


## Original Investigation

# Conjunctival Lymphoma—An International Multicenter Retrospective Study

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**IMPORTANCE** To date, the clinical features of the various subtypes of conjunctival lymphoma (CL) have not been previously evaluated in a large cohort.

**OBJECTIVE** To characterize subtype-specific clinical features of CL and their effect on patient outcome.

**DESIGN, SETTING, AND PARTICIPANTS** A retrospective multicenter study was performed. Patient data were collected from January 1, 1980, through December 31, 2010. The dates of the analysis were May 15, 2015, to August 20, 2015. The median follow-up period was 43 months. Seven eye cancer centers were involved in the study. In total, 268 patients with CL were identified, 5 of whom were excluded because of missing clinical data.

**MAIN OUTCOMES AND MEASURES** Overall survival, disease-specific survival, and progression-free survival were the primary end points.

**RESULTS** Two hundred sixty-three patients with CL were included in the study. Their mean age was 61.3 years, and 55.1% (145 of 263) were female. All lymphomas were of B-cell type. The most frequent subtype was extranodal marginal zone lymphoma (EMZL) (68.4% [180 of 263]), followed by follicular lymphoma (FL) (16.3% [43 of 263]), mantle cell lymphoma (MCL) (6.8% [18 of 263]), and diffuse large B-cell lymphoma (DLBCL) (4.6% [12 of 263]). Conjunctival lymphoma commonly manifested in elderly individuals (age range, 60-70 years old), with EMZL having a female predilection (57.8% [104 of 180]) and MCL having a marked male predominance (77.8% [14 of 18]). Unlike EMZL and FL, DLBCL and MCL were frequently secondary diseases (41.7% [5 of 12] and 88.9% [16 of 18], respectively), with MCL showing a frequent occurrence of stage IVE lymphoma (61.1% [11 of 18]) and bilateral manifestation (77.8% [14 of 18]). Localized disease (stage IE or IIE) was commonly treated with external beam radiation therapy (EBRT) with or without chemotherapy, while widespread lymphoma (stage IIIE or IVE) and MCL of any stage were managed with chemotherapy with or without EBRT. Diffuse large B-cell lymphoma and MCL had a poor prognosis, with 5-year disease-specific survival of 55.0% and 9.0%, respectively, in contrast to EMZL (97.0%) and FL (82.0%). Further survival predictors included age (EMZL), sex (FL), and Ann Arbor staging classification (EMZL and FL). The American Joint Committee on Cancer TNM staging showed limited prognostic usefulness, only being able to predict survival for patients with DLBCL.

**CONCLUSIONS AND RELEVANCE** Conjunctival lymphoma consists of mainly 4 subtypes of B-cell non-Hodgkin lymphoma: EMZL, FL, MCL, and DLBCL. Mantle cell lymphoma is characterized by a particularly high frequency of secondary disease of stage IVE and bilateral manifestation. The histological subtype is the main outcome predictor, with MCL and DLBCL having a markedly poorer prognosis than EMZL and FL.

*JAMA Ophthalmol.* doi:10.1001/jamaophthalmol.2015.6122  
Published online February 18, 2016.

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Lymphomas are neoplasms derived from clonal proliferations of lymphocytes and comprise a diverse group of diseases with more than 40 different subtypes.<sup>1</sup> Both nodal and extranodal forms can occur. Ocular adnexal lymphomas (OALs) constitute 2% of all extranodal lymphomas, and 25% to 30% of all OALs are located in the conjunctiva.<sup>2,3</sup>

Conjunctival lymphoma (CL) consists of mainly 4 subtypes of B-cell non-Hodgkin lymphoma (B-NHL). The 2 low-grade malignant neoplasias are extranodal marginal zone lymphoma (EMZL) and follicular lymphoma (FL), while the 2 high-grade B-NHLs are diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL). Extranodal marginal zone lymphoma constitutes more than one-half of the conjunctival B-NHLs.<sup>3,4</sup>

Conjunctival lymphoma occurs most frequently in middle-aged and elderly individuals as a painless patch that is salmon pink.<sup>4-6</sup> Generally, it is described as an indolent disease with a favorable survival.<sup>4,6</sup> However, previous studies<sup>6,7</sup> of CL have been based on cohorts of patients with different lymphoma subtypes. Because of the great diversity in clinical behavior and prognosis of different lymphoma subtypes, analyses focusing on each subtype are needed. Therefore, the aim of the present study was to evaluate subtype-specific clinical features of CL and their effect on survival in a large cohort of patients from 7 eye cancer centers.

## Methods

### Study Design

Eligible patients with a diagnosis of CL were identified from the databases of 7 eye cancer centers. The cases were collected from January 1, 1980, through December 31, 2010. The dates of the analysis were May 15, 2015, to August 20, 2015.

For histopathological examination, the specimens were stained with hematoxylin-eosin and analyzed immunohistochemically using a panel of antibodies. Current guidelines<sup>1</sup> recommend the following panel of antibodies for small cell lymphomas: CD3, CD5, CD10, CD20, CD23, CD79a, cyclin D-1, Bcl-2, Bcl-6, multiple myeloma oncogene 1 (MUM-1), methylation-inhibited binding protein 1 (MIB-1), and  $\kappa$  and  $\lambda$  light-chains. Guidelines recommend the following panel of antibodies for large cell lymphomas: CD3, CD5, CD10, CD20, CD30, CD79a, Bcl-2, Bcl-6, MUM-1, and MIB-2. Because the data collection spans over 30 years and encompasses 7 international eye cancer centers, not all the samples were analyzed in this uniform manner. However, the cancer centers have reviewed the specimens based on the current guidelines and reclassified them according to *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*.<sup>1</sup>

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 were obtained from the Danish Data Protection Agency.

