Lymphoma of the Lacrimal Gland — An International Multicenter Retrospective Study

STINE DAHL VEST, LAUGE HJORTH MIKKELSEN, FREDERIK HOLM, PETER KRISTIAN RASMUSSEN, TINE GADEGAARD HINDSO, MARINA K.H. KNUDSEN, SARAH E. COUPLAND, BITA ESMAELI, PAUL T. FINGER, GERARDO F. GRAUE, HANS E. GROSSNIKLAUS, SANTOSH G. HONAVAR, KAUSTUBH MULAY, LENE D. SJÖ, MATTHEW C. SNIEGOWSKI, GEETA K. VEMUGANTI, BRADLEY A. THURO, AND STEFFEN HEEGAARD

• PURPOSE: To characterize the clinical features of subtype-specific lacrimal gland lymphoma and their effect on patient survival.

• DESIGN: Multicenter retrospective interventional 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: A total of 260 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 = 258) and T-cell lymphomas constituted 1% (n = 2). The most frequent lymphoma subtypes were extranodal marginal zone B-cell lymphoma (EMZL) (n = 177, 68%), follicular lymphoma (FL) (n = 26, 10%), diffuse large B-cell lymphoma (DLBCL) (n = 25, 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: 93.4%) having the best prognosis and DLBCL (5-year DSS: 52.6%) having the poorest.

• CONCLUSIONS: 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 ocular adnexa. Prognosis is good and the histologic subtype is a significant predictor for disease-specific survival. (Am J Ophthalmol 2020;219:107–120. © 2020 Elsevier Inc. All rights reserved.)

Accepted for publication Jun 10, 2020.

From the Eye Pathology Section, Department of Pathology (S.D.V., L.H.M., F.H., M.K.H.K., L.D.S., S.H.), and the Department of Ophthalmology (L.H.M., P.K.R., T.G.H., S.H.), Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; Department of Cellular and Molecular Pathology, University of Liverpool, Liverpool, United Kingdom (S.E.C.); Orbital Oncology and Ophthalmic Plastic Surgery, Department of Plastic Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA (B.E., M.E.S., B.A.T.); The New York Eye Cancer Center, New York, New York, USA (P.T.F., G.F.G.); Section of Ocular Oncology, Emory Eye Center, Atlanta, Georgia, USA (H.E.G.); Department of Ophthalmic and Facial Plastic Surgery, Orbit and Ocular Oncology (S.G.H.), Centre for Sight, Hyderabad, India; Department of Ocular Oncology and Oculoplastics (S.G.H.), LV Prasad Eye Institute, Hyderabad, India; National Reporting Centre for Ophthalmic Pathology (K.M.), Centre for Sight, Hyderabad, India; Ophthalmic Pathology Services (Visiting Faculty) (G.K.V.), LV Prasad Eye Institute, Hyderabad, India; and School of Medical Sciences, University of Hyderabad, Hyderabad, India (G.K.V.).

Inquiries to Steffen Heegaard, Department of Pathology, Rigshospitalet, University of Copenhagen, Frederik V's Vej, 11, 1. Sal, DK-2100 Copenhagen Ø, Denmark; e-mail: sthe@sund.ku.dk

LYMPHOMAS COMPRISE A HETEROGENEOUS GROUP OF malignant neoplasms derived from clonal expansion of B lymphocytes, T lymphocytes, or natural killer 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). 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% and 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 B-cell 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 therefore seeks to describe epidemiologic trends, clinical features, and prognosis of patients with malignant lacrimal gland non-Hodgkin lymphoma in a large cohort of patients from 6 different eye cancer centers.

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.06.015

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]	44 (17)	19 (7)	51 (20)	130 (50)	14 (5)	2 (1)	260 (100)
B-cell lymphomas							
EMZL							
No. of patients (% within center)[b]	19 (43)	9 (47)	31 (61)	109 (84)	8 (57)	1 (50)	177 (68)
Median age, years	71	65	64	51	58	59	55
Male-to-female ratio	5:14	2:7	10:21	79:30	2:6	1:0	99:78
FL							
No. of patients (% within center)[b]	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 center)[b]	3 (7)	4 (21)	9 (18)	9 (7)	0	0	25 (10)
Median age, years	79	80	68	65	NA	NA	69
Male-to-female ratio	1:2	1:3	2:7	7:2	NA	NA	11:14
MCL							
No. of patients (% within center)[b]	10 (23)	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 center)[b]	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 center)[b]	0	0	0	1 (1)	1 (7)	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 center)[b]	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 center)[b]	1 (2)	0	0	0	0	0	1 (0.4)
Median age, years	66	NA	NA	NA	NA	NA	66
Male-to-female ratio	1:0	NA	NA	NA	NA	NA	1:0
HGBCL							
No. of patients (% within center)[b]	1 (2)	0	0	0	0	0	1 (0.4)
Median age, years	39	NA	NA	NA	NA	NA	39
Male-to-female ratio	0:1	NA	NA	NA	NA	NA	0:1
BCL, NOS							
No. of patients (% within center)[b]	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 center)[b]	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

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; HGBCL = high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements; HOU = Houston, Texas, USA; HYD = Hyderabad, India; LIV = Liverpool, United Kingdom; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; NA = not applicable; NY = New York, New York, USA; PL = plasmacytoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; SLL/CLL = small lymphocytic lymphoma.

[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.

METHODS

• **STUDY DESIGN:** This study is a retrospective interventional case series based on data from 6 international eye cancer centers: Copenhagen, Denmark; Liverpool, United Kingdom; Atlanta, Georgia, USA; New York, New York, USA; Hyderabad, India; and Houston, Texas, USA. All eye cancer centers are large centers and the Copenhagen Center has national patient uptake from Denmark. 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). Twenty-seven patients from the Danish cohort have been published earlier.[6] Furthermore, 1 case of lymphoplasmacytic lymphoma has been published earlier.[7]

• **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] All specimens were reviewed and reclassified by the respective cancer centers according to the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues, 4th edition or the revised 4th edition.[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.

