1	0	1	1
>60	18 (56)	10 (50)	5 (56)	7 (100)	1	1	1	7 (88)	0	1	1	0	0
Primary disease	22 (69)	16 (80)	4 (44)	3 (43)	1	0	0	1 (13)	1	2	1	0	0
Disseminated disease	5 (16)	2 (10)	3 (33)	3 (43)	0	0	1	0	1	0	0	1	1
Relapsed disease	5 (16)	2 (10)	2 (22)	1 (14)	0	1	0	7 (88)	0	0	0	0	0
Laterality													
Unilateral	24/31 (77)	15 (75)	9 (100)	5 (71)	0	0	1	0	2	2	1	1	1
Bilateral	7/31 (23)	5 (25)	0	2 (29)	1	1	0	8 (100)	0	0	0	0	0
Ann Arbor stage													
IE	24 (75)	12 (60)	3 (33)	1 (14)	0	0	0	3 (38)	1	2	1	0	0
IIE	2 (6)	3 (15)	2 (22)	2 (29)	1	0	0	3 (38)	1	0	0	0	0

IIIE	2 (6)	0	2 (22)	1 (14)	0	0	0	0	0	0	0	1	1
IVE	4 (13)	5 (25)	2 (22)	3 (43)	0	1	1	2 (25)	0	0	0	0	0
AJCC TNM stage[b]													
T1	0	0	0	0	0	0	0	0	0	0	0	0	0
T2	0	0	0	0	0	0	0	0	0	0	0	0	0
T3	22/22 (100)	16/16 (100)	4/4 (100)	3/3 (100)	1	0	0	1/1 (100)	1/1	1/1	1	0	0
T4	0	0	0	0	0	0	0	0	0	0	0	0	0
Recurrence													
Yes	21 (66)	12 (60)	7 (78)	7 (100)	1	1	0	3/7 (43)	2	0	1	0	1
No	11 (34)	8 (40)	2 (22)	0	0	0	1	4/7 (57)	0	2	0	1	0
Site of recurrence													
OAR	7/21 (33)	5/12 (42)	1/5 (20)	1/6 (17)	0	1	0	0	0	0	1	0	0
OAR plus nodal and/or extranodal	7/21 (33)	3/12 (25)	1/5 (20)	1/6 (17)	0	0	0	0	0	0	0	0	0
Nodal and/or extranodal	7/21 (33)	4/12 (33)	3/5 (20)	4/6 (67)	1	0	0	3/3 (100)	2	0	0	0	1
Disease status at last follow-up													
Complete remission	15/31 (48)	9 (45)	1 (11)	2 (29)	0	0	1	2 (25)	1	1	1	1	0
Alive with disease	5/31 (16)	5 (25)	0	2 (29)	0	0	0	1 (13)	1	0	0	0	0
Dead from	8/31	3 (15)	6 (67)	3	1	0	0	1	0	0	0	0	1

lymphoma	(26)			(43)				(13)					
Dead from other causes than lymphoma	3/31 (10)	3 (15)	2 (22)	0	0	1	0	4 (50)	0	1	0	0	0

Table 3. Clinical and Staging Characteristics of Patients by Subtype of Lymphoma of the Eyelid

Abbreviations: AJCC, American Joint Committee on Cancer; ALCL, anaplastic large cell lymphoma; BCL, NOS, B-cell lymphoma, not otherwise specified; C-ALCL, primary cutaneous anaplastic large cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; LyP, lymphomatoid papulosis; MCL, mantle cell lymphoma; MF, mycosis fungoides; OAR, ocular adnexal region; PTCL, peripheral T-cell lymphoma; SLL/CLL, small lymphocytic lymphoma; TCL, NOS, T-cell lymphoma, not otherwise specified.

[a]Data are not specified for all patients.

[b]Only primary lymphoma of the eyelid were staged according to the AJCC staging system.

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Table 4. Management of Patients by Subtype and Stage of Lymphoma of the Eyelid[a]							
	No. (%) patients						
Stage	EBRT	EBRT plus CTX	CTX	CTX plus Rituximab	EBRT and CTX plus Rituximab	Rituximab	Surgery
B-CELL LYMPHOMAS							
EMZL							
IE or IIE	13 (46)	7 (25)	0	0	1 (4)	0	7 (25)
IIIE or IVE	0	2 (40)	2 (40)	0	0	1 (20)	0
FL[b]							
IE or IIE	4 (24)	4 (24)	3 (18)	1 (6)	2 (12)	1 (6)	2 (12)
IVE	0	1 (20)	2 (40)	1 (20)	1 (20)	0	0
DLBCL							
IE or IIE	0	4 (80)	1 (20)	0	0	0	0
IIIE or IVE	0	2 (50)	1 (25)	0	1 (25)	0	0
MCL							
IE or IIE	0	3 (60)	1 (20)	0	0	0	1 (20)
IIIE or IVE	0	1 (25)	0	2 (50)	1 (25)	0	0
LPL[c]							
IIE	0	1	0	0	0	0	0
SLL/CLL[d]							
IVE	0	0	1	0	0	0	1
T-CELL LYMPHOMAS							
MF							
IE or IIE	1 (25)	2 (50)	1 (25)	0	0	0	0
IIIE or IVE	0	2 (100)	0	0	0	0	0
PTCL[e]							
IE or IIE	0	1	0	0	0	0	1

