Orbital Lymphoma—An International Multicenter Retrospective Study

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• PURPOSE: To investigate and characterize the clinical features of subtype-specific orbital lymphoma.
• DESIGN: Retrospective, interventional case series.
• METHODS: The study included 7 international eye cancer centers. Patient data were collected from January 1, 1980 through December 31, 2017. A total of 797 patients with a histologically verified orbital lymphoma were included. The primary endpoints were overall survival, disease-specific survival, and progression-free survival.
• RESULTS: The median age was 64 years, and 51% of patients (n = 407) were male. The majority of lymphomas were of B-cell origin (98%, n = 779). Extranodal marginal zone B-cell lymphoma (EMZL) was the most frequent subtype (57%, n = 452), followed by diffuse large B-cell lymphoma (DLBCL) (15%, n = 118), follicular lymphoma (FL) (11%, n = 91), and mantle cell lymphoma (MCL) (8%, n = 66). Localized Ann Arbor stage IE EMZL and FL were frequently treated with external beam radiation therapy. DLBCL, MCL, and disseminated EMZL and FL were primarily treated with chemotherapy. EMZL and FL patients had a markedly better prognosis (10-year disease-specific survival of 92% and 71%, respectively) than DLBCL and MCL patients (10-year disease-specific survival of 41% and 32%, respectively).
• CONCLUSIONS: Four lymphoma subtypes were primarily found in patients with orbital lymphoma: EMZL, DLBCL, FL, and MCL. The histologic subtype was found to be the main predictor for outcome, with EMZL and FL patients having a markedly better prognosis than DLBCL and MCL. (Am J Ophthalmol 2019;199:44–57. © 2018 Elsevier Inc. All rights reserved.)

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LYMPHOMAS ARE A HETEROGENEOUS GROUP OF MALIGNANT TUMORS ARISING AS CLONAL EXPANSIONS OF B LYMPHOCYTES, T LYMPHOCYTES, OR NK CELLS.[1] Lymphoma is the most frequent neoplasm of the orbit.[2,3] The most common lymphoma subtypes of the ocular adnexa (OA) are of B-cell origin and include extranodal marginal zone B-cell lymphoma (EMZL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and mantle cell lymphoma (MCL).[2,3] T-cell and NK-cell lymphomas rarely arise as primary tumors in the orbit.[2,3]

The aim of the present study was to describe the major subtypes of orbital lymphoma (OL), including clinical features and prognostic outcome, in a large cohort from 7 international eye cancer centers. Furthermore, the aim was to describe the distribution of OL subtypes in the different centers to see if any geographic variation was present in 7 international centers around the world. To our knowledge, the present study is by far the largest study on OL to date.

METHODS

• STUDY DESIGN: This study was a retrospective observational case series based on data from 7 international eye cancer centers: Copenhagen, Denmark; Liverpool, England; Houston, Texas, USA; New York, New York, USA; Atlanta, Georgia, USA; Hyderabad, India; and Melbourne, Australia. Patients with OL were included (ie, a tumor involving the lacrimal gland, extraocular muscles, or orbital fat/connective tissue). 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

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TABLE 1. Eye Cancer Center Distribution of Patients by Subtype of Orbital Lymphoma

	Eye Cancer Center						
	CPH	LIV	HOU	HYD	NY	ATL	MEL
Subtype, N (%)	256 (32)	94 (12)	188 (24)	159 (20)	29 (4)	14 (2)	57 (7)
B-cell lymphomas							
EMZL							
No. of patients	137	53	87	116	18	7	34
Median age, y	71	63	65	51	63	59	72
Male-to-female ratio	62:75	14:39	38:49	84:32	5:13	2:4	21:13
FL							
No. of patients	19	10	27	14	9	2	10
Median age, y	63	65	59	56	65	77	65
Male-to-female ratio	8:11	1:9	15:12	10:4	3:6	0:2	3:7
DLBCL							
No. of patients	41	17	37	15	0	2	6
Median age, y	75	74	60	45	NA	68	59
Male-to-female ratio	19:22	5:12	15:22	10:5	NA	0:2	1:5
MCL							
No. of patients	30	3	30	0	1	1	1
Median age, y	71	64	68	NA	77	63	67
Male-to-female ratio	24:6	3:0	19:11	NA	1:0	1:0	1:0
PL							
No. of patients	0	3	0	0	0	0	0
Median age, y	NA	69	NA	NA	NA	NA	NA
Male-to-female ratio	NA	2:1	NA	NA	NA	NA	NA
LPL							
No. of patients	3	3	1	0	0	0	0
Median age, y	79	71	47	NA	NA	NA	NA
Male-to-female ratio	3:0	1:2	1:0	NA	NA	NA	NA
BL/BLL							
No. of patients	1	0	1	4	1	0	0
Median age, y	56	NA	73	6	21	NA	NA
Male-to-female ratio	0:1	NA	0:1	2:2	0:1	NA	NA
B-LBL							
No. of patients	3	0	0	1	0	0	0
Median age, y	9	NA	NA	12	NA	NA	NA
Male-to-female ratio	2:1	NA	NA	1:0	NA	NA	NA
SLL/CLL							
No. of patients	4	0	0	1	0	0	3
Median age, y	69	NA	NA	39	NA	NA	65
Male-to-female ratio	2:2	NA	NA	0:1	NA	NA	1:2
HCL							
No. of patients	0	1	0	0	0	0	0
Median age, y	NA	40	NA	NA	NA	NA	NA
Male-to-female ratio	NA	1:0	NA	NA	NA	NA	NA
BCL-NOS							
No. of patients	14	2	1	2	NA	2	1
Median age, y	62	61	86	45	NA	76	47
Male-to-female ratio	8:6	2:0	0:1	1:1	NA	0:2	0:1
T-cell lymphomas							
PTCL-NOS							
No. of patients	2	0	2	6	0	0	0
Median age, y	51	NA	42	29	NA	NA	NA
Male-to-female ratio	1:1	NA	2:0	6:0	NA	NA	NA
ALCL							

Continued on next page

TABLE 1. Eye Cancer Center Distribution of Patients by Subtype of Orbital Lymphoma (*Continued*)

	Eye Cancer Center						
	CPH	LIV	HOU	HYD	NY	ATL	MEL
No. of patients	1	0	0	0	0	0	1
Median age, y	54	NA	NA	NA	NA	NA	54
Male-to-female ratio	1:0	NA	NA	NA	NA	NA	1:0
MF							
No. of patients	0	0	2	0	0	0	0
Median age, y	NA	NA	56	NA	NA	NA	NA
Male-to-female ratio	NA	NA	2:0	NA	NA	NA	NA
T-LBL							
No. of patients	1	0	0	0	0	0	0
Median age, y	23	NA	NA	NA	NA	NA	NA
Male-to-female ratio	1:0	NA	NA	NA	NA	NA	NA
TCL-NOS							
No. of patients	NA	2	NA	NA	NA	NA	1
Median age, y	NA	87	NA	NA	NA	NA	34
Male-to-female ratio	NA	1:1	NA	NA	NA	NA	0:1

ALCL = anaplastic large cell lymphoma; ATL = Atlanta, Georgia, USA; B-LBL = precursor B-cell lymphoblastic lymphoma; BCL-NOS = B-cell lymphoma not otherwise specified; BL = Burkitt lymphoma; BLL = Burkitt-like lymphoma; CPH = Copenhagen, Denmark; DLBCL = diffuse large B-cell lymphoma; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; HCL = hairy cell lymphoma; HOU = Houston, Texas, USA; HYD = Hyderabad, India; LIV = Liverpool, England; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; MEL, Melbourne, Australia; MF = mycosis fungoides; 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; TCL-NOS = T-cell lymphoma not otherwise specified; T-LBL = precursor T-cell lymphoblastic lymphoma.

approvals for this retrospective study were obtained from the Danish Data Protection Agency and the Local Ethics Committee (J no. H-B-2009-054).