### Clinical Data

Clinical data were recorded. These variables included age, sex, symptoms and clinical findings, laterality, systemic involve-

### Key Points

**Question:** What are the subtype-specific clinical features of conjunctival lymphoma and their effect on patient outcome?

**Findings:** Conjunctival mantle cell lymphoma and diffuse large B-cell lymphoma are frequently secondary diseases, with mantle cell lymphoma having a high occurrence of stage IVE lymphoma and bilateral manifestation. These lesions have a markedly poorer prognosis (5-year disease-specific survival, 55.0% for diffuse large B-cell lymphoma and 9.0% for mantle cell lymphoma) than their low-grade counterparts extranodal marginal zone lymphoma and follicular lymphoma (5-year disease-specific survival, 97.0% and 82.0%, respectively).

**Meaning:** These data suggest that the histological subtype is a major outcome predictor for patients with conjunctival lymphoma.

ment according to the Ann Arbor staging classification,<sup>8</sup> treatment modalities and response to therapy, survival duration, and cause of death.

Systemic involvement and laterality were determined using clinical information and diagnostic tools available at the time of diagnosis. Currently, a complete diagnostic procedure includes full-body positron emission tomography-computed tomography, computed tomography or magnetic resonance imaging of the conjunctiva, and a bone marrow biopsy.

Primary CL was defined as a biopsy-verified lymphoma limited to the ocular adnexal region (OAR) (stage IE) with or without involvement of unilateral preauricular or submandibular lymph nodes or adjacent structures (stage IIE) and no history of lymphoma disease. Therefore, secondary lymphoma included systemic lymphoma with a secondary manifestation in the OAR and ocular adnexal relapse of systemic lymphoma. The extent of ocular adnexal involvement of primary lymphomas was also evaluated according to the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging system for OAL.<sup>9</sup>

### Statistical Analysis

Overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS) were considered the primary end points. Overall survival was defined as the date of diagnosis to the date of death from any cause or the date of last contact, the latter being a censored event. Disease-specific survival was defined as the date of diagnosis to the date of death from lymphoma or to the date of last contact, the latter being a censored event. Progression-free survival was calculated from the date of diagnosis to either the date of first relapse or progression after initial treatment to the date of death from any cause or to the date of last contact, with the last 2 being censored events. Life tables and Kaplan-Meier plots were generated to visualize survival outcomes, and different risk groups were compared using the log-rank test. Individual risk factors were compared using the  $\chi^2$  test. Statistical calculations were performed using a software program (IBM SPSS Package, version 22; IBM Corporation).

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

| Subtype              | Eye Cancer Center |                 |                 |                |                 |                 |                |
|----------------------|-------------------|-----------------|-----------------|----------------|-----------------|-----------------|----------------|
|                      | CPH<br>(n = 79)   | LIV<br>(n = 70) | HYD<br>(n = 34) | NY<br>(n = 31) | HOU<br>(n = 31) | ATL<br>(n = 10) | MEL<br>(n = 8) |
| <b>EMZL</b>          |                   |                 |                 |                |                 |                 |                |
| No. of patients      | 53                | 39              | 26              | 24             | 24              | 9               | 5              |
| Median age, y        | 67                | 65              | 48              | 60             | 48              | 53              | 52             |
| Male to female ratio | 2:3               | 1:3             | 3:1             | 3:5            | 3:5             | 4:5             | 1:4            |
| <b>FL</b>            |                   |                 |                 |                |                 |                 |                |
| No. of patients      | 9                 | 14              | 7               | 6              | 4               | 1               | 2              |
| Median age, y        | 69                | 70              | 64              | 71             | 56              | 62              | 61             |
| Male to female ratio | 1:2               | 1:4             | 6:1             | 1:1            | 1:1             | 1:0             | 2:0            |
| <b>DLBCL</b>         |                   |                 |                 |                |                 |                 |                |
| No. of patients      | 4                 | 5               | 1               | 0              | 2               | 0               | 0              |
| Median age, y        | 74                | 75              | 82              | NA             | 48              | NA              | NA             |
| Male to female ratio | 1:3               | 3:2             | 1:1             | NA             | 1:1             | NA              | NA             |
| <b>MCL</b>           |                   |                 |                 |                |                 |                 |                |
| No. of patients      | 12                | 4               | 0               | 1              | 1               | 0               | 0              |
| Median age, y        | 70                | 70              | NA              | 73             | 34              | NA              | NA             |
| Male to female ratio | 3:1               | 4:0             | NA              | 0:1            | 1:0             | NA              | NA             |
| <b>PL</b>            |                   |                 |                 |                |                 |                 |                |
| No. of patients      | 0                 | 5               | 0               | 0              | 0               | 0               | 0              |
| Median age, y        | NA                | 62              | NA              | NA             | NA              | NA              | NA             |
| Male to female ratio | NA                | 1:4             | NA              | NA             | NA              | NA              | NA             |
| <b>LPL</b>           |                   |                 |                 |                |                 |                 |                |
| No. of patients      | 1                 | 3               | 0               | 0              | 0               | 0               | 0              |
| Median age, y        | 79                | 69              | NA              | NA             | NA              | NA              | NA             |
| Male to female ratio | 0:1               | 0:3             | NA              | NA             | NA              | NA              | NA             |
| <b>BL</b>            |                   |                 |                 |                |                 |                 |                |
| No. of patients      | 0                 | 0               | 0               | 0              | 0               | 0               | 1              |
| Median age, y        | NA                | NA              | NA              | NA             | NA              | NA              | 15             |
| Male to female ratio | NA                | NA              | NA              | NA             | NA              | NA              | 1:0            |

Abbreviations: ATL, Atlanta, Georgia; BL, Burkitt lymphoma; CPH, Copenhagen, Denmark; DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; HOU, Houston, Texas;

HYD, Hyderabad, India; LIV, Liverpool, England; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MEL, Melbourne, Australia; NA, not applicable; NY, New York, New York; PL, plasmacytoma.

