Malignant Lymphoma of the Lacrimal Gland

A Nation-Based Study

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Objective: To characterize the clinicopathologic features of lacrimal gland lymphoma.

Methods: All cases of lacrimal gland lymphoma from January 1, 1975, through December 31, 2009, were retrieved from The Danish Registry of Pathology. Histologic specimens were reevaluated using a panel of monoclonal antibodies. Clinical files from all patients with confirmed lymphoma were collected.

Results: Twenty-seven patients with lacrimal gland lymphoma were identified. Eight of the patients were men and 19 were women; the median (range) age was 69 (43-87) years. The distribution of lymphoma subtypes was as follows: extranodal marginal zone lymphoma, 10 (37%); follicular lymphoma, 5 (19%); diffuse large B-cell lymphoma, 4 (15%); mantle cell lymphoma, 3 (11%); chronic lymphocytic leukemia/small lymphatic lymphoma, 2 (7%); and unclassified B-cell lymphoma, 3 (11%). Twenty-two patients (81%) had stage I or II lymphoma, 1 patient (4%) had stage III lymphoma, and 4 patients (15%) had stage IV lymphoma. Patients with stage I or II lymphoma were treated with radiotherapy (15 [67%]), chemotherapy (3 [14%]), chemotherapy plus radiotherapy (1 [5%]), and surgery (3 [14%]). Patients presenting with stage III or IV lymphoma were treated with chemotherapy alone. Complete remission was observed in 23 of the patients (85%), although 12 (44%) of these had a relapse, independent of subtype, stage, or treatment. The 5-year overall survival was 70%.

Conclusions: Malignant lymphoma of the lacrimal gland is relatively rare and is mostly prevalent in elderly women. The distribution of lacrimal gland lymphoma subtypes resembles that of lymphoma subtypes of the salivary glands. The majority of lacrimal gland lymphomas are low grade, and the prognosis is relatively good.

Arch Ophthalmol. 2011;129(10):1275-1280

Malignant lymphomas are neoplasms derived from clonal proliferations of lymphocytes. Malignant lymphomas comprise a diverse group of diseases, with more than 40 different subtypes defined in the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. Both nodal and extranodal forms can occur. Ocular adnexal lymphomas (ie, lymphomas of the orbit, eyelids, conjunctiva, lacrimal gland, and lacrimal sac) constitute 2% of all extranodal lymphomas and are the most common malignant tumors of the orbit. Lacrimal gland lymphomas are relatively rare, representing 7% to 26% of ocular adnexal lymphomas. However, 37% of all malignant tumors of the lacrimal gland are lymphomas (S. Von Holstein, MD, unpublished data, 2010).

Lymphomas of the lacrimal gland have previously been classified as an orbital disease, with respect to clinical features and prognosis. In fact, the lacrimal gland is the only orbital structure to contain lymphoid tissue and is recognized as part of the eye-associated lymphoid tissue. In contrast, the orbit itself does not contain lymphoid cells or lymphatic vessels and is regarded as an extralymphatic site. Primary lacrimal gland lymphoma is associated with a higher risk for systemic disease mortality compared with the corresponding risk associated with primary lymphoma of the orbit and conjunctiva. However, the literature on lymphoma subtype–specific prognosis is limited to studies including relatively few patients.

In this study, we evaluate the histologic and clinical features of a large population comprising all patients with histologically verified lacrimal gland lymphoma who were...
diagnosed in Denmark from January 1, 1975, through December 31, 2009.