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, 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 7 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 Tumors of Hematopoietic and Lymphoid Tissues (4th edition, 2008).[4] The classification for Burkitt-like lymphoma (BLL) has changed in the newest revised 4th edition of the WHO classification from 2017,[1] and BLL is now defined by the 11q chromosomal aberration. However, all lymphomas in the present study were classified according to the 4th edition of the WHO classification from 2008.[4]

• **CLINICAL DATA:** The clinical data collected included age, sex, symptoms, clinical findings, systemic involvement according to the Ann Arbor staging classification[5] and to the American Joint Committee on Cancer (AJCC) TNM classification system,[6] data about treatment modalities and response to therapy, survival duration, and cause of death. All clinical parameters were not available in all patients. Nowadays, a complete diagnostic examination of OL usually includes the following (1) computed tomography (CT), full-body positron emission tomography–computed tomography (PET-CT), or magnetic resonance imaging (MRI); and (2) a bone-marrow biopsy.[7]

Primary OL was defined as follows: (1) a biopsy-proven stage IE (E = extranodal) lymphoma (located to the ocular adnexal region) or stage IIE lymphoma (involvement of unilateral preauricular or submandibulary lymph nodes or adjacent structures); and (2) no history of prior lymphoma. Secondary lymphoma was defined as a systemic lymphoma with a secondary orbital manifestation of disease or a relapse of lymphoma affecting the orbit. As defined by the AJCC/TNM classification system, only primary lymphomas were classified according to AJCC/TNM.[6]

• **STATISTICAL ANALYSIS:** Overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) were the primary endpoints. OS was defined as the date of diagnosis of OL to death by any cause or to last follow-up, with the latter being a censored event. DSS was defined as

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

	N (%) of Patients															
	B-Cell Lymphomas											T-Cell Lymphomas				
	EMZL	DLBCL	FL	MCL	SLL/CLL	BL/BLL	LPL	B-LBL	PL	HCL	BCL-NOS	PTCL-NOS	ALCL	MF	T-LBL	TCL-NOS
Characteristics	452 (57)	118 (15)	91 (11)	66 (8)	8 (1)	7 (1)	7 (1)	4 (0.5)	3 (0.4)	1 (0.1)	22 (3)	10 (1)	2 (0.3)	2 (0.3)	1 (0.1)	3 (0.4)
Sex																
Men	227 (50)	50 (42)	40 (44)	48 (73)	3 (37)	2 (29)	5 (71)	3 (75)	2 (67)	1 (100)	11 (50)	9 (90)	2 (100)	2 (100)	1 (100)	1 (33)
Women	225 (50)	68 (58)	51 (56)	18 (27)	5 (63)	5 (71)	2 (29)	1 (25)	1 (33)	0	11 (50)	1 (10)	0	0	0	2 (67)
Age at presentation, y																
≤60	196 (43)	40 (34)	39 (43)	9 (14)	2 (25)	6 (86)	2 (29)	4 (100)	1 (33)	1 (100)	9 (41)	9 (90)	2 (100)	1 (50)	1 (100)	1 (33)
>60	256 (57)	78 (66)	52 (57)	57 (86)	6 (75)	1 (14)	5 (71)	0	2 (67)	0	13 (59)	1 (10)	0	1 (50)	0	2 (67)
Primary disease	338/447 (75)	63/116 (54)	53/91 (58)	7/64 (11)	6/8 (75)	5/7 (71)	1/7 (14)	1/4 (25)	2/3 (67)	0	19/22 (86)	6/10 (60)	0	0	1/1 (100)	1 (33)
Disseminated disease	70/447 (16)	29/116 (25)	13/91 (14)	25/64 (39)	1/8 (13)	0	4/7 (57)	2/4 (50)	1/3 (33)	0	2/22 (9)	2/10 (20)	1/2 (50)	0	0	2 (67)
Relapsed disease	39/447 (9)	24/116 (21)	25/91 (28)	32/64 (50)	1/8 (13)	2/7 (29)	2/7 (29)	1/4 (25)	0	1/1 (100)	1/22 (5)	2/10 (20)	1/2 (50)	2/2 (100)	0	0
Laterality																
Unilateral	395/450 (88)	108/118 (92)	72/89 (81)	36/66 (55)	8/8 (100)	7/7 (100)	5/7 (71)	4/4 (100)	3/3 (100)	1/1 (100)	20/22 (91)	9/10 (90)	1/2 (50)	2/2 (100)	1 (100)	3 (100)
Bilateral	55/450 (12)	10/118 (8)	17/89 (19)	30/66 (45)	0	0	2/7 (29)	0	0	0	2/22 (9)	1/10 (10)	1/2 (50)	0	0	0
Ann Arbor stage																
IE	329/425 (78)	62/111 (55)	45/82 (55)	11/66 (17)	7/8 (88)	4/6 (66)	0	2/4 (50)	2/3 (67)	0	14/18 (78)	6/9 (67)	0	0	0	1 (33)
IIE	26/425 (6)	15/111 (14)	14/82 (17)	2/66 (3)	0	1/6 (17)	0	0	0	0	2/18 (11)	1/9 (11)	1/2 (50)	0	0	0
IIIE	10/425 (2)	2/111 (2)	7/82 (9)	3/66 (4)	0	0	3/5 (60)	0	0	0	0	0	0	0	1 (100)	1 (33)
IVE	60/425 (14)	32/111 (29)	16/82 (19)	50/66 (76)	1/8 (12)	1/6 (17)	2/5 (40)	2/4 (50)	1/3 (33)	1/1 (100)	2/18 (11)	2/9 (22)	1/2 (50)	2/2 (100)	0	1 (33)
AJCC TNM stage[b]																
T2	319/329 (97)	48/60 (80)	43/50 (86)	6/6 (100)	5/5 (100)	5/6 (83)	0	1/1 (100)	2/2 (100)	0	15/18 (83)	6/6 (100)	0	2/2 (100)	0	1 (100)
T3	7/329 (2)	4/60 (7)	5/50 (10)	0	0	0	0	0	0	0	0	0	0	0	0	0
T4	3/329 (1)	8/60 (13)	2/50 (4)	0	0	1/6 (17)	1/1 (100)	0	0	0	3/18 (17)	0	0	0	0	0
Relapse/progression																
Yes	111/424 (26)	59/107 (55)	34/82 (41)	43/62 (69)	2/8 (25)	4/6 (67)	4/7 (57)	1/4 (25)	3/3 (100)	1/1 (100)	8/20 (40)	2/10 (20)	1/1 (100)	2/2 (100)	0	3 (100)
No	313/424 (74)	48/107 (45)	48/82 (59)	19/62 (31)	6/8 (75)	2/6 (33)	3/7 (43)	3/4 (75)	0	0	12/20 (60)	8/10 (80)	0	0	1/1 (100)	0
Site of recurrence																
OAR	40/107 (37)	10/45 (22)	12/30 (40)	9/31 (29)	0	0	0	1/1 (100)	0	0	4/8 (50)	NA	1/1 (100)	NA	0	1 (33)
OAR plus nodal and/or extranodal	20/107 (19)	13/45 (29)	5/30 (17)	7/31 (23)	0	0	0	0	0	0	1/8 (12)	NA	0	NA	0	2 (67)
Nodal and/or extranodal	47/107 (44)	22/45 (49)	13/30 (43)	15/31 (48)	2/2 (100)	1/1 (100)	3/3 (100)	0	3/3 (100)	1 (100)	3/8 (38)	NA	0	NA	0	0
Disease status at last follow-up																
Complete remission	289/446 (65)	37/116 (31)	43/91 (47)	15/61 (25)	2/8 (25)	2/7 (29)	0	2/4 (50)	0	0	9/20 (45)	7/10 (70)	0	0	1 (100)	0