• **CLINICAL DATA:** The clinical data collected included age, sex, symptoms, clinical findings, systemic involvement according to the Ann Arbor staging classification[8] and the American Joint Committee on Cancer (AJCC) TNM classification system,[9] 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 evaluation 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. Furthermore, primary lacrimal gland lymphoma was defined as a lymphoma primarily involving the lacrimal gland in contrast to an orbital lymphoma with minor infiltration of the lacrimal gland. 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. Bilateral lacrimal gland lymphoma without involvement of lymph nodes and bone marrow were classified as Ann Arbor stage IE.

As defined by the AJCC/TNM system, only primary lymphomas were classified according to AJCC/TNM.[9]

• **STATISTICAL ANALYSIS:** Overall survival (OS) and disease-specific survival (DSS) were considered the primary endpoints. Overall survival 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. Disease-specific survival 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 exact test. $P < .05$ 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:** Malignant lymphoma of the lacrimal gland was identified in 260 patients (Tables 1 and 2). The majority of lacrimal gland lymphomas were of B-cell origin (258 of 260 [99%]). Eight B-cell lymphoma subtypes were identified according to the WHO lymphoma classification[1]: EMZL (n = 177, 68%), FL (n = 26, 10%), DLBCL (n = 25, 10%), MCL (n = 17, 7%), SLL/CLL (n = 3, 1%), Burkitt lymphoma (BL) (n = 2, 1%), plasmacytoma (PL) (n = 2, 1%), lymphoplasmacytic lymphoma (LPL) (n = 1, 0.4%), and high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBCL) (n = 1, 0.4%). The 1 HGBCL was a triple-hit lymphoma with translocations involving *MYC*, *BCL2*, and *BCL6*. Four lymphomas (2%) were of B-cell origin but could not be further classified: B-cell lymphoma, not otherwise specified (BCL-NOS). Only 1 T-cell lymphoma subtype was identified: peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) (n = 2, 1%).

TABLE 2. Clinical and Staging Characteristics of Patients by Subtype of Lacrimal Gland Lymphoma[a]

		B-Cell Lymphoma, N (%)[b]										T-Cell Lymphoma, N (%)[b]
	All 260 (100)	EMZL 177 (68)	FL 26 (10)	DLBCL 25 (10)	MCL 17 (7)	SLL/CLL 3 (1)	BL 2 (1)	PL 2 (1)	LPL 1 (0.4)	HGBCL 1 (0.4)	BCL-NOS 4 (2)	PTCL-NOS 2 (1)
Sex												
Male	136 (52)	99 (56)	10 (38)	11 (44)	8 (47)	1 (33)	1 (50)	2 (100)	1 (100)	0	1 (25)	2 (100)
Female	124 (48)	78 (44)	16 (62)	14 (56)	9 (53)	2 (67)	1 (50)	0	0	1/1 (100)	3 (75)	0
Age at presentation, y												
≤60	144 (55)	114 (64)	10 (38)	6 (24)	4 (24)	1 (33)	2 (100)	1 (50)	0	1/1 (100)	3 (75)	2 (100)
>60	116 (45)	63 (36)	16 (62)	19 (76)	13 (76)	2 (67)	0	1 (50)	1 (100)	0	1 (25)	0
Disease group												
Primary disease	182/258 (71)	146/176 (83)	11/26 (42)	14/25 (56)	1/16 (6)	1/3 (33)	1/2 (50)	2/2 (100)	0	1/1 (100)	4/4 (100)	1/2 (50)
Disseminated disease	31/258 (12)	13/176 (7)	1/26 (4)	6/25 (24)	10/16 (63)	1/3 (33)	0	0	0	0	0	0
Relapsed disease	45/258 (17)	17/176 (10)	14/26 (54)	5/25 (20)	5/16 (31)	1/3 (33)	1/2 (50)	0	1/1 (100)	0	0	1/2 (50)
Laterality												
Unilateral	227/260 (87)	160/177 (90)	19/26 (73)	23/25 (92)	11/17 (65)	3/3 (100)	2/2 (100)	2/2 (100)	0	1/1 (100)	4/4 (100)	2/2 (100)
Bilateral	33/260 (13)	17/177 (10)	7/26 (27)	2/25 (8)	6/17 (35)	0	0	0	1/1 (100)	0	0	0
Ann Arbor stage												
IE	198/252 (79)	154/174 (89)	14/23 (61)	16/25 (64)	2/16 (13)	2/3 (67)	1/2 (50)	2/2 (100)	0	1/1 (100)	4/4 (100)	2/2 (100)
IIE	16/252 (6)	5/174 (3)	5/23 (22)	4/25 (16)	2/16 (13)	0	0	0	0	0	0	0
IIIE	6/252 (2)	4/174 (2)	2/23 (9)	0	0	0	0	0	0	0	0	0
IVE	32/252 (13)	11/174 (6)	2/23 (9)	5/25 (20)	12/16 (75)	1/3 (33)	1/2 (50)	0	0	0	0	0
Unknown stage	8/260 (3)	3/177 (2)	3/26 (12)	0	1/17 (6)	0	0	0	1/1 (100)	0	0	0
AJCC TNM stage[c]												
T2	182/182 (100)	146/146 (100)	11/11 (100)	14/14 (100)	1/1 (100)	1/1 (100)	1/1 (100)	2/2 (100)	0	1/1 (100)	4/4 (100)	1/1 (100)
Relapse/progression												
Yes	67/252 (27)	27/173 (16)	13/24 (54)	11/23 (48)	11/17 (65)	0	2/2 (100)	2/2 (100)	0	0	1/4 (25)	0
No	185/252 (73)	146/173 (84)	11/24 (46)	12/23 (52)	6/17 (35)	3/3 (100)	0	0	1/1 (100)	1/1 (100)	3/4 (75)	2/2 (100)
Site of recurrence												
OA	14/51 (27)	7/22 (32)	2/11 (18)	3/9 (33)	2/6 (33)	NA	NA	0	NA	NA	0	NA
OA plus nodal and/or extranodal	15/51 (29)	7/22 (32)	3/11 (27)	3/9 (33)	2/6 (33)	NA	NA	0	NA	NA	0	NA
Nodal and/or extranodal	22/51 (43)	8/22 (36)	6/11 (55)	3/9 (33)	2/6 (33)	NA	NA	2/2 (100)	NA	NA	1/1 (100)	NA
Disease status at last follow-up												
Complete remission	177/259 (68)	144/177 (81)	11/26 (42)	8/24 (33)	9/17 (53)	0	0	0	0	1/1 (100)	2/4 (50)	2/2 (100)
Alive with disease	33/259 (13)	16/177 (9)	8/26 (31)	2/24 (8)	4/17 (24)	1/3 (33)	1/2 (50)	0	1/1 (100)	0	0	0
Dead of lymphoma	25/259 (10)	6/177 (3)	5/26 (19)	7/24 (29)	3/17 (18)	0	1/2 (50)	2/2 (100)	0	0	1/4 (25)	0