METHODS

DATA COLLECTION AND BIOPSY SPECIMENS

The study was performed as a case series. Patients diagnosed as having lymphoma of the lacrimal gland were identified using systematized nomenclature of medicine codes (SNOMED codes) to search the Danish Registry of Pathology for the years 1975 through 2009. Formalin-fixed, paraffin-embedded specimens from all the identified cases were retrieved from the archives of several Danish pathology departments. For histopathologic examination, all sections were stained with hematoxylin and eosin and by immunohistochemistry, using the following panel of antibodies: bcl-2, bcl-6, CD3, CD5, CD10, CD20, CD23, CD79a, cyclin D-1, MUM-1, and MB-1 (Ki-67). Two independent pathologists (E.R. and S.H.) performed the examinations and reviewed the samples in consensus to reclassify the specimens according to the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues.2

CLINICAL DATA

Clinical files from the identified patients were retrieved and reviewed to record the following data: year of diagnosis, sex, age, symptoms and clinical findings, staging procedures, evidence of systemic involvement according to the Ann Arbor staging classification3 and the TNM staging system of ocular adnexal lymphomas,4 presence of B-symptoms, paracranial findings including serum lactate dehydrogenase levels, performance status, treatment modalities and response to therapy, recurrence-free period, time and localization of relapse, survival duration, disease stage at last follow-up, and time and cause of death. If the clinical files did not provide information on the date and cause of death, additional data were obtained from the Danish Registry of Causes of Death.

Response criteria were assessed as complete remission, partial remission, stable disease, or relapsed/progressive disease, as defined in the revised response criteria for malignant lymphoma.5 We defined primary lymphoma of the lacrimal gland as follows: (1) a biopsy-verified lymphoma of the lacrimal gland, with no evidence of concurrent systemic lymphoma after a clinical evaluation, including a bone marrow biopsy and 1 or more imaging techniques (positron emission tomography, full-body magnetic resonance imaging, or full-body computed tomography) and (2) no history of lymphoma disease. Secondary lymphoma of the lacrimal gland was defined as a lymphoma of the lacrimal gland with concurrent systemic lymphoma at the time of evaluation and/or a history of lymphoma disease.

Lymphoma imaging evaluation has changed significantly during the 33-year study period, in line with the development of new techniques. In the present study, imaging evaluation during the period from 1975 to 1994 consisted of 1 or more procedures, such as regional computed tomography/magnetic resonance imaging, chest radiograph, and abdominal ultrasonography. From 1995 to 2009, imaging evaluation included positron emission tomography and/or full-body computed tomography and/or full-body magnetic resonance imaging.

STATISTICAL ANALYSES

Overall survival and progression-free survival were considered primary end points. Overall survival was defined as the time from the date of diagnosis to the date of death from any cause, or to the date of last contact, the latter being a censoring event. Progression-free survival was calculated as the time from the date of diagnosis to the date of first relapse/progression after initial treatment, the date of death from any cause, or the date of last contact, the latter 2 being censoring events.6 The Kaplan-Meier method was used to visualize the overall survival and progression-free survival.

The influence of clinical characteristics, specifically lymphoma subtypes, on overall survival and progression-free survival was assessed by using Cox regression models (with age as an underlying scale).7 Analyses were conducted both unadjusted and after adjustment for sex and age at the time of diagnosis. P < .05 was considered significant. Statistical calculations were performed using SAS, version 9.1 (SAS Institute, Cary, North Carolina). The study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee and the Danish Data Protection Agency.

RESULTS

CLINICAL FEATURES

Twenty-seven patients with malignant lymphoma of the lacrimal gland were identified in Denmark (population: approximately 5 1/2 million). Eight (30%) of the patients were men and 19 (70%) were women; the median (range) age was 69 (43-87) years (Table 1). Cases were evenly distributed during the 35-year study period.

Of the 27 patients, 15 (56%) were diagnosed as having primary lacrimal gland lymphoma and 12 (44%) had secondary lacrimal gland involvement. Women predominated in the group with primary lymphoma, whereas for the secondary lymphoma group, women were slightly more prevalent than men. The distribution of primary and secondary lymphoma subtypes is shown in Table 1.

Swelling (23 [85%]) was the most frequent symptom (Figure 1). Seven patients (26%) also reported pain and/or irritation, and 6 (22%) reported proptosis (Table 2).

Symptom duration ranged from 1 to 96 months (median, 5.5 months). The most frequent clinical signs were a visible or palpable mass of the lacrimal gland (23 [85%]) and proptosis or displacement of the eyeball (15 [56%]).