## Results

In total, 268 patients with CL were identified from the databases of the following 7 eye cancer centers: Copenhagen, Denmark (n = 84); Liverpool, England (n = 70); Hyderabad, India (n = 34); New York, New York (n = 31); Houston, Texas (n = 31); Atlanta, Georgia (n = 10); and Melbourne, Australia (n = 8) (Table 1). Five patients from Copenhagen were excluded because of missing data, leaving 263 patients for analysis. All CLs were of B-NHL type. Seven subtypes of B-NHL were identified: EMZL (n = 180), FL (n = 43), MCL (n = 18), DLBCL (n = 12), plasmacytoma (PL) (n = 5), lymphoplasmacytic lymphoma (LPL) (n = 4), and Burkitt lymphoma (n = 1). The median follow-up period was 43 months.

### Extranodal Marginal Zone Lymphoma

#### Clinical Features

In total, 180 cases (68.4%) of EMZL were identified. One hundred four patients (57.8%) were female (Table 2). The median age was 60 years (age range, 8-92 years). Most patients had pri-

mary disease (158 of 180 [87.8%]) with a unilateral manifestation (147 of 180 [81.7%]). Tumor or swelling (90.3% [112 of 124]) was the most common symptom, and the most common clinical sign was a tumor mass (90.3% [112 of 124]) (eTable in the Supplement) (Figure 1). The median symptom duration was 6 months (range, 0.5-48 months). Most patients were initially seen with stage IE lymphoma (156 of 174 [89.7%]) according to the Ann Arbor staging classification (Table 2). The AJCC TNM staging was performed on the 159 patients with primary EMZL, 123 (77.4%) of whom had stage T1 disease.

#### Treatment

Patients with localized disease (stage IE or IIE) were mainly treated with EBRT with or without chemotherapy (90 of 109 [82.6%]), while patients with widespread disease (stage IIIE or IVE) were commonly managed with chemotherapy with or without EBRT (6 of 9 [66.7%]) (Table 3). The median EBRT dose was 20 Gy (range, 15-45 Gy) (to convert to rad, multiply by 100). The applied chemotherapy types included cyclophosphamide, vincristine, and prednisone (CVP), as well as cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone

Table 2. Clinical and Staging Characteristics of Patients by Subtype of Conjunctival Lymphoma<sup>a</sup>

| Characteristic                       | No. (%) of Patients |                |                   |                 |               |                |               |
|--------------------------------------|---------------------|----------------|-------------------|-----------------|---------------|----------------|---------------|
|                                      | EMZL<br>(n = 180)   | FL<br>(n = 43) | DLBCL<br>(n = 12) | MCL<br>(n = 18) | PL<br>(n = 5) | LPL<br>(n = 4) | BL<br>(n = 1) |
| Sex                                  |                     |                |                   |                 |               |                |               |
| Male                                 | 76 (42.2)           | 20 (46.5)      | 6 (50.0)          | 14 (77.8)       | 1             | 0              | 1             |
| Female                               | 104 (57.8)          | 23 (53.5)      | 6 (50.0)          | 4 (22.2)        | 4             | 4              | 0             |
| Age at presentation, y               |                     |                |                   |                 |               |                |               |
| ≤60                                  | 92 (51.1)           | 16 (37.2)      | 2 (16.7)          | 1 (5.6)         | 1             | 1              | 1             |
| >60                                  | 88 (48.9)           | 27 (62.8)      | 10 (83.3)         | 17 (94.4)       | 4             | 3              | 0             |
| Primary disease                      | 158 (87.8)          | 27 (62.8)      | 7 (58.3)          | 2 (11.1)        | 5             | 2              | 1             |
| Disseminated disease                 | 13 (7.2)            | 10 (23.3)      | 3 (25.0)          | 12 (66.7)       | 0             | 1              | 0             |
| Relapsed                             | 9 (5.0)             | 6 (14.0)       | 2 (16.7)          | 4 (22.2)        | 0             | 0              | 0             |
| Laterality                           |                     |                |                   |                 |               |                |               |
| Unilateral                           | 147 (81.7)          | 29 (67.4)      | 10 (83.3)         | 4 (22.2)        | 4             | 3              | 1             |
| Bilateral                            | 33 (18.3)           | 14 (32.6)      | 2 (16.7)          | 14 (77.8)       | 1             | 0              | 0             |
| Ann Arbor stage                      |                     |                |                   |                 |               |                |               |
| IE                                   | 156/174 (89.7)      | 28 (65.1)      | 7 (58.3)          | 2 (11.1)        | 4             | 1              | 1             |
| IIE                                  | 6/174 (3.4)         | 5 (11.6)       | 1 (8.3)           | 1 (5.6)         | 1             | 1              | 0             |
| IIIE                                 | 1/174 (0.6)         | 4 (9.3)        | 3 (25.0)          | 4 (22.2)        | 0             | 0              | 0             |
| IVE                                  | 11/174 (6.3)        | 6 (14.0)       | 1 (8.3)           | 11 (61.1)       | 0             | 1              | 0             |
| AJCC TNM stage                       |                     |                |                   |                 |               |                |               |
| T1                                   | 123/159 (77.4)      | 19/28 (67.9)   | 3/6 (50.0)        | 1/3 (33.3)      | 4             | 2              | 1             |
| T2                                   | 35/159 (22.0)       | 5/28 (17.9)    | 3/6 (50.0)        | 2/3 (66.7)      | 0             | 0              | 0             |
| T3                                   | 1/159 (0.6)         | 4/28 (14.3)    | 0                 | 0               | 0             | 0              | 0             |
| T4                                   | 0                   | 0              | 0                 | 0               | 1             | 0              | 0             |
| Recurrence                           |                     |                |                   |                 |               |                |               |
| Yes                                  | 64/169 (37.9)       | 18/42 (42.9)   | 8 (66.7)          | 13/16 (81.3)    | 5             | 3              | 0             |
| No                                   | 105/169 (62.1)      | 24/42 (57.1)   | 4 (33.3)          | 3/16 (18.8)     | 0             | 1              | 0             |
| Site of recurrence                   |                     |                |                   |                 |               |                |               |
| OAR                                  | 31/50 (62.0)        | 6/18 (33.3)    | 0                 | 1/12 (8.3)      | 0             | 0              | 0             |
| OAR plus nodal and/or extranodal     | 5/50 (10.0)         | 4/18 (22.2)    | 3/7 (42.9)        | 7/12 (58.3)     | 5             | 0              | 0             |
| Nodal and/or extranodal              | 14/50 (28.0)        | 8/18 (44.4)    | 4/7 (57.1)        | 4/12 (33.3)     | 0             | 3              | 0             |
| Disease status at last follow-up     |                     |                |                   |                 |               |                |               |
| Complete remission                   | 110 (61.1)          | 23 (53.5)      | 2 (16.7)          | 4 (22.2)        | 0             | 0              | 1             |
| Alive with disease                   | 28 (15.6)           | 10 (23.3)      | 1 (8.3)           | 2 (11.1)        | 1             | 1              | 0             |
| Dead from lymphoma                   | 7 (3.9)             | 8 (18.6)       | 6 (50.0)          | 11 (61.1)       | 3             | 2              | 0             |
| Dead from other causes than lymphoma | 35 (19.4)           | 2 (4.7)        | 3 (25.0)          | 1 (5.6)         | 1             | 0              | 0             |