Continued on next page

TABLE 2. Clinical and Staging Characteristics of Patients by Subtype of Lacrimal Gland Lymphoma[a] (*Continued*)

		B-Cell Lymphoma, N (%)[b]									T-Cell Lymphoma, N (%)[b]	
	All 260 (100)	EMZL 177 (68)	FL 26 (10)	DLBCL 25 (10)	MCL 17 (7)	SLL/CLL 3 (1)	BL 2 (1)	PL 2 (1)	LPL 1 (0.4)	HGBCL 1 (0.4)	BCL-NOS 4 (2)	PTCL-NOS 2 (1)
Dead from other causes	24/259 (9)	11/177 (6)	2/26 (8)	7/24 (29)	1/17 (6)	2/3 (67)	0	0	0	0	1/4 (25)	0
Median time to last follow-up, months (range)	18 (0-372)	16 (1-372)	67 (0-223)	14 (0-135)	25 (4-232)	23 (21-147)	9 (4-14)	95 (77-113)	0	49 (NA)	52 (6-116)	10 (9-11)

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; HGBCL = high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; NA = not applicable; OA = ocular adnexa; PL = plasmacytoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; SLL/CLL = small lymphocytic lymphoma.

[a]Data not specified in all cases.

[b]Number of patients with the characteristic out of the number 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.

Thirteen of 25 OA-DLBCLs were subdivided further according to the algorithm by Hans and associates[10] into germinal center B-cell (GCB)-like DLBCL or non-GCB DLBCL. Of these, 12 (86%) were categorized as non-GCB subtype and 1 (14%) was categorized as GCB subtype. Regarding MYC status, it was possible to retrieve the data from the Danish registry, which revealed 1 DLBCL to be of double expressor phenotype with increased protein expression for BCL2 and MYC.

The distribution of lymphoma subtypes differed between eye cancer centers (Table 1). Hyderabad, Houston, Copenhagen, and Liverpool contributed the 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 (43%-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 (23%) (Table 1).

• **CLINICAL FEATURES:** Of the 260 patients, 136 (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 (99 of 177 [56%]), whereas women predominated in FL (16 of 26 [62%]) and DLBCL (14 of 25 [56%]), and an almost equal distribution was seen in MCL (53% female) (Tables 1 and 2). Most patients (182 of 258 [71%]) were diagnosed as having primary lymphoma, although 31 patients (12%) had systemic lymphoma with secondary lacrimal gland manifestation, and 45 patients (17%) were diagnosed as having a relapse of lymphoma in the lacrimal gland (Table 2).

According to the Ann Arbor staging classification, 198 patients (79%) had stage IE, 16 patients (6%) had stage IIE, 6 patients (2%) had stage IIIE, and 32 patients (13%) had stage IVE (Table 2). According to the TNM classification system, all primary lacrimal gland lymphomas were classified as having TNM stage T2 (Table 2). TNM stage T1 is, per definition, not possible in lymphomas of the lacrimal gland.[9] In 227 of 260 patients (87%) the lacrimal gland lymphoma was unilateral, whereas 33 patients (13%) had bilateral lacrimal gland involvement (Table 2). The most common site of local invasion was the orbit (n = 190, 73%) (Table 3).

The most common symptoms reported from the ocular adnexal region were a visible or palpable mass of the lacrimal gland (125 of 236 [53%]), periorbital swelling (117 of 236 [50%]), and/or proptosis (112 of 236 [47%]) (Table 3). The median symptom duration was 4 months (range 0-96 months). B-symptoms (ie, fever, night sweats, and weight loss) were reported by 6 patients (3%), of whom 2 were diagnosed as having advanced-stage disease (Ann

TABLE 3. Frequency of Symptoms, Clinical Signs, and Local Spread at Presentation of Lacrimal Gland Lymphoma[a]