The lacrimal gland was the presenting site of the lymphoma in 21 (78%) of the patients (Table 1). Of these 21 patients, 4 (19%) were diagnosed as having an advanced stage of disease (Ann Arbor stage III or IV). B-symptoms (ie, fever, night sweats, and weight loss) were reported by 4 of the 27 patients (15%). None of the 27 patients had previously received a diagnosis of an autoimmune disease.

Eighteen patients (67%) were classified as having stage 1 at the time of diagnosis. Of these, 15 patients had primary lymphoma. Four patients (15%) had stage II disease, 1 (4%) had stage III, and 4 (15%) had stage IV (disseminated disease).

The 15 cases of primary lymphoma of the lacrimal gland were additionally classified according to the TNM staging system of ocular adnexal lymphomas8 (Table 1). In 7 cases (47%), the tumor mass was limited to the lacrimal gland (T2b), whereas in 2 cases (13%) there was bilateral lacrimal gland involvement (bT2b), and in 6 cases (40%) the tumor mass extended to the posterior part of the orbit (T2c).
The 27 lacrimal gland lymphoma cases were reclassified as extranodal marginal zone lymphoma (10 [37%]) (Figure 1), follicular lymphoma (5 [19%]), diffuse large B-cell lymphoma (4 [15%]), mantle cell lymphoma (3 [11%]), or chronic lymphocytic leukemia/small lymphocytic lymphoma (2 [7%]). Three cases (11%) could not be further classified because of insufficient tissue material or an uncharacteristic phenotype.

INITIAL THERAPY

Patients with localized disease (stage I or II) were treated with radiotherapy (15 [67%]), chemotherapy (3 [14%]), chemotherapy in combination with radiotherapy (1 [5%]), and surgery (3 [14%]). Patients with widespread disease (stage III or IV) were treated with chemotherapy alone (Table 1).

TREATMENT OUTCOME AND SURVIVAL

Relapse or disease progression was experienced by 12 patients (44%), with a median of 40 months, during a follow-up period ranging from 4 to 290 months. Three patients (11%) had a relapse in the ocular adnexal region and 1 of these in the lacrimal gland.

The 5-year progression-free survival was 59%. The median progression-free survival from the time of diagnosis of lacrimal gland lymphoma was 65 months. Overall 5-year survival was 100% in follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and mantle cell lymphoma; 75% in extranodal marginal zone lymphoma; 25% in diffuse large B-cell lymphoma; and 33% in unclassified B-cell lymphoma (Figure 2). For the entire study group, the 5-year overall survival was 70%. Sixteen patients (59%) died during follow-up. Of these 16 patients, 7 (44%) died of lymphoma.