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

	N (%) of Patients															
	B-Cell Lymphomas											T-Cell Lymphomas				
	EMZL	DLBCL	FL	MCL	SLL/CLL	BL/BLL	LPL	B-LBL	PL	HCL	BCL-NOS	PTCL-NOS	ALCL	MF	T-LBL	TCL-NOS
Alive with disease	62/446 (14)	10/116 (9)	21/91 (23)	15/61 (25)	3/8 (38)	1/7 (14)	4/7 (57)	2/4 (50)	0	1 (100)	0	0	0	0	0	1 (33)
Dead of lymphoma	20/446 (4)	47/116 (41)	15/91 (17)	25/61 (41)	0	4/7 (57)	2/7 (29)	0	3/3 (100)	0	4/20 (20)	2/10 (20)	1/2 (50)	2/2 (100)	0	1 (33)
Dead from other causes	75/446 (17)	22/116 (19)	12/91 (13)	6/61 (9)	3/8 (38)	0	1/7 (14)	0	0	0	7/20 (35)	1/10 (10)	1/2 (50)	0	0	1 (33)

AJCC = American Joint Committee on Cancer; ALCL = anaplastic large cell lymphoma; B-LBL = precursor B-cell lymphoblastic lymphoma; BCL-NOS = B-cell lymphoma not otherwise specified; BL = Burkitt lymphoma; BLL = Burkitt-like lymphoma; DLBCL = diffuse large B-cell lymphoma; E = extranodal; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; HCL = hairy cell lymphoma; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; MF = mycosis fungoides; NA = not applicable; OAR = ocular adnexal region; PL = plasmacytoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; SLL/CLL = small lymphocytic lymphoma; TCL-NOS = T-cell lymphoma not otherwise specified; T-LBL = precursor T-cell lymphoblastic lymphoma.

[a]Not specified in all cases.

[b]Primary lymphomas were staged according to AJCC classification.

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. PFS was defined as the date of diagnosis to either the date of first relapse or progression after initial treatment, the date of death by any cause, or the date of last contact, with the latter 2 being censored events. Survival outcomes were calculated and visualized using life tables and Kaplan-Meier plots, and different risk groups were compared using the log-rank test. Risk factors were compared using the χ^2 test. $P \leq .05$ was considered significant. Statistical analysis and calculation were made using IBM SPSS Package, version 22 (IBM Corporation, Armonk, New York, USA).

RESULTS

SEVEN HUNDRED NINETY-SEVEN PATIENTS WITH OL WERE identified (Tables 1 and 2). The majority of OL were of B-cell origin (98%, n = 779). Ten B-cell lymphoma subtypes were identified according to the WHO lymphoma classification[4]: EMZL (n = 452), DLBCL (n = 118), FL (n = 91), MCL (n = 66), small lymphocytic lymphoma (SLL/CLL, n = 8), lymphoplasmacytic lymphoma (LPL, n = 7), Burkitt/Burkitt-like lymphoma (BL/BLL, n = 7), precursor B-cell lymphoblastic lymphoma (B-LBL, n = 4), plasmacytoma (PL, n = 3), and hairy cell lymphoma (HCL, n = 1). Twenty-two lymphomas were of B-cell origin but could not be classified further (BCL-NOS) (Tables 1 and 2).

Four T-cell lymphoma subtypes were identified: peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS, n = 10); anaplastic large-cell lymphoma (T-ALCL, n = 2) (1 ALK-negative, 1 unknown); mycosis fungoides (MF, n = 2); and precursor T-cell lymphoblastic lymphoma (T-LBL, n = 1). Three lymphomas were of T-cell origin but could not be classified further (TCL-NOS) (Tables 1 and 2).

The median follow-up time was 35 months (range, 0-399 months). Fifty-one percent of patients were men (n = 407), and the median age was 64 years (range, 2-100 years). The most common symptoms were periorbital swelling (49%), a mass (49%), and proptosis (37%). The most common clinical signs were an objective mass (68%) and proptosis (48%) (Table 3, Figure 1). The conjunctiva was the most common site of local invasion (Table 3).

• **MAJOR NON-HODGKIN B-CELL LYMPHOMA SUBTYPES:** *Extranodal marginal zone B-cell lymphoma. Clinical Features*

Of the 779 patients with B-cell lymphomas, 452 (58%) had EMZL (Tables 1 and 2, Figure 1). The median age was 63 years (range, 13-100 years). The median symptom duration before diagnosis was 5 months (range, 0-96 months). The vast majority of these patients had stage IE and TNM T2 lymphoma.