LyP[f]							
IE	0	0	0	0	0	0	1
C-ALCL[f]							
IE	0	1	0	0	0	0	0
ALCL[g]							
IIIE	0	0	1	0	0	0	0
TCL, NOS[g]							
IIIE	0	1	0	0	0	0	0

Table 4. Management of Patients by Subtype and Stage of Lymphoma of the Eyelid
Abbreviations: ALCL, anaplastic large cell lymphoma; C-ALCL, primary cutaneous anaplastic large cell lymphoma; CTX, chemotherapy; DLBCL, diffuse large B-cell lymphoma; EBRT, external beam radiation therapy; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; LyP, lymphomatoid papulosis; MCL, mantle cell lymphoma; MF, mycosis fungoides; PTCL, peripheral T-cell lymphoma; SLL/CLL, small lymphocytic lymphoma; TCL, NOS, T-cell lymphoma, not otherwise specified.
[a]Data are not specified for all patients. All percentages are row percentages. No data was available for the BCL, NOS.
[b]None of the cases of FL were stage IIIE.
[c]The case of LPL was stage IIE.
[d]The case of SLL/CLL was stage IVE.
[e]The 2 cases of PTCL were stage IE and IIE.
[f]Both cases of LyP and the case of C-ALCL were stage IE.
[g]The cases of ALCL and TCL, NOS were stage IIIE.

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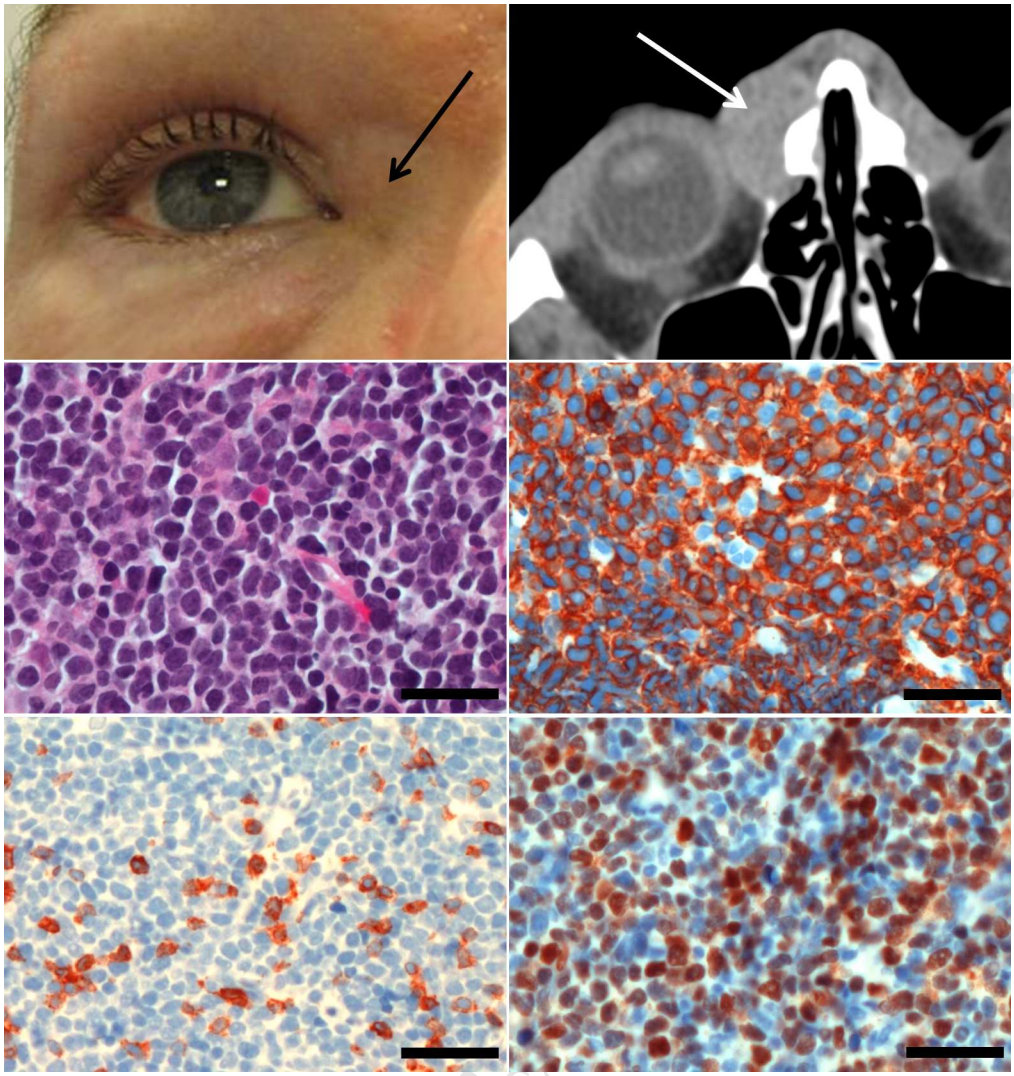