**Table 1. Clinical and Staging Characteristics of 27 Patients With Lymphoma of the Lacrimal Gland, Distributed According to Lymphoma Subtype**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Patients, No. (%)</th>
<th>EMZL (n=10)</th>
<th>FL (n=5)</th>
<th>DLBCL (n=4)</th>
<th>MCL (n=3)</th>
<th>CLL/SLL (n=2)</th>
<th>BCL, uncl (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8 (30)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
<td>19 (70)</td>
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<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>3</td>
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<tr>
<td>Age at presentation, y</td>
<td></td>
<td></td>
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<tr>
<td>≤70</td>
<td>15 (56)</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>&gt;70</td>
<td>12 (44)</td>
<td>6</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Primary lymphoma of the LG</td>
<td>15 (56)</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Secondary lymphoma of the LG</td>
<td>12 (44)</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>0</td>
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<td>LG as presenting lymphoma site</td>
<td>21 (78)</td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>3</td>
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<td>Laterality</td>
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<tr>
<td>Unilateral</td>
<td>24 (89)</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Bilateral</td>
<td>3 (11)</td>
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<td>0</td>
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<td>Serum LDH level</td>
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<td>Normal</td>
<td>22 (81)</td>
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<td>5</td>
<td>2</td>
<td>3</td>
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<td>3</td>
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<tr>
<td>Elevated</td>
<td>1 (4)</td>
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<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>Not analyzed</td>
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<td>0</td>
<td>2</td>
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<td>Initial therapy</td>
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<tr>
<td>Surgery alone</td>
<td>3 (11)</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Radiotherapy alone</td>
<td>15 (56)</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Alkylating agents</td>
<td>5 (19)</td>
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<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Agents plus radiotherapy</td>
<td>1 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>CHOP</td>
<td>2 (7)</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CEOF + rituximab</td>
<td>1 (4)</td>
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<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>TNM staging of primary LG lymphoma, No. (% of this group)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>T2b</td>
<td>7 (47)</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>bT2b</td>
<td>2 (13)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>T2c</td>
<td>6 (40)</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<td>Ann Arbor staging at presentation in the LG</td>
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<td>Stage I</td>
<td>18 (67)</td>
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<td>4</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>3</td>
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<tr>
<td>Stage II</td>
<td>4 (15)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stage III</td>
<td>1 (4)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>4 (15)</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Recurrence or progression</td>
<td>12 (44)</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: BCL, uncl, B-cell lymphoma, unclassified; CEOF, cyclophosphamide, epirubicin, vincristine, and prednisone; CHOP, cyclophosphamide, hydroxydaurubicin, vincristine, and prednisone; CLL/SLL, chronic lymphocytic leukemia/small lymphatic lymphoma; DLBCL, diffuse large B-cell lymphoma; EMZL, extranodal marginal zone lymphoma; FL, follicular lymphoma; LDH, lactate dehydrogenase; LG, lacrimal gland; MCL, mantle cell lymphoma.

aData are given as number (percentage) of patients unless otherwise indicated.

LYMPHOMA SUBCLASSIFICATION

The 27 lacrimal gland lymphoma cases were reclassified as extranodal marginal zone lymphoma (10 [37%]) (Figure 1), follicular lymphoma (5 [19%]), diffuse large B-cell lymphoma (4 [15%]), mantle cell lymphoma (3 [11%]), or chronic lymphocytic leukemia/small lymphocytic lymphoma (2 [7%]). Three cases (11%) could not be further classified because of insufficient tissue material or an uncharacteristic phenotype.
phoma progression, at a median (range) of 61 (4-149) months after initial diagnosis.

The lymphoma subtypes for these 7 patients were extranodal marginal zone lymphoma (n=2), follicular lymphoma (n=1), diffuse large B-cell lymphoma (n=2), and unclassified B-cell lymphoma (n=2) (Figure 2).

No clinical factors influenced patient mortality with any statistical significance, whether unadjusted or adjusted for...
sex and age at diagnosis. Moreover, an additional multivariate analysis that lumped the 2 variables most promising in terms of predicting untimely death (low-grade vs high-grade lymphoma subtypes and localized lymphoma [stage I or II] vs systemic involvement [stage III or IV]) did not show significant difference in mortality.

In the present case series study, we investigated 27 patients with lacrimal gland lymphoma in a relatively stable population of approximately 5\(\frac{1}{2}\) million people during a 35-year period, to correlate clinicopathologic features with prognosis. We found that most of the patients were elderly (median age, 69 years), with a predominance of women for the entire patient group (female to male ratio, 2:4), in accordance with other studies of lacrimal gland lymphoma.\(^6,13\) but in contrast to the predominance of men in patients with salivary gland lymphoma.\(^19,20\) In the primary lacrimal gland lymphoma group, this female predominance was notably larger compared with such predominance in other lacrimal gland lymphoma studies.\(^12,14\)

The distribution of lymphoma subtypes in our study confirms that extranodal marginal zone lymphoma is the most frequent lymphoma subtype of the lacrimal gland. However, the frequency of extranodal marginal zone lymphoma was lower compared with the frequency of lymphoma of the ocular adnexal region.\(^4\) Likewise, the frequency of follicular lymphoma seems to be higher in the lacrimal gland than in the ocular adnexal region.\(^8\) Results from our case series indicate that the distribution of lymphoma subtypes resembles that of the salivary glands more than that of the ocular adnexal region.\(^4,19,20\)