Treatment

Treatment information was available in 382 of 452 patients, of whom 362 were staged according to Ann Arbor (Table 4). Stage IE patients were primarily treated with

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

	B-Cell Lymphoma, N (%)											T-Cell Lymphoma, N (%)				
Symptoms[b]	EMZL 452 (57)	DLBCL 118 (15)	FL 91 (11)	MCL 66 (8)	SLL/CLL 8 (1)	BL/BLL 7 (1)	LPL 7 (1)	B-LBL 4 (0.5)	PL 3 (0.4)	HCL 1 (0.1)	BCL- NOS 22 (3)	PTCL- NOS 10 (1)	ALCL 2 (0.3)	MF 2 (0.3)	T-LBL 1 (0.1)	TCL-NOS 3 (0.4)
Mass	158 (46)	44 (48)	39 (57)	33 (70)	3 (60)	4 (57)	2 (50)	0	NA	NA	6 (35)	6 (67)	1 (50)	1 (50)	1 (100)	NA
Swelling	159 (37)	50 (55)	38 (56)	33 (70)	4 (80)	3 (43)	2 (50)	1 (25)	NA	NA	4 (24)	7 (78)	1 (50)	1 (50)	0	NA
Proptosis	144 (42)	34 (37)	18 (26)	8 (17)	1 (20)	4 (57)	2 (50)	3 (75)	NA	NA	8 (47)	2 (22)	0	1 (50)	1 (100)	NA
Epiphora	32 (9)	11 (12)	8 (12)	11 (23)	1 (20)	0	1 (25)	0	NA	NA	3 (18)	1 (11)	0	0	0	NA
Irritation/pain	61 (18)	24 (26)	8 (12)	15 (32)	2 (40)	4 (57)	0	1 (25)	NA	NA	3 (18)	2 (22)	0	0	0	NA
Diplopia	32 (9)	26 (29)	10 (15)	11 (23)	1 (20)	1 (14)	0	1 (25)	NA	NA	0	0	1 (50)	0	0	NA
Ptosis	45 (13)	17 (19)	6 (9)	4 (9)	0	0	0	1 (25)	NA	NA	2 (12)	0	0	2 (100)	0	NA
Redness	2 (1)	0	0	2 (4)	0	0	0	0	NA	NA	0	0	0	0	0	NA
Decreased VA	21 (5)	14 (15)	6 (9)	0	0	0	0	1 (25)	NA	NA	3 (18)	0	0	0	1 (100)	NA
B-symptoms	14 (6)	8 (9)	1 (1)	10 (21)	0	0	0	1 (25)	NA	NA	3 (18)	1 (11)	1 (50)	0	0	NA
Not stated	112	27	23	19	3	0	3	0	NA	NA	5	1	0	0	0	NA
Median (range) symptom duration, m[c]	5 (0-96)	2 (0-36)	5.5 (0.25-36)	3 (0.13-24)	3.5 (2-5)	3.5 (0.5-23)	5 (4-6)	1 (0.25-1)	NA	NA	6 (1-24)	4.5 (1-13)	2	1 (1-1)	1	NA
Signs[b]																
Mass	235 (70)	57 (63)	49 (73)	41 (89)	3 (60)	4 (57)	2 (50)	0	NA	NA	5 (29)	4 (44)	1 (50)	1 (50)	1 (100)	NA
Proptosis	178 (53)	43 (47)	20 (30)	14 (30)	4 (80)	5 (71)	2 (50)	3 (75)	NA	NA	10 (56)	5 (56)	1 (50)	1 (50)	1 (100)	NA
Displacement	147 (44)	40 (44)	22 (33)	7 (15)	3 (60)	5 (71)	0	1 (25)	NA	NA	6 (35)	5 (56)	1 (50)	1 (50)	0	NA
Limited motility	123 (37)	40 (44)	14 (21)	8 (17)	1 (20)	3 (43)	0	1 (25)	NA	NA	4 (24)	7 (78)	0	0	1 (100)	NA
Resistance	46 (14)	17 (19)	6 (9)	6 (13)	3 (60)	0	0	2 (50)	NA	NA	2 (12)	0	0	0	0	NA
Epiphora	11 (3)	1 (1)	6 (9)	2 (4)	2 (40)	0	0	1 (25)	NA	NA	1 (6)	1 (11)	0	0	0	NA
Diplopia	27 (8)	22 (24)	7 (10)	9 (20)	0	0	0	0	NA	NA	0	0	1 (50)	0	0	NA
Ptosis	42 (13)	9 (10)	7 (10)	5 (11)	2 (40)	0	1 (25)	1 (25)	NA	NA	2 (12)	0	0	2 (100)	0	NA
Chemosis	28 (8)	18 (20)	7 (10)	7 (15)	0	2 (29)	0	0	NA	NA	2 (12)	1 (11)	0	1 (50)	0	NA
Edema	38 (11)	10 (11)	8 (12)	2 (4)	1 (20)	1 (14)	0	1 (25)	NA	NA	4 (24)	0	0	0	0	NA
Erythema	2 (1)	0	0	1 (2)	0	0	0	0	NA	NA	0	0	0	0	0	NA
Ectropion	0	0	0	0	0	0	0	0	NA	NA	0	1 (11)	0	0	0	NA
Not stated	118 (26)	27	24	20	3	0	3	0	NA	NA	5	1	0	0	0	NA
Lacrimal gland involvement	178 (17)	26 (22)	26 (29)	17 (26)	3 (38)	2 (29)	1 (14)	0	2 (67)	0	4 (18)	2 (20)	0	0	0	0
Local spread																

Continued on next page

TABLE 3. Frequency of Symptoms, Clinical Signs, and Local Spread at Presentation of Orbital Lymphoma[a] (*Continued*)

	B-Cell Lymphoma, N (%)										T-Cell Lymphoma, N (%)				
Symptoms[b]	EMZL 452 (57)	DLBCL 118 (15)	FL 91 (11)	MCL 66 (8)	SLL/CLL 8 (1)	BL/BLL 7 (1)	LPL 7 (1)	B-LBL 4 (0.5)	PL 3 (0.4)	HCL 1 (0.1)	BCL- NOS 22 (3)	PTCL- NOS 10 (1)	ALCL 2 (0.3)	MF 2 (0.3)	T-LBL 1 (0.1)	TCL-NOS 3 (0.4)
Eyelid	14 (3)	8 (7)	9 (10)	11 (17)	0	0	0	0	0	0	1 (5)	0	1 (50)	1 (50)	0	0
conjunctiva	50 (11)	4 (3)	8 (9)	13 (20)	0	0	0	0	0	0	1 (5)	0	0	0	0	0
Lacrimal sac	3 (1)	0	2 (2)	1 (2)	0	1 (14)	0	0	0	0	0	0	0	0	0	0
Intraocular	1 (0)	0	1 (1)	0	0	0	1 (14)	0	0	0	0	0	0	0	0	0

ALCL = anaplastic large cell lymphoma; B-LBL = precursor B-cell lymphoblastic lymphoma; BCL-NOS = B-cell lymphoma not otherwise specified; BL = Burkitt lymphoma; BLL = Burkitt-like lymphoma; DLBCL = diffuse large B-cell lymphoma; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; HCL = hairy cell lymphoma; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; MF = mycosis fungoides; NA = not applicable; PL = plasmacytoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; SLL/CLL = small lymphocytic lymphoma; TCL-NOS = T-cell lymphoma not otherwise specified; T-LBL = precursor T-cell lymphoblastic lymphoma; VA = visual acuity.

[a]Data are not specified for all patients.