Abbreviations: AJCC, American Joint Committee on Cancer; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma;

MCL, mantle cell lymphoma; OAR, ocular adnexal region; PL, plasmacytoma.

<sup>a</sup> Data are not specified for all patients.

(CHOP) in combination with rituximab (R-CHOP), alkylating agents, and unspecified chemotherapy.

#### Treatment Outcome and Survival

Disease recurrence was observed in 37.9% (64 of 169) of patients with conjunctival EMZL (Table 2). The time to recurrence was accessible in 33 of these patients, with a median of 24 months (range, 3-192 months). Survival data were available for all 180 patients with EMZL. The median PFS was 11.3 years. The OS rates at 5, 10, and 20 years were 83.0%, 65.0%, and 43.0%, respectively (median, 16.3 years; 95% CI, 11.9-20.7 years), whereas the 5-year, 10-year, and 20-year DSS rates were 97.0%, 93.0%, and 89.0%, respectively (Figure 2A). Analysis of low-grade CLs, including EMZL, showed that an Ann Arbor stage higher than IE was associated with decreased DSS ( $P = .03$ ) (Figure 2B). Furthermore, patients older than 60 years with EMZL had

poorer DSS (20-year DSS, 83.0%) than younger patients (20-year DSS, 100.0%) ( $P = .01$ ).