Sjögren syndrome is a common, slowly progressing autoimmune disease, characterized by lymphocytic infiltration and destruction of exocrine glands and epithelia.\(^21\) Patients with Sjögren syndrome are predisposed to lymphoma, and the incidence rate of salivary gland lymphomas in patients with Sjögren syndrome is 7.5\%.\(^22,23\) In fact, 20\% of patients with salivary gland lymphoma have a history of Sjögren syndrome.\(^20\) In our study, none of the patients had a history of Sjögren syndrome or any other autoimmune disease, indicating that the development of lacrimal gland lymphoma in conjunction with Sjögren syndrome is rare.\(^12,14,23\)

The 5-year overall survival for the entire patient group was 70\%, suggesting a relatively good prognosis for the majority of patients with lacrimal gland lymphoma. All patients with follicular lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma were alive 5 years after their initial diagnosis, consistent with the reported good prognosis for these low-grade subtypes.\(^13\) Furthermore, all 3 patients diagnosed as having mantle cell lymphoma were alive at the end of the study period and had achieved complete remission. This result was unexpected because mantle cell lymphoma has one of the poorest prognoses of all lymphomas.\(^24\) The high survival rate for mantle cell lymphoma observed in the present study may be due to the fact that all 3 patients received rituximab-containing chemotherapy and/or autologous stem cell transplantation at some point during their treatment.\(^25\) The 5-year overall survival for extranodal marginal zone lymphoma in our study was 75\%. This is comparable with reports on extranodal marginal zone lymphoma of the ocular adnexal region\(^4\) and confirms previous findings of extranodal marginal zone lymphoma involving the lacrimal gland.\(^24\) However, 5-year overall survival for extranodal marginal zone lymphoma involving the salivary gland has been reported to be from 95\% to 100\%.\(^19,20\) These differences in survival rates may indicate that lacrimal gland lymphoma is associated with a worse prognosis than salivary gland lymphoma. Of the 4 patients with diffuse large B-cell lymphoma involving the lacrimal gland, 2 were diagnosed as having primary lacrimal gland lymphomas, and both died of causes other than lymphoma. In contrast, the 2 patients diagnosed as having secondary diffuse large B-cell lymphoma died of their disease 4 and 21 months after initial diagnosis. Our study corroborates other study results that suggest that patients diagnosed as having systemic diffuse large B-cell lymphoma have a worse prognosis than those diagnosed as having localized ocular adnexal diffuse large B-cell lymphoma.\(^26\)

In the present study, survival rates for patients with lymphoma of the lacrimal gland only and those with lymphoma extending to either the posterior orbit or opposite lacrimal gland were not statistically significantly different. However, this could be because of the relatively few patients included in this study.

Disease recurrence or progression, involving both ocular and extraocular sites, was experienced by 6 of the 17 patients (35\%) with low-grade lymphoma, with a median time of 60 months after initial diagnosis. In contrast, 4 of the 7 patients (57\%) with high-grade lymphoma experienced a relapse with a median time of 30 months after initial diagnosis. Our study confirms that recurrence in low-grade lymphoma may occur after a relatively longer period, emphasizing the importance of an extended follow-up period.\(^27\) In patients with high-grade lymphoma, relapse is expected to be much more frequent and within a shorter period.\(^25,26\)
Although, to our knowledge, our study is the largest case series of lacrimal gland lymphomas to date, the study includes only a relatively few patients. The statistical power of this study is therefore limited.

In conclusion, lacrimal gland lymphoma is a relatively rare disease, predominantly affecting elderly women. The distribution of lacrimal gland lymphoma subtypes resembles the distribution of salivary gland lymphoma subtypes. The majority of lacrimal gland lymphomas diagnosed in our study population were low grade, and the prognosis was relatively good.

Submitted for Publication: February 2, 2011; accepted April 1, 2011.
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Author Contributions: As principal investigator, Dr Rasmussen had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.

Financial Disclosure: None reported.

Funding/Support: The study was supported by grants from The Danish Eye Health Society, 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 M. Kristian Kjaer and Wife Foundation.

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