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

[c]Median symptom duration not specified for all patients.

external beam radiation therapy (EBRT) as monotherapy (83%, 239 out of 279). Stage IVE patients were often treated with chemotherapy (73%, 40 out of 55), mostly in combination with rituximab with or without EBRT. The median radiation dose was 26 Gy (range, 4-60 Gy, registered in 110 patients). Combination regimens, such as CVP (cyclophosphamide, vincristine, and prednisone) and CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone) or R-CHOP (with rituximab) were commonly used in stage IVE disease. However, a variety of combination regimens and single agents were used, including corticosteroids.

Treatment Outcome and Survival

Disease status at last follow-up is listed in Table 2. Time to relapse/progression was accessible in 66 of 111 patients with relapse/progression. Median duration before relapse/progression was 36 months (range, 2-198 months). Median PFS was 24 months (range, 1-376 months). Survival data were available in 447 patients. Five-year, 10-year, and 20-year OS were 80%, 62%, and 34%, respectively. The 5-year, 10-year, and 20-year DSS were 96%, 92%, and 84%, respectively (median survival, 34 months; 95% confidence interval [CI], 28-40 months) (Figure 2). EMZL patients who experienced relapse/progression had a poorer prognosis (10-year DSS, 81%) compared to nonrelapse/nonprogression (10-year DSS, 100%) ($P < .001$, log-rank test). The DSS was not different in patients with stage IE/IIE (10-year DSS, 92%) and stage IIIE/IVE (10-year DSS, 89%) ($P = .27$, log-rank test).

When comparing treatment regimens, stage IE patients treated with EBRT combined with chemotherapy were not found to have a better 10-year DSS than patients treated with EBRT alone ($P = .29$, log-rank test). The date of diagnosis was available in 361 EMZL patients, of whom 303 were diagnosed after year 2000. There was no difference in 10-year DSS between patients diagnosed and treated for EMZL after year 2000 and patients diagnosed and treated before year 2000 ($P = .76$, log-rank test).

Diffuse large B-cell lymphoma. Clinical Features

One hundred eighteen patients (15%) were diagnosed with DLBCL (Table 2). The median age was 67 years (range, 3-96 years). The median duration of symptoms was 2 months (range, 0-36 months). The vast majority of these patients had stage IE and TNM T2 lymphoma.

Treatment

Treatment information was available in 106 DLBCL patients, and 99 of these patients were staged according to the Ann Arbor staging system (Table 4). Patients with stage IE were primarily treated with EBRT (89%, 49 out of 55) and chemotherapy (71%, 39 out of 55). Of the stage IVE patients, 93% (27 out of 29) were treated with chemotherapy, mostly in combination with rituximab. Median radiation

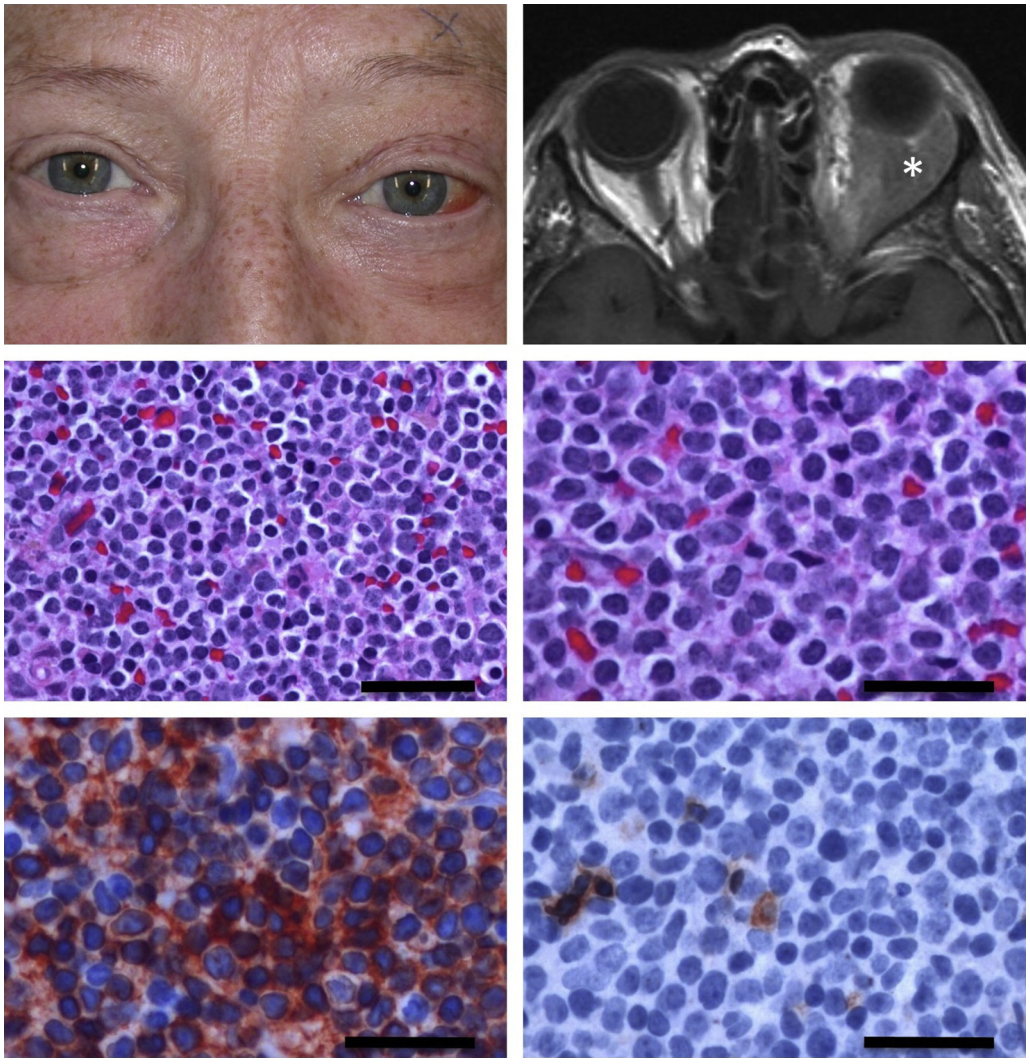


FIGURE 1. Clinical and histologic findings of orbital extranodal marginal zone B-cell lymphoma. (Top left) Redness, proptosis, and downward displacement of the left eyeball in a 66-year-old woman with extranodal marginal zone B-cell lymphoma of the left orbit. (Top right) Magnetic resonance imaging of the orbit showing a diffusely infiltrating tumor (asterisk) of the left orbit. (Middle left) Numerous lymphocytic tumor cells have diffusely infiltrated the orbit (hematoxylin-eosin, bar = 50 μm). (Middle right) The tumor cells have small to medium-sized, irregular nuclei, resembling centrocytes (hematoxylin-eosin, bar = 50 μm). (Bottom left) The majority of tumor cells react with CD 79α, indicating B-cell origin (bar = 50 μm). (Bottom right) Positivity for CD 3 (T-cell marker) are only shown in a few reactive lymphocytic cells (bar = 50 μm).

dose was 30.6 Gy (range, 4-60 Gy, registered in 33 patients). The most frequently applied chemotherapy regimen was R-CHOP.