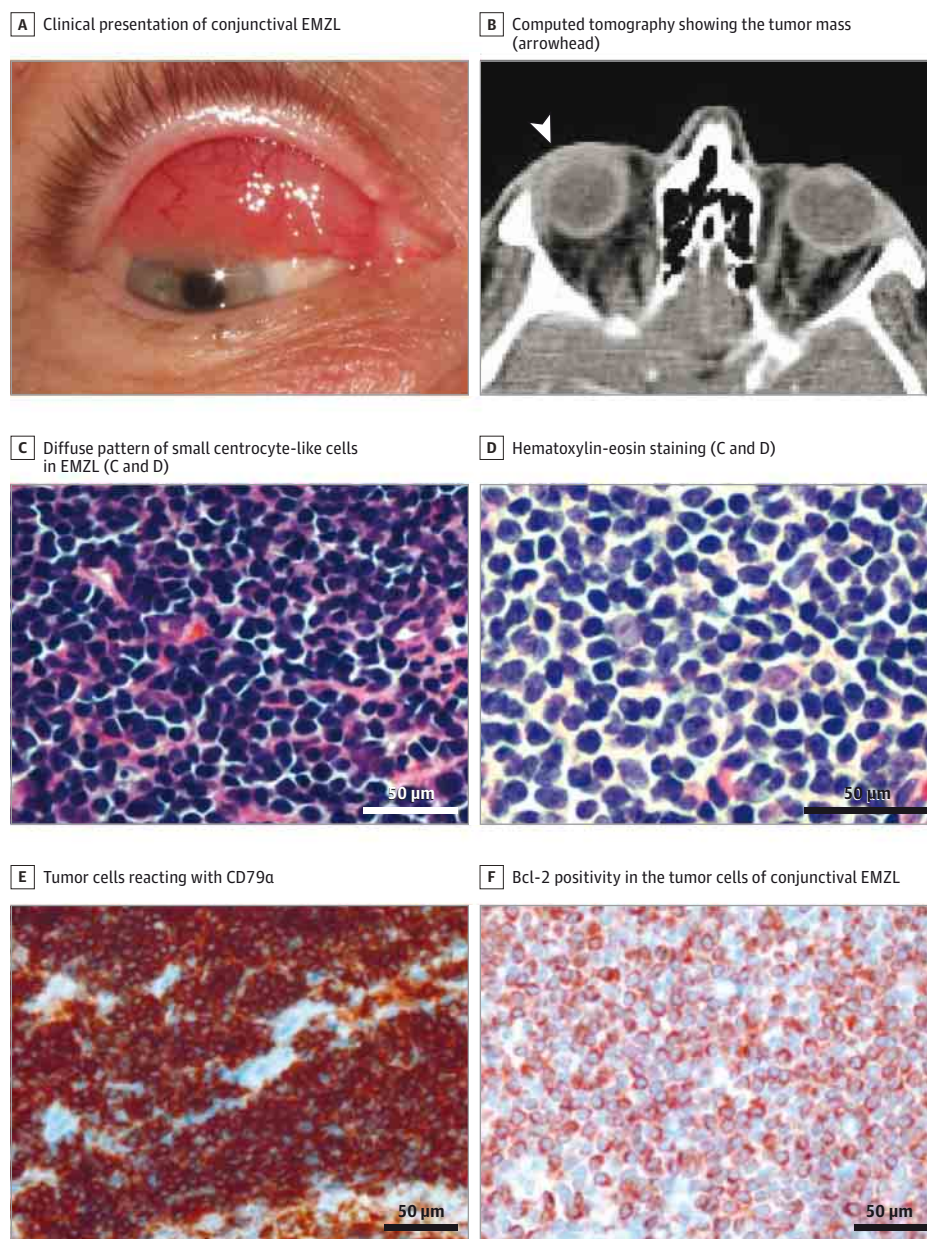
#### Follicular Lymphoma

##### Clinical Features

Forty-three cases (16.3%) of FL were identified from the database. Twenty-three patients (53.5%) were female (Table 2). The median age was 67 years (age range, 33-89 years). Most patients had primary CL (27 of 43 [62.8%]) with unilateral manifestation (29 of 43 [67.4%]). Tumor or swelling (21 of 25 [84.0%]) was the most common symptom, and the most common clinical sign was a tumor mass (22 of 26 [84.6%]). The median symptom duration was 6 months (range, 2-48 months) (eTable in the Supplement). Most patients were initially seen with stage IE lymphoma (28 of 43 [65.1%]) according to the Ann Arbor staging classification (Table 2). The AJCC TNM staging was performed on the 28



Figure 1. Clinical and Histological Findings of EMZL



EMZL indicates extranodal marginal zone lymphoma.

patients with conjunctival FL, 19 (67.9%) of whom were seen with stage T1 disease.

#### Treatment

Patients with localized disease were mainly treated with EBRT with or without chemotherapy (22 of 24 [91.7%]), while patients with widespread disease were commonly managed with chemotherapy with or without EBRT (8 of 10 [80.0%]) (Table 3). The median EBRT dose was 20 Gy (range, 20-45 Gy). The applied chemotherapy types included CHOP, R-CHOP, alkylating agents, antimetabolites, and unspecified chemotherapy.

#### Treatment Outcome and Survival

Disease recurrence was observed in 42.9% (18 of 42) of patients with conjunctival FL (Table 2). The time to recurrence was accessible in 6 of these patients, with a median of 28 months (range, 13-161 months). Survival data were available for all 43 patients with FL. The median PFS was 6.7 years. The OS rates at 5 and 10 years were 75.0% and 59.0%, respectively, whereas the 5-year and 10-year DSS rates were 82.0% and 65.0%, respectively (Figure 2A). Analysis of low-grade CLs, including FL, showed that an Ann Arbor stage higher than IE was associated with decreased DSS ( $P = .03$ ) (Figure 2B). Furthermore, female patients with FL had

Table 3. Management of Patients by Subtype of Conjunctival Lymphoma

| Stage                  | No. (%) of Patients <sup>a</sup> |               |          |                    |                             |           |         |
|------------------------|----------------------------------|---------------|----------|--------------------|-----------------------------|-----------|---------|
|                        | EBRT                             | EBRT Plus CTX | CTX      | CTX Plus Rituximab | EBRT and CTX Plus Rituximab | Rituximab | Surgery |
| <b>EMZL</b>            |                                  |               |          |                    |                             |           |         |
| IE or IIE              | 75 (68.8)                        | 15 (13.8)     | 7 (6.4)  | 1 (9.2)            | 0                           | 9 (8.3)   | 2 (1.8) |
| IIIE or IVE            | 2 (22.2)                         | 1 (11.1)      | 4 (44.4) | 1 (11.1)           | 0                           | 1 (11.1)  | 0       |
| <b>FL</b>              |                                  |               |          |                    |                             |           |         |
| IE or IIE              | 14 (58.3)                        | 8 (33.3)      | 2 (8.3)  | 0                  | 0                           | 0         | 0       |
| IIIE or IVE            | 1 (10.0)                         | 3 (30.0)      | 3 (30.0) | 2 (20.0)           | 0                           | 1 (10.0)  | 0       |
| <b>DLBCL</b>           |                                  |               |          |                    |                             |           |         |
| IE or IIE              | 5 (62.5)                         | 1 (12.5)      | 0        | 2 (25.0)           | 0                           | 0         | 0       |
| IIIE or IVE            | 0                                | 3 (75.0)      | 0        | 1 (25.0)           | 0                           | 0         | 0       |
| <b>MCL</b>             |                                  |               |          |                    |                             |           |         |
| IE or IIE              | 0                                | 0             | 1        | 0                  | 1                           | 0         | 0       |
| IIIE or IVE            | 2 (14.3)                         | 5 (35.7)      | 2 (14.3) | 5 (35.7)           | 0                           | 0         | 0       |
| <b>PL<sup>b</sup></b>  |                                  |               |          |                    |                             |           |         |
| IE or IIE              | 4                                | 1             | 0        | 0                  | 0                           | 0         | 0       |
| <b>LPL<sup>c</sup></b> |                                  |               |          |                    |                             |           |         |
| IE or IIE              | 2                                | 0             | 0        | 0                  | 0                           | 0         | 0       |
| <b>BL<sup>d</sup></b>  |                                  |               |          |                    |                             |           |         |
| IE or IIE              | 0                                | 0             | 1        | 0                  | 0                           | 0         | 0       |