		B-Cell Lymphoma, N (%)										T-Cell Lymphoma, N (%)
	All 260 (100)	EMZL 177 (68)	FL 26 (10)	DLBCL 25 (10)	MCL 17 (7)	SLL/CLL 3 (1)	BL 2 (1)	PL 2 (1)	LPL 1 (0.4)	HGBCL 1 (0.4)	BCL-NOS 4 (2)	PTL-NOS 2 (1)
Symptoms[b]												
First presenting symptom in OAR	213 (90)	159 (95)	19 (86)	15 (68)	10 (71)	3 (100)	2 (100)	NA	1 (100)	NA	3 (100)	1 (50)
Mass	125 (53)	86 (51)	10 (45)	14 (67)	9 (64)	1 (33)	1 (50)	NA	0	1 (100)	2 (67)	1 (50)
Swelling	117 (50)	80 (48)	9 (41)	14 (67)	8 (57)	1 (33)	1 (50)	NA	0	1 (100)	2 (67)	1 (50)
Dry eye	15 (6)	3 (2)	5 (23)	1 (5)	3 (21)	2 (67)	0	NA	1 (100)	0	0	0
Epiphora	18 (8)	12 (7)	1 (5)	0	3 (21)	0	0	NA	0	0	1 (33)	1 (50)
Irritation/pain	55 (23)	28 (17)	8 (36)	6 (29)	7 (50)	3 (100)	2 (100)	NA	1 (100)	0	0	0
Proptosis	112 (47)	83 (50)	10 (45)	8 (38)	4 (29)	2 (67)	0	NA	1 (100)	1 (100)	2 (67)	1 (50)
Diplopia	26 (11)	6 (4)	8 (36)	3 (14)	5 (36)	2 (67)	0	NA	1 (100)	1 (100)	0	0
Ptosis	23 (10)	16 (10)	2 (9)	2 (10)	3 (21)	0	0	NA	0	0	0	0
Decreased VA	23 (10)	8 (5)	7 (32)	2 (10)	3 (21)	2 (67)	0	NA	1 (100)	0	0	0
B-symptoms	6 (3)	1 (1)	0	2 (10)	2 (14)	0	0	NA	0	0	1 (33)	0
Not stated	24	10	4	4	3	0	0	2	0	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)	3 (NA)	4 (2-6)	3 (1-5)
Signs[b]												
Mass	177 (75)	131 (78)	16 (76)	13 (62)	11 (79)	2 (67)	1 (50)	NA	0	0	1 (33)	2 (100)
Proptosis	127 (54)	101 (60)	6 (29)	9 (43)	4 (29)	3 (100)	1 (50)	NA	0	1 (100)	2 (67)	0
Displacement	126 (54)	99 (59)	7 (33)	9 (43)	4 (29)	3 (100)	1 (50)	NA	0	1 (100)	2 (67)	0
Restricted eye movement	94 (40)	75 (45)	5 (24)	9 (43)	2 (14)	0	0	NA	0	0	1 (33)	2 (100)
Diplopia	8 (3)	2 (1)	2 (10)	1 (5)	3 (21)	0	0	NA	0	0	0	0
Ptosis	22 (9)	13 (8)	3 (14)	1 (5)	2 (14)	2 (67)	0	NA	1 (100)	0	0	0
Chemosis	20 (9)	11 (7)	0	4 (19)	3 (21)	0	2 (100)	NA	0	0	0	0
Epiphora	13 (6)	6 (4)	3 (14)	0	1 (7)	2 (67)	0	NA	0	0	1 (33)	0
Edema	11 (5)	6 (4)	2 (10)	0	1 (7)	1 (33)	1 (50)	NA	0	0	0	0
Resistance	13 (6)	5 (3)	1 (5)	1 (5)	2 (14)	2 (67)	0	NA	0	1 (100)	1 (33)	0
Not stated	25	10	5	4	3	0	0	2	0	0	1	0
Systemic disease												
Autoimmune disease	6	3	3	0	0	0	0	NA	0	0	0	0
Local spread[b]												
Orbit	190 (73)	134 (76)	19 (73)	19 (76)	7 (41)	1 (33)	2 (100)	2 (100)	0	1 (100)	3 (75)	2 (100)
Conjunctiva	25 (10)	19 (11)	4 (15)	1 (4)	1 (6)	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
Lacrimal sac	0	0	0	0	0	0	0	0	0	0	0	0

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; HGBCL = high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; NA = not applicable; PL = plasmacytoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; SLL/CLL = small lymphocytic lymphoma.

[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.

TABLE 4. Management of Patients by Subtype of Lacrimal Gland Lymphoma[a]

No. (%) of Patients[b]													
Stage	EBRT	EBRT and CTX	CTX	CTX + Rituximab	EBRT and CTX + Rituximab	Rituximab or Rituximab + EBRT	Surgery	Surgery and EBRT	Zevalin and Rituximab	BM Transplant	GM-CSF and Zevalin	No Treatment	Unknown
B-cell lymphomas													
EMZL	138 (80)	8 (5)	3 (2)	13 (8)	0	2 (1)	2 (1)	3 (2)	3 (2)	0	1 (1)	1 (1)	4 (2)
IE	133 (89)	6 (4)	0	2 (1)	0	1 (1)	2 (1)	3 (2)	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 (48)	0	7 (28)	2 (8)	0	0	0	0	0	0	1 (4)	0
IE	3 (19)	10 (63)	0	1 (6)	1 (6)	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)
HGBCL	0	0	0	0	1 (100)	0	0	0	0	0	0	0	0

Continued on next page

TABLE 4. Management of Patients by Subtype of Lacrimal Gland Lymphoma[a] (*Continued*)

Stage	No. (%) of Patients[b]												
	EBRT	EBRT and CTX	CTX	CTX + Rituximab	EBRT and CTX + Rituximab	Rituximab or Rituximab + EBRT	Surgery	Surgery and EBRT	Zevalin and Rituximab	BM Transplant	GM-CSF and Zevalin	No Treatment	Unknown
IE	0	0	0	0	1 (100)	0	0	0	0	0	0	0	0
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

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 therapy; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; GM-CSF = granulocyte-macrophage colony-stimulating factor; HGBCL = high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements; 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.

[a]Data not specified for all patients.