Treatment Outcome and Survival

Data on time to relapse/progression were accessible in 22 of 59 patients with relapse/progression. The median duration before relapse/progression was 34 months (range, 1-192 months). Survival data were available in 117 patients. The median PFS was 17 months (range, 0-239 months). The 5-year and 10-year OS were 38% and 28%, respectively, and the 5-year and 10-year DSS were 54% and 41%, respectively (median survival, 23 months; 95% CI, 14-32 months).

Male patients had a poorer outcome (10-year DSS, 35%) compared to female patients (10-year DSS, 49%) ($P = .04$, log-rank test). Patients with relapse/progression had a poorer outcome (10-year DSS, 23%) compared to nonrelapse/nonprogression (10-year DSS, 87%) ($P < .001$, log-rank test). Patients with secondary DLBCL had a poorer outcome (10-year DSS, 36%) compared to primary DLBCL (10-year DSS, 48%) ($P = .01$, log-rank test) (Figure 2). Stage IIIE/IVE patients had a poorer outcome (10-year DSS, 25%) compared to stage IE/IIE (10-year DSS, 51%) ($P < .001$, log-rank test).

There was no difference in DSS when comparing stage IE DLBCL patients treated with rituximab-based chemotherapy (with/without EBRT) with stage IE DLBCL

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

Stage	No. (%) of Patients					
	EBRT	EBRT Plus CTX	CTX	CTX Plus Rituximab	EBRT and CTX Plus Rituximab	Rituximab or Rituximab Plus EBRT
B-cell lymphomas						
EMZL						
IE	239 (85)	20 (7)	7 (3)	5 (2)	2 (1)	6 (2)
IIE	5 (25)	9 (45)	1 (5)	4 (20)	1 (5)	0
IIIE	1 (12)	3 (38)	1 (12)	2 (25)	1 (12)	0
IVE	12 (22)	6 (11)	8 (15)	18 (32)	8 (15)	3 (5)
FL						
IE	19 (53)	9 (25)	3 (8)	2 (6)	3 (8)	0
IIE	4 (31)	4 (31)	3 (22)	1 (8)	0	1 (8)
IIIE	1 (33)	0	1 (33)	1 (33)	0	0
IVE	0	2 (14)	3 (21)	6 (43)	3 (22)	0
DLBCL						
IE	16 (29)	21 (38)	1 (2)	5 (9)	12 (22)	0
IIE	3 (21)	5 (36)	1 (7)	4 (29)	1 (7)	0
IIIE	0	1 (50)	0	1 (50)	0	0
IVE	2 (7)	6 (21)	1 (3)	12 (41)	8 (28)	0
MCL						
IE	4 (40)	3 (30)	0	2 (20)	1 (10)	0
IIE	0	0	2 (100)	0	0	0
IIIE	0	0	0	1 (100)	0	0
IVE	5 (10)	3 (6)	7 (15)	26 (54)	6 (13)	1 (2)
PL						
IE or IIE	0	2 (100)	0	0	0	0
IIIE or IVE	0	1 (100)	0	0	0	0
LPL[b]						
IIIE or IVE	1 (20)	2 (40)	0	1 (20)	1 (20)	0
BL/BLL						
IE or IIE	0	5 (100)	0	0	0	0
IIIE or IVE	0	1 (100)	0	0	0	0
B-LBL						
IE or IIE	0	0	1 (100)	0	0	0
IIIE or IVE	0	0	1 (100)	0	0	0
SLL/CLL						
IE or IIE	3 (100)	0	0	0	0	0
IIIE or IVE	1 (100)	0	0	0	0	0
HCL[c]						
IIIE or IVE	0	1 (100)	0	0	0	0
BCL, NOS						
IE or IIE	6 (50)	4 (33)	2 (17)	0	0	0
IIIE or IVE	0	1 (100)	0	0	0	0
T-cell lymphomas						
PTCL, NOS						
IE or IIE	0	3 (75)	1 (25)	0	0	0
IIIE or IVE	0	0	1 (50)	1 (50)	0	0
ALCL						
IE or IIE	0	0	1 (100)	0	0	0
IIIE or IVE	0	0	1 (100)	0	0	0
MF[b]						
IIIE or IVE	1 (50)	1 (50)	0	0	0	0

Continued on next page

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

Stage	No. (%) of Patients					
	EBRT	EBRT Plus CTX	CTX	CTX Plus Rituximab	EBRT and CTX Plus Rituximab	Rituximab or Rituximab Plus EBRT
T-LBL[c]						
IIIE or IVE	0	0	1 (100)	0	0	0
TCL NOS[b]						
IIIE or IVE	0	2 (100)	0	0	0	0

ALCL = anaplastic large cell lymphoma; B-LBL = precursor B-cell lymphoblastic lymphoma; BCL-NOS = B-cell lymphoma not otherwise specified; BL = Burkitt lymphoma; BLL = Burkitt-like lymphoma; CTX = chemotherapy; DLBCL = diffuse large B-cell lymphoma; E = extranodal; EBRT = external beam radiation therapy; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; HCL = hairy cell lymphoma; LPL = lymphoplasmacytic lymphoma; MCL = mantle cell lymphoma; MF = mycosis fungoides; PL = plasmacytoma; PTCL-NOS = peripheral T-cell lymphoma not otherwise specified; SLL/CLL = small lymphocytic lymphoma; TCL-NOS = T-cell lymphoma not otherwise specified; T-LBL = precursor T-cell lymphoblastic lymphoma.

[a]Data are not specified for all patients.

[b]All LPL, MF, TCL-NOS were stage IIIE or IVE disease.

[c]The only case of HCL was stage IVE disease and the only case of T-LBL was stage IIIE disease.

patients not receiving rituximab ($P = .20$, log-rank test), and this was also the case for stage IVE DLBCL ($P = .51$, log-rank test). The date of diagnosis was available in 93 patients with DLBCL, of whom 79 were diagnosed after year 2000. There was no difference in 10-year DSS between patients diagnosed and treated for DLBCL after year 2000 with patients diagnosed and treated before year 2000 ($P = .38$, log-rank test).

When comparing risk factors, secondary DLBCL was associated with a higher frequency of relapse/progression ($P < .001$, χ^2 test). Stage IIIE/IVE DLBCL were also associated with a higher frequency of relapse/progression ($P = .004$, χ^2 test).

Follicular lymphoma. Clinical Features

Ninety-one patients with FL were identified (11%) (Tables 1 and 2). Median age was 62 years (range, 39-95 years). Median duration of symptoms was 5.5 months (range, 0.25-36 months). The vast majority of these patients had stage IE and TNM T2 lymphoma.