Abbreviations: BL, Burkitt lymphoma; CTX, chemotherapy; DLBCL, diffuse large B-cell lymphoma; EBRT, external beam radiation therapy; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; PL, plasmacytoma.

<sup>a</sup> Data are not specified for all patients. All percentages are row percentages.

<sup>b</sup> All conjunctival PLs were stage IE or IIE disease.

<sup>c</sup> No treatment data were available for LPL higher than stage IIE.

<sup>d</sup> The case of conjunctival BL was stage IE disease.

poorer DSS (10-year DSS, 43.0%) than male patients (10-year DSS, 100.0%) ( $P = .008$ ).

### Diffuse Large B-Cell Lymphoma

#### Clinical Features

Twelve cases of DLBCL (4.6%) were identified from the database. Six patients (50.0%) were male (Table 2). The median age was 74 years (age range, 30-89 years). Almost half of all the cases were secondary lymphomas (5 of 12 [41.7%]). Most patients were initially seen with unilateral disease (10 of 12 [83.3%]). Tumor or swelling (3 of 7 [42.9%]) and irritation or pain (3 of 7 [42.9%]) were the most common symptoms, while the most common clinical sign was a tumor mass (5 of 7 [71.4%]) (eTable in the [Supplement](#)). The median symptom duration was 5 months (range, 0.5-48 months). Just over half of the patients were seen with stage IE lymphoma (7 of 12 [58.3%]) according to the Ann Arbor staging classification (Table 2). The AJCC TNM staging was performed on 6 patients with primary DLBCL, 3 of whom had stage T1 disease and 3 of whom had stage T2 disease.

#### Treatment

Patients with localized disease were mainly treated with EBRT with or without chemotherapy (6 of 8 [75.0%]), while patients with widespread lymphoma were managed with chemotherapy with or without EBRT (4 of 4) (Table 3). Information on EBRT doses was available in 3 patients, and the median dose was 30 Gy (range, 26-40 Gy). The applied chemotherapy types included R-CHOP and unspecified chemotherapy.

### Treatment Outcome and Survival

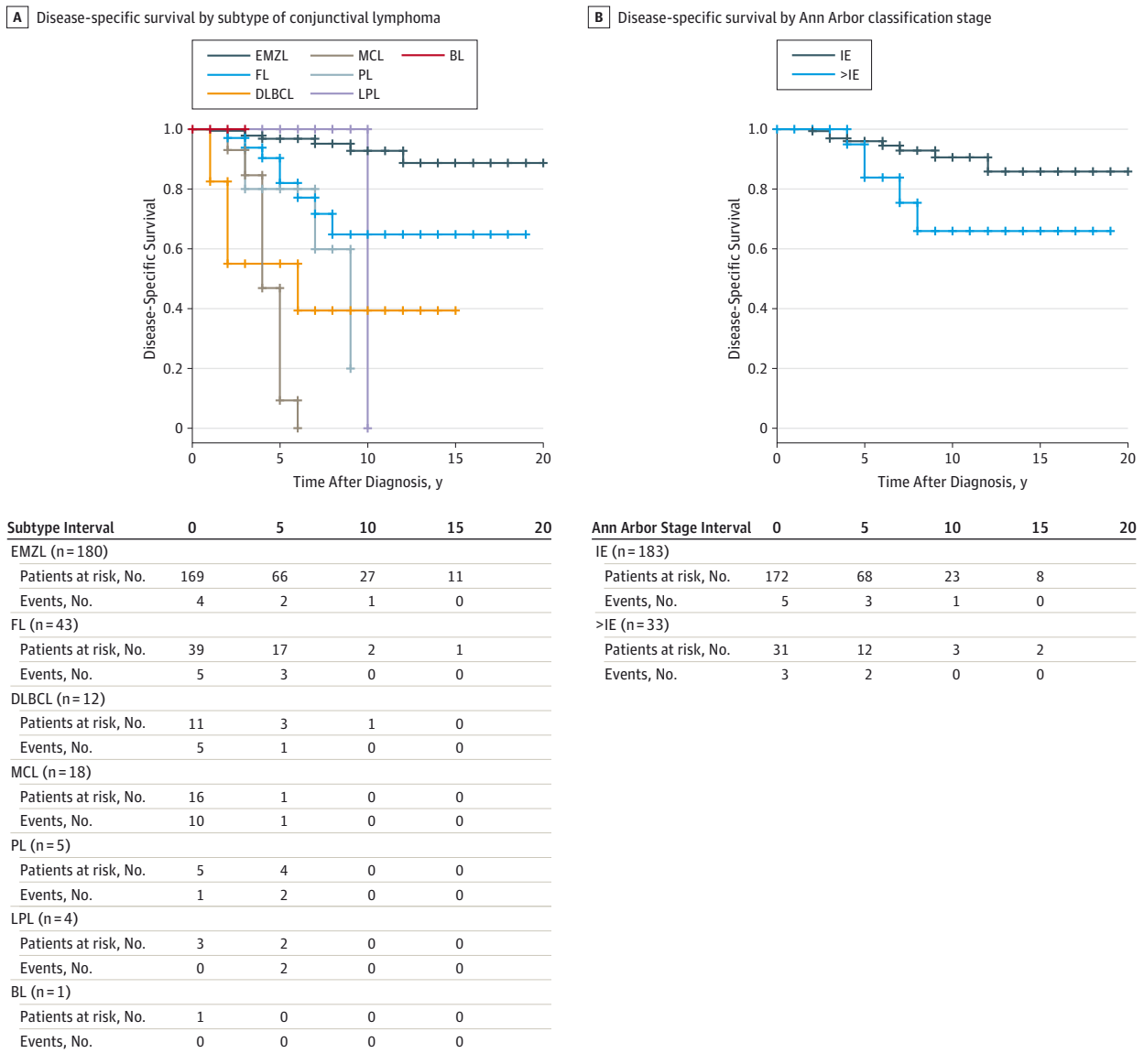
Disease recurrence was observed in 66.7% (8 of 12) of patients with conjunctival DLBCL (Table 2). The time to recurrence was accessible in 4 of these patients, with a median of 10 months (range, 2-23 months). Survival data were available for all 12 patients with DLBCL. The median PFS was 3.5 years. The 5-year and 10-year OS was 44.0% and 16.0%, respectively (median, 4.7 years; 95% CI, 0.1-7.9 years), whereas the 5-year and 10-year DSS was 55.0% and 39.0%, respectively (median, 5.8 years; 95% CI, 0.1-10.1 years) (Figure 2A). Advanced AJCC TNM stage (T2 vs T1) was associated with a poor DSS for patients with conjunctival DLBCL ( $P = .03$ ).