[b]Number of patients, (%) = percentage of patients with data specified stratified by Ann Arbor stage.

Arbor stage III or IV). The most common clinical signs were an objective mass of the lacrimal gland (177 of 235 [75%]), proptosis (127 of 235 [54%]), displacement of the eyeball (126 of 235 [54%]), and/or objectively restricted eye movement (94 of 235 [40%]) (Table 3). Three EMZL patients had a history of Sjögren syndrome, 1 FL patient had a history of hypogammaglobulinemia, and 2 FL patients had systemic autoimmune disease, not otherwise specified.

• **TREATMENT OUTCOME AND SURVIVAL:** Treatment regimens of all lymphoma subtypes are listed in Table 4. Disease status at last follow-up was available for 259 of 260 patients (99%), and the median follow-up period was 18 months (range 0-372 months). The 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). The 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: $P < .001$, pooled log-rank test; DSS: $P < .001$, pooled log-rank test). Of the 4 major lymphoma subtypes, EMZL had the highest DSS, and the DSS of DLBCL was significantly lower compared to EMZL ($P < .001$, pairwise log-rank test). However, no significant difference in DSS for DLBCL was seen compared to MCL ($P = .34$, pairwise log-rank test) and FL ($P = .07$, pairwise log-rank test). Furthermore, DSS for EMZL was not significantly different compared to MCL ($P = .051$, pairwise log-rank test) and FL ($P = .23$, pairwise log-rank test).

EMZL and DLBCL patients with progression/relapse had a significantly lower DSS compared to patients with no progression/relapse (EMZL: $P = .002$; DLBCL: $P = .01$; log-rank test). Examining risk factors for progression/relapse, a high Ann Arbor stage (stage III/IVE) was significantly associated with an increased frequency of progression/relapse for the entire group of patients ($P < .001$, Fisher exact test) and patients with the DLBCL subtype ($P = .01$, Fisher exact test). There was no significant difference in DSS or OS between primary and secondary lymphomas collectively (DSS: $P = .162$; OS: $P = .103$; log-rank test) or within the 4 major lymphoma subtypes EMZL, FL, DLBCL, and MCL ($P > .05$, log-rank test). Neither did any other clinical characteristics show a significant difference in DSS between risk groups within the 4 major lymphoma subtypes EMZL, FL, DLBCL, and MCL ($P > .05$, log-rank test). There was no significant difference in subtype-specific DSS between eye cancer centers ($P > .05$, 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, constituting 68% of all cases (n = 177) (Figure 1). Most patients had primary lymphoma of the lacrimal gland

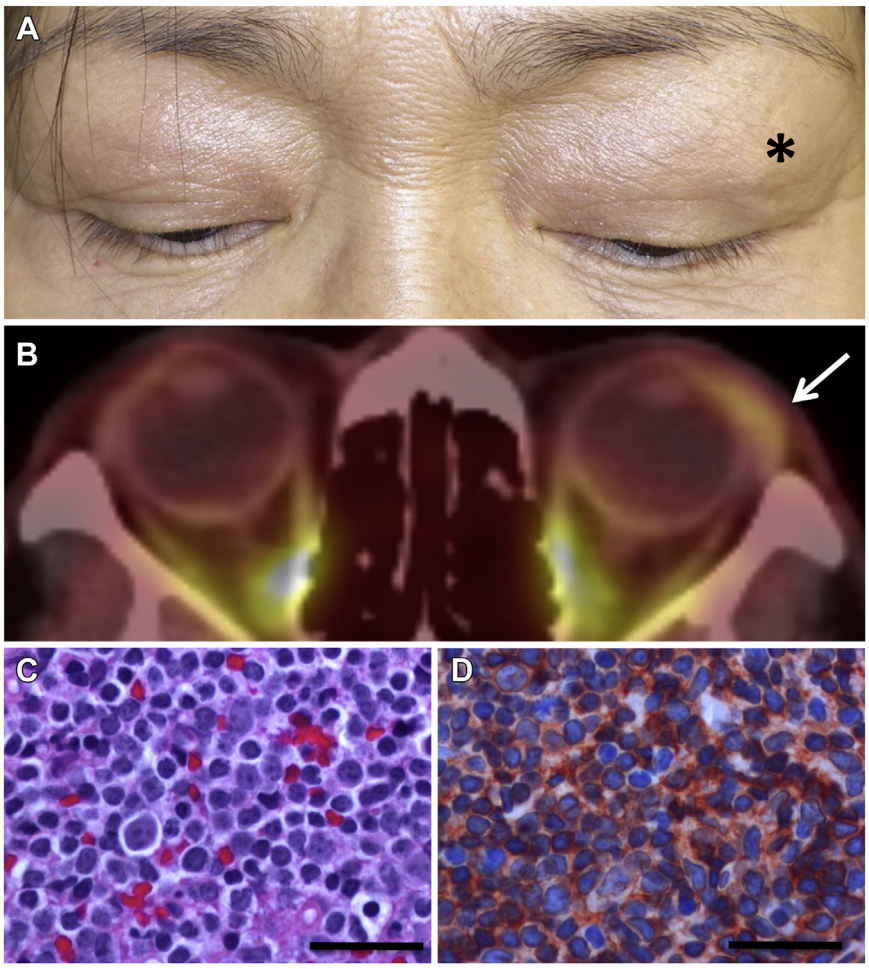


FIGURE 1. Clinical and histologic findings of a lacrimal gland extranodal marginal zone B-cell lymphoma. (A) Left-sided orbital mass (asterisk) in 68-year-old woman with an extranodal marginal zone B-cell lymphoma of the left lacrimal gland. Symptoms at presentation were a palpable mass, periorbital swelling, epiphora, and irritation. (B) Coronal plane Positron Emission Tomography/Computed Tomography 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 demonstrate positive immunoreaction for the B-cell marker CD79α (anti-CD 79α, bar = 50 μm).