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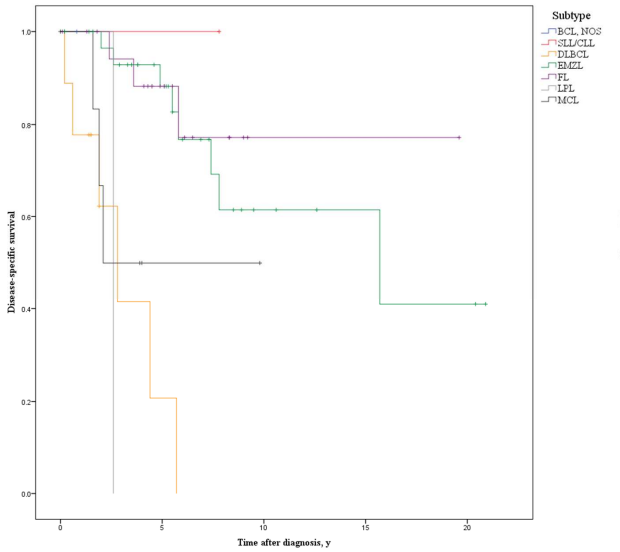
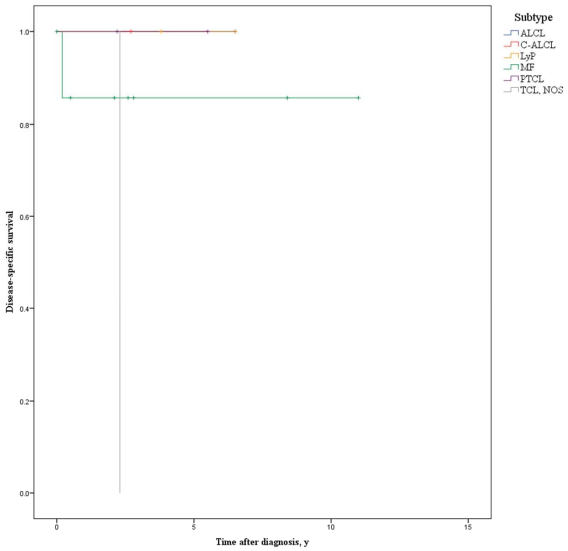


Subtype Interval, y	0	5	10	15	20
EMZL (n = 32)					
Patients at risk, No.	31	21	6	2	1
Events, No.	3	4	0	1	0
FL (n = 20)					
Patients at risk, No.	20	9	1	1	0
Events, No.	2	1	0	0	0
DLBCL (n = 9)					
Patients at risk, No.	9	1	0	0	0
Events, No.	6	1	0	0	0
MCL (n = 7)					
Patients at risk, No.	7	1	0	0	0
Events, No.	3	0	0	0	0
LPL (n = 1)					
Patients at risk, No.	1	0	0	0	0
Events, No.	1	0	0	0	0
SLL (n = 1)					
Patients at risk, No.	1	1	0	0	0
Events, No.	0	0	0	0	0
BCL, NOS (n = 1)					
Patients at risk, No.	1	0	0	0	0
Events, No.	0	0	0	0	0



Subtype Interval, y	0	5	10	15
MF (n = 8)				
Patients at risk, No.	8	2	1	0
Events, No.	1	0	0	0
PTCL, NOS (n = 2)				
Patients at risk, No.	2	1	0	0
Events, No.	0	0	0	0
LyP (n = 2)				
Patients at risk, No.	2	1	0	0
Events, No.	0	0	0	0
C-ALCL (n = 1)				
Patients at risk, No.	1	0	0	0
Events, No.	0	0	0	0
ALCL (n = 1)				
Patients at risk, No.	1	1	0	0
Events, No.	0	0	0	0
TCL, NOS (n = 1)				
Patients at risk, No.	1	0	0	0
Events, No.	1	0	0	0

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