### Mantle Cell Lymphoma

#### Clinical Features

Eighteen cases of MCL (6.8%) were identified from the database. Fourteen patients (77.8%) were male (Table 2). The median age was 72 years (age range, 34-90 years). Most patients had secondary disease (16 of 18 [88.9%]) with a bilateral manifestation (14 of 18 [77.8%]). Tumor or swelling (10 of 14 [71.4%]) was the most common symptom, and the most common clinical signs were a tumor mass and chemosis (6 of 14 [42.9%], respectively) (eTable in the [Supplement](#)). The median symptom duration was 4 months (range, 1-24 months). Most patients were initially seen with stage IVE MCL (11 of 18 [61.1%]) according to the Ann Arbor staging classification (Table 2). The AJCC TNM staging was performed on the 2 cases of primary conjunctival MCL, both of which were T2 disease.

Figure 2. Disease-Specific Survival Among Patients With Conjunctival Lymphoma



A, Disease-specific survival is associated with the subtype of conjunctival lymphoma. EMZL has the most favorable disease-specific survival, while MCL has the poorest disease-specific survival ( $P = <.001$ ). B, Stage  $>IE$  is associated with lower disease-specific survival than stage IE for low-grade conjunctival

lymphomas ( $P = .03$ ). BL indicates Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; and PL, plasmacytoma.

Treatment

Patients with conjunctival MCL mainly received chemotherapy with or without EBRT treatment for both localized (2 of 2) and widespread disease (12 of 14 [85.7%]) (Table 3). Information on EBRT dose was available in one patient, who received 30 Gy. The applied chemotherapy types included CHOP, R-CHOP, and alkylating agents, as well as hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) and unspecified chemotherapy.

Treatment Outcome and Survival

Disease recurrence was observed in 81.3% (13 of 16) of patients with conjunctival MCL (Table 2). The time to recur-

rence was accessible in 7 of these patients, with a median of 24 months (range, 4-49 months). Survival data were available for all 18 patients with MCL. The median PFS was 2.7 years. Overall survival and DSS at 5 years and 10 years were 9.0% and 0.0%, respectively (median, 3.9 years; 95% CI, 2.9-4.8 years) (Figure 2A). Survival outcomes did not appear to be different in patients who received rituximab-containing chemotherapy compared with other treatment regimens ( $P = .50$ ).

Plasmacytoma

Five cases of PL were identified from the database. The diagnosis of PL was made in association with the clinical information presented at a multidisciplinary tumor board. Four pa-

tients were female, and the median age was 62 years (age range, 16-64 years) (Table 2). Unilateral lesions were seen in 4 cases. All 5 PLs were primary disease, 4 stage IE lymphomas and one stage IIE lymphoma. These conjunctival lesions were managed with EBRT with or without chemotherapy (Table 3). All 5 patients had recurrence of disease. Survival data were available for all 5 PL cases. Overall survival and DSS at 5 years were 80.0% (4 of 5) (median, 8.5 years; 95% CI, 5.5-11.9 years), while OS at 10 years was 0% (0 of 5) (Figure 2A).

### Lymphoplasmacytic Lymphoma

Four cases of LPL were identified from the database. The diagnosis of LPL was made in association with the clinical information presented at a multidisciplinary tumor board (eg, raised serum IgM levels and increased serum viscosity values). All 4 patients with LPL in the study were female, with a median age of 74 years (age range, 26-83 years) (Table 2). Unilateral disease (3 of 3) and primary presentation (2 of 3) were common among patients with LPL. These conjunctival lesions were all managed with EBRT (Table 3). All patients had recurrence of disease. Survival data were available for 3 patients with LPL. Overall survival and DSS at 5 years and 10 years were 100% (3 of 3) and 0% (0 of 3), respectively (median, 9.4 years; 95% CI, 1.1-17.7 years) (Figure 2A).