(146 of 176 [83%]) (Table 2). The median age was 55 years (range 13-100 years) and 56% of patients were men (Tables 1 and 2). The vast majority of patients were classified as Ann Arbor stage IE (154 of 174 [89%]) (Table 2).

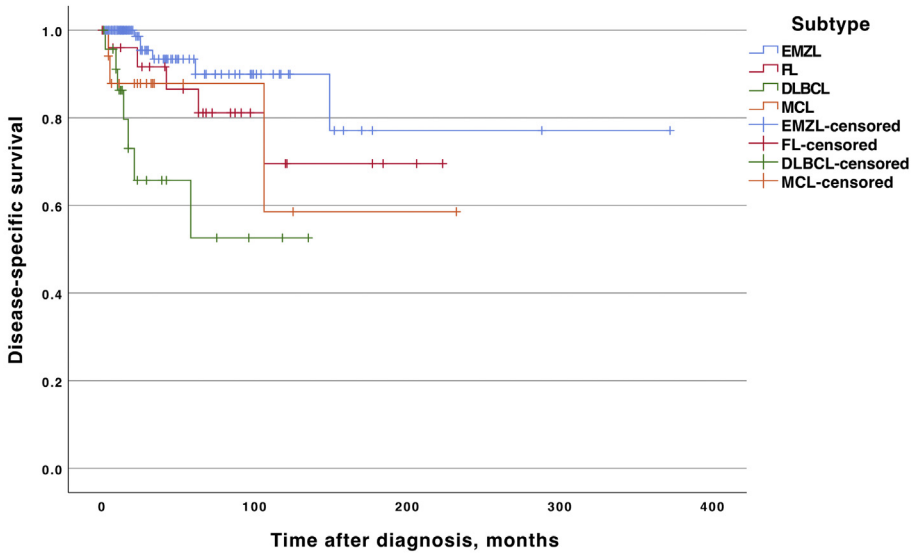
Treatment

Treatment information was available in 173 of 177 patients (98%). Stage IE patients were primarily treated with external beam radiation therapy (EBRT) as monotherapy (133 of 150 [89%]) (Table 4). Stage IVE patients were most frequently treated with chemotherapy in combination with rituximab (5 of 11 [45%]) (Table 4). The median radiation dose was 24 Gy (range 4-100 Gy, registered in 20 patients), most commonly given as 12-20 fractions of 1.5-2 Gy, but regimens of 2 fractions of 2 Gy were also seen.

Treatment outcome and survival

Complete systemic and local remission of disease was seen in 81% of EMZL patients (144 of 177) with a median follow-up period of 16 months (range 1-372 months) (Table 2). Progression or relapse of disease, either local or systemic, was observed in 27 patients (16%) (Table 2), and the time to relapse was accessible in 15 of these patients, with a median of 36 months (range 5-187 months). The 5-, 10-, and 20-year OS were 77.8%, 71.3%, and 48.9%, respectively (median OS, 158 months; 95% CI 53-263 months), whereas the 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 = .52, log-rank test). Furthermore, there was no significant



Subtype, interval, years	0	5	10	15	20	25	30
EMZL (N=177)							
Patients at risk, No.	104.5	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=25)							
Patients at risk, No.	17.5	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			

FIGURE 2. Disease-specific survival among patients with lacrimal gland lymphoma. Disease-specific survival is associated with lymphoma subtype. Life table showing number of patient at risk of dying of lymphoma and number of patients with the event at each time point. DLBCL = diffuse large B-cell lymphoma; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma.

difference in DSS between patients receiving EBRT given as 12-20 fractions of 1.5-2 Gy compared to 2 fractions of 2 Gy ($P = .76$; log-rank test).

Follicular lymphoma. Clinical features

Twenty-six cases (10%) of FL of the lacrimal gland were identified, with 11 cases (42%) 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 (Tables 1 and 2). Most patients were stage IE (14 of 23 [61%]) according to the Ann Arbor staging classification (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 (6 of 13 [46%]) or EBRT in combination with chemotherapy (5 of 13 [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, vincristine, prednisone), were commonly used.

Treatment outcome and survival

Complete systemic and local remission of disease was seen in 42% of FL patients (11 of 26), whereas 19% of patients (5 of 26) died of lymphoma (Table 2). The median follow-up period was 67 months (range 0-223 months). Progression or relapse of disease, either local or systemic, was observed in 54% of patients (13 of 24) (Table 2), and the time to relapse/progression was accessible in 8 of these patients, with a median of 43 months (range 7-218 months). The 5- and 10-year OS were 86.5%, and 69.5%, respectively (median OS, 177 months, 95% CI 42-312 months), as well as the 5- and 10-year DSS, which were also 86.5% and 69.5% (Figure 2).

For localized FL stage IE there was no significant difference in DSS for patients treated with a combination regimen of EBRT and chemotherapy compared to patients treated with EBRT as monotherapy ($P = .80$, log-rank test).

Diffuse large B-cell lymphoma. Clinical features

Twenty-five cases (10%) of DLBCL of the lacrimal gland were identified, with 14 cases (56%) being primary lymphoma of the lacrimal gland (Table 2). The median age was 69 years (range 28-85 years), and 56% of patients were women (Tables 1 and 2). Most patients were stage IE (16 of 25 [64%]) according to the Ann Arbor staging classification, although 20% of patients were stage IVE (5 of 25) (Table 2).

Treatment

Treatment information was available for all patients. Stage IE patients were primarily treated with chemotherapy in combination with EBRT (10 of 16 [63%]). Patients with stage IIE and IVE were primarily treated with chemotherapy in combination with rituximab, with the most common regimen being R-CHOP (IIE: 3 of 4 [75%]; IVE: 3 of 5 [60%]) (Table 4).