Treatment

Treatment information was available in 74 patients, of whom 69 were staged according to Ann Arbor (Table 4). Patients with stage IE lymphoma were primarily treated with EBRT (86%, 31 out of 36). All stage IVE FL (100%, n = 14) were treated with chemotherapy, often in combination with rituximab with or without EBRT. Median radiation dose was 26 Gy (range, 4-40 Gy, registered in 17 patients). The chemotherapy applied was primarily CVP, CHOP, and R-CHOP.

Treatment Outcome and Survival

Data concerning time to relapse or progression were accessible in 22 of 34 patients with relapse/progression. Median duration before relapse/progression was 92 months (range, 13-223 months). The median PFS was 51 months (range, 1-218 months). Survival data were available in 91 patients. The 5-year and 10-year OS were 85% and 54%, respectively, and the 5-year and 10-year DSS were 88% and 71%, respectively (median survival 63 months; 95% CI, 53-73 months) (Figure 2). Patients with relapse/progression had a poorer outcome (10-year DSS, 54%) compared to nonrelapse/nonprogression (10-year DSS, 95%) ($P = .05$, log-rank test). Patients with secondary orbital FL had a poorer outcome (10-year DSS, 85%) compared to primary orbital FL (10-year-DSS, 82%) ($P = .01$, log-rank test). When comparing risk factors, there was no association between secondary disease and relapse/progression ($P = .21$, χ^2 test). The 10-year DSS was not different when comparing stage IE/IIE with stage IIIE/IVE ($P = .17$, log-rank test).

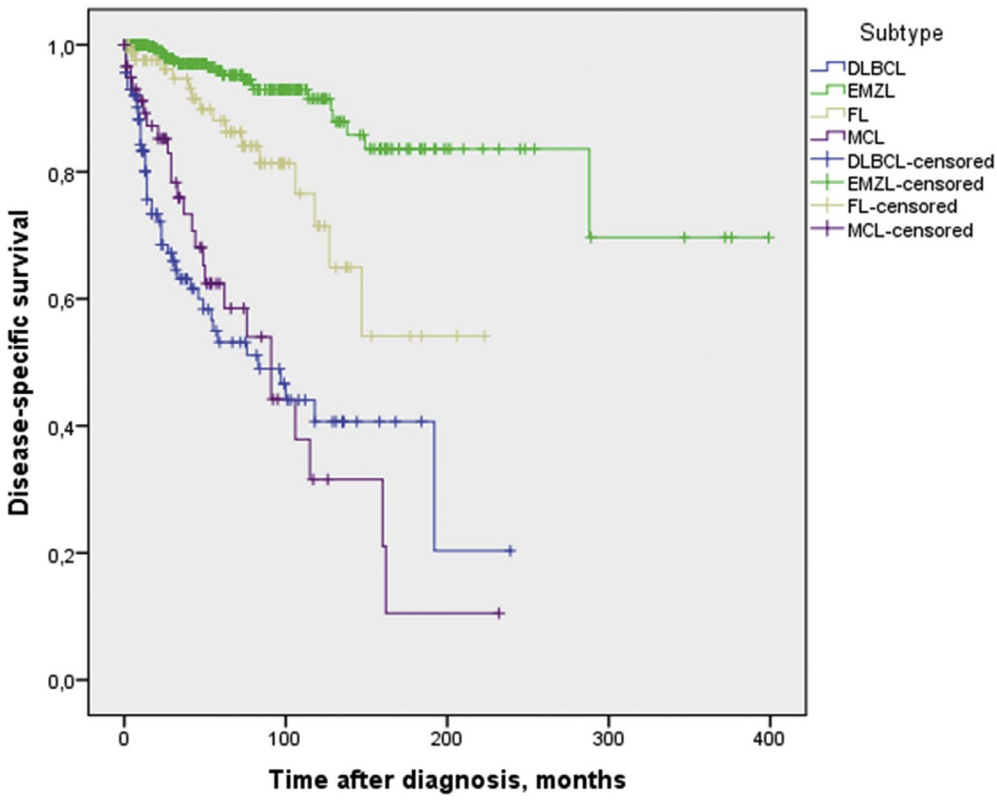
There was no difference in DSS when comparing stage IE FL patients treated with EBRT as monotherapy compared to stage IE FL patients treated with EBRT plus chemotherapy ($P = .43$, log-rank test). The date of diagnosis was available in 68 patients with FL, of whom 57 were diagnosed after year 2000. There was no difference in 10-year DSS when comparing patients diagnosed and treated for FL after year 2000 with patients diagnosed and treated before year 2000 ($P = .79$, log-rank test).

Mantle cell lymphoma. Clinical Features

Sixty-six patients with MCL were identified (8%). Median age was 69 years (range, 35-90 years). The median duration of symptoms was 3 months (range, 0-24 months). The vast majority of these patients had stage IVE disease.

Treatment

All 61 patients with information about therapy were staged according to Ann Arbor (Table 4). Six out of 10



Subtype interval, y	0	5	10	15	20	25	30	35
EMZL (N = 452)								
Patients at risk, No.	444	151	57	21	9	4	3	
Events, No.	10	5	4	0	1	0	0	
FL (N = 91)								
Patients at risk, No.	90	49	13	3	0			
Events, No.	8	5	2	0				
DLBCL (N = 118)								
Patients at risk, No.	115	29	11	3	0			
Events, No.	41	5	0	1				
MCL (N = 66)								
Patients at risk, No.	60	16	4	1				
Events, No.	17	6	2	0				

FIGURE 2. Disease-specific survival among patients with orbital lymphoma. Disease-specific survival is associated with the orbital lymphoma subtype. The low-grade lymphoma subtypes extranodal marginal zone B-cell lymphoma and follicular lymphoma have a more favorable disease-specific survival than the high-grade lymphoma subtypes diffuse large B-cell lymphoma and mantle cell lymphoma. DLBCL = diffuse large B-cell lymphoma; EMZL = extranodal marginal zone B-cell lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma.

stage IE patients were treated with chemotherapy (60%), of which 3 were in combination with rituximab. Among the stage IVE patients, the majority were treated with chemotherapy (88%, 42 out of 48) often in combination with rituximab with or without EBRT. Median radiation dose was 30 Gy (range 4 40 Gy, registered in 13 patients). The chemotherapy applied was primarily CHOP and CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) in combination with rituximab.

Treatment Outcome and Survival

Time to relapse/progression was accessible in 24 of 43 patients with relapse progression. Median duration before relapse/progression was 24 months (range, 0-103 months). Median PFS was 23 months (range, 0-126 months). Survival data were available in 61 patients. The 5-year and 10-year OS were 53% and 22%, respectively, and the 5-year and 10-year DSS were 62% and 32% (median survival, 34 months; 95% CI, 23-45) (Figure 2). There was no

difference in DSS when comparing stage IE/IIE with stage IIIE/IVE MCL ($P = .92$, log-rank test).