### Burkitt Lymphoma

One patient with Burkitt lymphoma was identified from the database. He was 15-year-old boy who had primary CL (stage IE) with unilateral manifestation. The patient received 2 cycles of CHOP, with a cumulative dose of doxorubicin at 120 mg/m<sup>2</sup>. The patient was in complete remission at 25 months after the diagnosis.

## Discussion

Among 263 patients, CL was found to consist of mainly 4 subtypes of B-NHL: EMZL (68.4% [n = 180]), FL (16.3% [n = 43]), MCL (6.8% [n = 18]), and DLBCL (4.6% [n = 12]). The histological subtype was the main outcome predictor, with MCL and DLBCL (5-year DSS, 9.0% and 55.0%, respectively) having a markedly poorer prognosis than EMZL and FL (5-year DSS, 97.0% and 82.0%, respectively). This result is in accord with our group's and others' previous findings.<sup>4,10,11</sup> Age older than 60 years (for EMZL), female sex (for FL), Ann Arbor stage higher than IE (for EMZL and FL), and T category exceeding T1 of the AJCC TNM staging classification (for DLBCL) were likewise predictive of poor outcome.

The retrospective design of this multicenter study poses some inherent limitations. The data were pooled across 7 eye cancer centers over a 30-year period, entailing incomplete medical records and varying diagnostic methods. Furthermore, the median follow-up was 43 months, which—given the indolent nature of many of the lesions—may not have been enough time to detect the outcome variables. On the other hand, multicenter studies like this one provide valuable information on rare lesions and should be encouraged to obtain a reasonable number of patients.

The predominance of EMZL, observed in the conjunctiva, is found at many other mucosa-associated lymphoid tissue (MALT) sites, such as the stomach and the lungs,<sup>12,13</sup> with the exception of Waldeyer ring (nasopharynx and oropharynx) and Peyer patches (ileum), which are seldom sites for EMZL to develop, despite the abundance of MALT.<sup>14-16</sup> The frequency of DLBCL is markedly low in the conjunctiva (5%) compared with the remaining OAR (13%)<sup>3</sup> and compared with many MALT sites, particularly Waldeyer ring, where DLBCL is the dominant subtype.<sup>12,14,15,17,18</sup> The low frequency of DLBCL in the conjunctiva is corroborated by the results of other studies.<sup>3,4,11</sup>

Extranodal marginal zone lymphoma was found to be more common in New York and Hyderabad than in Liverpool (*P* = .04), which may be due to an underlying selection bias because the aggressive subtypes were probably primarily managed in the largest eye cancer centers. Furthermore, EMZL and FL in Hyderabad, unlike at other participating centers, had a marked male predominance. This finding may be related to differing demographic patterns among geographical regions but is consistent with observations of our group's multicenter study<sup>19</sup> of ocular adnexal FL.

Current lymphoma treatment guidelines recommend R-CHOP or R-CHOP-like chemotherapy for management of MCL and DLBCL, as well as high-stage EMZL and FL with high tumor burden.<sup>20-23</sup> This type of therapy was only applied in 6 MCLs, 3 DLBCLs, 2 FLs, and 2 EMZLs in the present study, which may be owing to the fact that the study spanned over a 30-year period and rituximab has only been available since 1997. This rationale may partially explain the fact that the outcome of conjunctival DLBCL and MCL in the present study was poorer compared with survival rates of these lymphomas in general.<sup>24-27</sup>

The AJCC TNM staging classification allowed a precise characterization of the extent of local disease for CLs, which in turn provided a larger staging distribution.<sup>28</sup> The predictive ability of the T category for patients with DLBCL is consistent with the results of our group's multicenter study of ocular adnexal DLBCL.<sup>29</sup> However, because no associations to date have been detected between the T category and patient outcome for the remaining subtypes, the AJCC TNM staging may be of limited prognostic usefulness for CLs.

## Conclusions

The results of this study in 263 patients confirm that CL consists of mainly 4 subtypes of B-NHL: EMZL (68.4% [n = 180]), FL (16.3% [n = 43]), MCL (6.8% [n = 18]), and DLBCL (4.6% [n = 12]). The histological subtype was identified as the major outcome predictor, with MCL and DLBCL having a markedly poorer prognosis than EMZL and FL. The study was limited by its retrospective nature and loss to follow-up owing to the indolent nature of some of the CLs. However, multicenter studies like this one should be encouraged for future trials to include a reasonable number of patients.



## ARTICLE INFORMATION

**Submitted for Publication:** September 23, 2015; final revision received November 28, 2015; accepted December 5, 2015.

**Published Online:** February 18, 2016.  
doi:10.1001/jamaophthalmol.2015.6122.

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**Obtained funding:** Kirkegaard, Prause.

**Administrative, technical, or material support:** Rasmussen, Coupland, Esmaili, Finger, Graue, Grossniklaus, Khong, Mulay, Sjö, Toft, Thuro.

**Study supervision:** Rasmussen, Honavar, McKelvie, Prause, Ralfkiaer, Sjö, Toft, Vemuganti, Heegaard.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.

**Funding/Support:** This work was supported by grants from Fight for Sight Denmark, the Danish Cancer Society, the Danish Eye Research

Foundation, Synoptik Foundation, the Danish Foundation for Cancer Research, Engineer Lars Andersens Foundation, the A.P. Møller Foundation for the Advancement of Medical Science, and the Merchant Kjaer and Wife Kjaer, born la Cour-Holmens Foundation.

**Role of the Funder/Sponsor:** The funding sources and organizations had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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