Treatment outcome and survival

Complete systemic and local remission of disease was seen in 33% of DLBCL patients (8 of 24), whereas 29% died of lymphoma (7 of 24) and 29% died of other causes (7 of 24) (Table 2). The median follow-up period was 14 months (range 0-135 months). Progression or relapse of disease, either local or systemic, was observed in 48% of patients (11 of 23) (Table 2), and the time to relapse/progression was accessible in 2 of these patients, with a median of 17 months (range 15-19 months). The 3- and 5-year OS were 48.8% and 27.9%, respectively (median OS, 29 months, 95% CI 1-57 months), whereas the 3- and 5-year DSS were 65.7% and 52.6%, respectively (Figure 2).

Mantle cell lymphoma. Clinical features

Seventeen 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 (Tables 1 and 2). The vast majority had stage IVE disease (12 of 16 [75%]) (Table 2).

Treatment

Treatment information was available for all patients. The majority of stage IVE patients (9 of 12 [75%]) were treated with a rituximab-based chemotherapy regimen with or without 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

Complete systemic and local remission of disease was seen in 53% of MCL patients (9 of 17), while 24% were alive with disease (4 of 17) and 18% died of lymphoma (3 of 17) (Table 2). Median follow-up time was 25 months (range 4-232 months). Progression or relapse of disease, either local or systemic, was observed in 65% of patients (11 of 17) (Table 2), and the time to relapse/progression was accessible in 8 of these patients, with a median of 15 months (range 0-59 months). The 3- and 5-year OS were both 79.9% and 10-year OS were 53.2%. The 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. Details of rare B-cell and T-cell lymphoma subtypes are included in Tables 2-4. 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 1 patient with LPL was 66 years old (Tables 1 and 2). The 1 patient with HGBCL (triple-hit lymphoma) was 39 years old (Tables 1 and 2).

DISCUSSION

THE PRESENT STUDY IDENTIFIED 260 PATIENTS WITH MALIGnant lacrimal gland lymphoma from 6 international eye cancer centers. This is the largest reported collection of clinical and pathologic data including subtype distribution in patients with lacrimal gland lymphoma to date.

The 4 major subtypes of lymphoma identified in this study were EMZL (n = 177, 68%), FL (n = 26, 10%), DLBCL (n = 25, 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.[4,6,11,12] 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.[6] Thus, in the study by Rasmussen and associates, 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.[6] 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.[4,11–15]

The distribution of lymphoma subtypes differed between eye cancer centers. The center in Hyderabad had a markedly higher proportion of patients with EMZL (84%) than the remaining eye cancer centers (43%-61 %), while

the Copenhagen Center, which is a national eye cancer center, had a noticeably high proportion of MCL (23%) (Table 1). There was a slight male predominance for the entire group (52% male) and a significant male predominance in the group of patients with EMZL, while female patients 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 owing to the low number of MCL cases in the present study.[4,11] Male-to-female ratio varied between eye cancer centers, and in the EMZL group approximately 60% of patients came from the Hyderabad center, where male patients 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,[16,17] in contrast to national studies from Denmark, Canada, and the United states.[4,6,18] This might possibly be owing to different environmental exposures such as infectious organisms, work (inside vs outside), etc. Most patients in this study were adults, with a median age of 58 years (range 12-100 years) 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),[6] which is in contrast to this study. Part of this difference might be owing to the large proportion of EMZL patients from the tertiary eye cancer center in Hyderabad.

In the present study, 3 patients had a history of Sjögren syndrome. Furthermore, 2 patients had a nonspecified autoimmune disease. In the literature lacrimal gland lymphoma is frequently reported in the setting of Sjögren syndrome.[19,20] The inconsistency between the present study and the literature may be owing to missing data in 33 patients in the present study. However, in the largest study to date including 27 patients, none of the patients had a history of Sjögren syndrome.[6] This supports our data indicating that the development of lacrimal gland lymphoma in conjunction with Sjögren syndrome is rare.

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.[6] Overall survival and disease-specific survival was significantly different between lymphoma subtypes (OS: $P < .001$, pooled log-rank test; DSS: $P < .001$, pooled log-rank test), which has previously been shown in other anatomic sites of the OA.[11,21,22]

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.[23,24] 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.[25] 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 65.7% and 52.6%, which is in line with previous survival data of DLBCL of the OA.[26] Relapse or progression of disease was found to worsen the prognosis with 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) in both the entire group of patients and patients with the DLBCL subtype, which is in line with previous studies of orbital lymphoma.[11]

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.[27] Progression or relapse of disease was seen in 65% of the MCL patients in the present study, but this percentage has previously been recorded to be as high as 84% in the OA.[27] 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.[25] The majority of patients (75%) with stage IVE MCL in this study were treated with a rituximab-based chemotherapy regimen, which is a higher percentage than in the study of ocular adnexal MCL,[27] and this could thus be a possible explanation for the higher survival rates in the present study.

The retrospective design of the present study poses some limitations. Data were 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 months), which might not have been enough time to detect outcome variables.