Stage IVE MCL patients treated with chemotherapy and rituximab (with or without EBRT) had a better 10-year DSS than IVE MCL patients not receiving rituximab ($P = .01$, log-rank test). The date of diagnosis was available in 61 MCL patients, of whom 53 were diagnosed after year 2000. There was no difference in 10-year DSS between patients diagnosed and treated for MCL after year 2000 with patients diagnosed and treated before year 2000 ($P = .40$, log-rank test).

• **RARE B-CELL SUBTYPES:** See Tables 2, 3, and 4. Patients with BL/BLL were often young (median age, 12 years, range, 5-73 years); the same applies for B-LBL (median age, 10 years, range, 5-55 years). The rare B-cell subtypes were often treated with chemotherapy with or without EBRT. Rituximab was only chosen in 2 patients with LPL (Table 4).

• **T-CELL LYMPHOMAS:** See Tables 2, 3, and 4. PTCL-NOS (median age, 34 years, range, 2-61 years) and ALCL (median age, 54 years, range, 23-54 years) were primarily found in younger patients (Table 2). Ninety percent (n = 9) of PTCL-NOS patients were male. All T-cell lymphomas were treated with chemotherapy with or without EBRT. None of the T-cell lymphomas were treated with EBRT as monotherapy, and only 1 patient with PTCL-NOS received rituximab (Table 4).

DISCUSSION

SEVEN HUNDRED NINETY-SEVEN PATIENTS WITH OL WERE included in the present study, in which 7 contributing eye cancer centers participated. Currently, this international, multicenter study is the largest reported collection of clinical data and outcomes on patients with OL.

We found that most of the patients were elderly (median age, 64 years). Furthermore, patients with MCL tend to be slightly older than patients with EMZL, FL, and DLBCL, which is in line with previous reports.[3,8-11]

The distribution of lymphoma subtypes in our study confirms that EMZL was the most frequent subtype, followed by DLBCL, FL, and MCL.[2,3,8,11] A large study on 353 patients with ocular adnexal lymphoma (OAL) have also found EMZL (52%) to be the most common subtype, followed by FL (23%), DLBCL (8%), and MCL (5%).[2] In another study on 99 patients with OAL, 64% of patients had EMZL, 10% had FL, 9% had DLBCL, and 2% had MCL.[12] However, in this study, plasmacytoma (6%) and LPL (5%) were more common than MCL.[12] T-cell lymphomas are found to be very rare in the orbit (2%). It is more common for T-cell lymphomas to arise in the eyelids, owing to the higher occurrence of T-cell lymphomas in the skin.[11,13]

As expected, the low-grade lymphoma subtypes EMZL and FL were found to have a markedly better prognosis (10-year DSS of 92% and 71%, respectively) than the high-grade lymphoma subtypes DLBCL and MCL (10-year DSS of 41% and 32%, respectively).

It is generally acknowledged that primary localized stage IE EMZL and FL should be treated with EBRT as monotherapy.[3,14-19] A newly published review by the American Academy of Ophthalmology on treatment of OAL has found that radiotherapy has a very good effect on local control, disease-free survival, and overall survival in patients with OA-EMZL.[20] In our study, no difference in 10-year DSS was found between stage IE EMZL patients treated with EBRT as monotherapy and stage IE patients treated with EBRT in combination with chemotherapy ($P = .29$, log-rank test). The majority of stage IVE EMZL and FL patients were treated with chemotherapy or chemoimmunotherapy. The practice of using PET scanning as a diagnostic tool in the staging of lymphoma and detection of recurrences was not widely used until the first decade of the 21st century. Likewise, rituximab as immunotherapy was also not widely used until after year 2000. It would be expected that patients diagnosed and treated after year 2000 would have a better DSS than patients diagnosed and treated in the 1980s and 1990s. We were not able to detect any statistically significant difference in the 10-year DSS between patients diagnosed and treated before and after year 2000. However, the number of patients diagnosed with orbital lymphoma before year 2000 in the present study was relatively low. Chemoimmunotherapy is generally found to have a good effect on patient outcome when treating disseminated EMZL and FL.[14-16,18,21] Studies on newer treatment modalities in patients with OAL are small and sparse, and future treatment studies are needed to evaluate the effect of potential new treatment regimens.[16,20]

Stage IVE MCL patients treated with rituximab in combination with chemotherapy with/without EBRT were found to have a better 10-year DSS, compared to patients not treated with rituximab. Regarding patients with both stage IE and IVE DLBCL, there was no difference in 10-year DSS between patients treated with rituximab-based chemotherapy and patients not receiving rituximab. However, this could be owing to the low number of patients in the respective groups. Previous studies have found that the combination regimen R-CHOP has a significant effect on patient outcome in patients with ocular adnexal DLBCL and MCL.[10,22,23]

Regarding the distribution of OL subtypes among the centers, more patients in the Indian center (72%) was diagnosed with EMZL compared to the other centers (50%). Regarding the high-grade lymphomas, few patients had DLBCL (9%) and MCL (0%) in Hyderabad compared to the other centers. Whether these observations are owing to selection bias or demonstrate a true geographic variation is difficult to say from our data.

It has to be noted that the retrospective nature of this study has some inherent limitations. The study spans 38

years, in which time period different diagnostic and histopathologic methods and treatment regimens have evolved. The data were pooled across 7 international eye cancer centers and entailed incomplete medical records. With a median follow-up time of 35 months, there might not have been enough time to detect outcome variables, given that many of the tumors in this study are indolent.

The T-classification of the AJCC staging system is based on the anatomic location of a primary tumor.[6,24,25] Thus, OL is assumed to have a worse prognosis than conjunctival lymphoma and a better prognosis than lymphoma of the eyelids. Previous studies of OAL from our group have found a 5-year DSS of conjunctival and eyelid EMZL of 97% and 88%, respectively.[8,11] In the current study, the 5-year DSS of EMZL was found to be 96%, indicating that eyelid EMZL may have a poorer prognosis. However, the prognoses seem very similar for these locations. In comparison of the 5-year DSS of conjunctival,[8] eyelid,[11] and orbital FL, they also seem to be very similar (82%, 88%, and 88%, respectively). However, conjunctival MCL has been reported to have a very poor prognosis (5-year DSS, 9%)[8] compared to orbital MCL (5-year DSS, 53%) and eyelid MCL (5-year DSS, 50%).[11] The 5-year DSS was markedly worse in DLBCL of the eyelid (21%) compared to the conjunctiva (55%) and the orbit (54%). These results may indicate that the anatomic location of these high-grade lymphoma subtypes within the ocular adnexal region might play a prognostic role. However, the anatomic location with the poorest prognosis differs between the high-grade lymphoma subtypes. Other factors such as secondary disease or relapse always worsen the prognosis.

In conclusion, the vast majority of OLs are of B-cell origin, with EMZL, DLBCL, FL, and MCL being the most frequent subtypes. EBRT as monotherapy seems to be the best treatment in localized EMZL and FL, whereas R-CHOP seems to be the treatment of choice in high-grade DLBCL and MCL.

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