In summary, this international multicenter study of 260 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.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

STINE DAHL VEST: CONCEPTUALIZATION, METHODOLOGY, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Lauge Hjorth Mikkelsen:** Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - original draft, Writing - review & editing, Supervision. **Frederik Holm:** Formal analysis, Investigation, Resources, Writing - review & editing, Supervision. **Peter Kristian Rasmussen:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing. **Tine Gadegaard Hindso:** Investigation, Resources, Writing - review & editing. **Marina K.H. Knudsen:** Investigation, Resources, Writing - review & editing. **Sarah E. Coupland:** Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing. **Bita Esmaeli:** Conceptualization, Methodology, Investigation, Resources, Writing - review & editing. **Paul T. Finger:** Investigation, Resources, Writing - review & editing. **Gerardo F. Graue:** Investigation, Resources, Writing - review & editing. **Hans E. Grossniklaus:** Investigation, Writing - review & editing. **Santosh G. Honavar:** Investigation, Resources, Writing - review & editing. **Kaustubh Mulay:** Investigation, Resources, Writing - review & editing. **Lene D. Sjö:** Investigation, Resources, Writing - review & editing. **Matthew C. Sniegowski:** Investigation, Resources, Writing - review & editing. **Geeta K. Vemuganti:** Investigation, Resources, Writing - review & editing. **Bradley A. Thuro:** Investigation, Resources, Writing - review & editing. **Steffen Heegaard:** Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

FUNDING/SUPPORT: THE EYE CANCER FOUNDATION SUPPORTED THIS STUDY. LAUGE HJORTH MIKKELSEN WAS SUPPORTED BY Candys Foundation. The funding sources played no role in study design; in collection, analysis, and interpretation of data; in writing of the report; or in the decision to submit the article for publication. Financial Disclosures: The authors declare no proprietary or commercial interest in any product mentioned or any concept discussed in this article. All authors attest that they meet the current ICMJE criteria for authorship.

REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon, France: International Agency for Research in Cancer (IARC); 2017.
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;91(4):349–354.
3. Andreoli MT, Aakalu V, Setabutr P. Epidemiological trends in malignant lacrimal gland tumors. *Otolaryngol Head Neck Surg* 2015;152(2):279–283.
4. Ferry JA, Fung CY, Zukerberg L, et al. Lymphoma of the ocular adnexa: a study of 353 cases. *Am J Surg Pathol* 2007;31(2):170–184.
5. Andreasen S, Esmaeli B, Holstein SL, Mikkelsen LH, Rasmussen PK, Heegaard S. An update on tumors of the lacrimal gland. *Asia Pac J Ophthalmol (Phila)* 2017;6(2):159–172.
6. Rasmussen P, Ralfkiaer E, Prause JU, Sjö LD, Siersma VD, Heegaard S. Malignant lymphoma of the lacrimal gland. *Arch Ophthalmol* 2011;129(10):1275–1280.
7. Vangsted A, Mikkelsen LH, Jørgensen JS, Heegaard S. Lymphoplasmacytic lymphoma infiltrating both lacrimal glands in a patient with Waldenström's macroglobulinemia. *Am J Ophthalmol Case Rep* 2020;17:100597.
8. Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. *Cancer Res* 1971;31(11):1860–1861.
9. Amin MB, Edge S, Greene F, et al. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.
10. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* 2004;103(1):275–282.
11. Olsen TG, Holm F, Mikkelsen LH, et al. Orbital lymphoma—an international multicenter retrospective study. *Am J Ophthalmol* 2019;199:44–57.
12. Sjo LD. Ophthalmic lymphoma: epidemiology and pathogenesis. *Acta Ophthalmol* 2009;87:1–20.
13. 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;13(3):371–392.
14. Jamal B. Treatment of parotid non-Hodgkin lymphoma: a meta-analysis. *J Glob Oncol* 2018;4(4):1–6.
15. Kojima M, Shimizu K, Nishikawa M, et al. Primary salivary gland lymphoma among Japanese: a clinicopathological study of 30 cases. *Leuk Lymphoma* 2007;48(9):1793–1798.
16. 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):3727–3731.
17. Kao S-C, Kau H-C, Tsai C-C, et al. Lacrimal gland extranodal marginal zone B-cell lymphoma of MALT-type. *Am J Ophthalmol* 2007;143(2):311–316.
18. Farmer JP, Lamba M, Lamba WR, et al. Lymphoproliferative lesions of the lacrimal gland: clinicopathological, immunohistochemical and molecular genetic analysis. *Can J Ophthalmol* 2005;40(2):151–160.
19. Cassidy DT, McKelvie P, Harris GJ, Rose GE, McNab AA. Lacrimal gland orbital lobe cysts associated with MALT lymphoma and primary Sjogren's syndrome. *Orbit* 2005;24(4):257–263.

20. Coupland SE, Bermúdez Magner A, Chan ASY. Haematolymphoid tumours of the lacrimal gland. In: Grossniklaus HE, Eberhart CG, Kivelä TT, eds. WHO Classification of Tumours of the Eye. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2018:166–168.
21. Svendsen FH, Rasmussen PK, Coupland SE, et al. Lymphoma of the eyelid - an international multicenter retrospective study. *Am J Ophthalmol* 2017;177:58–68.
22. Kirkegaard MM, Rasmussen PK, Coupland SE, et al. Conjunctival lymphoma—an international multicenter retrospective study. *JAMA Ophthalmol* 2016;134(4):406–414.
23. Hindsø TG, Esmaeli B, Holm F, et al. International multicentre retrospective cohort study of ocular adnexal marginal zone B-cell lymphoma. *Br J Ophthalmol* 2020;104:357–362.
24. Rasmussen PK, Coupland SE, Finger PT, et al. Ocular adnexal follicular lymphoma: a multicenter international study. *JAMA Ophthalmol* 2014;132(7):851–858.
25. Mikkelsen LH, Würtz NS, Heegaard S. Recent advances in treating extra-ocular lymphomas. *Expert Rev Ophthalmol* 2018;13(4):205–217.
26. Munch-Petersen HD, Rasmussen PK, Coupland SE, et al. Ocular adnexal diffuse large B-cell lymphoma. *JAMA Ophthalmol* 2015;133(2):165–173.
27. Knudsen MKH, Rasmussen PK, Coupland SE, et al. Clinicopathological features of ocular adnexal mantle-cell lymphoma in an international multicenter cohort. *JAMA Ophthalmol* 2017;135(12):1367–1374.