

Prevalence and Nature of Systemic Involvement and Stage at Initial Examination in Patients With Orbital and Ocular Adnexal Lymphoma

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Objective: To determine the stage at initial examination and the prevalence of systemic involvement in patients with orbital and ocular adnexal lymphoma.

Methods: The medical records of all patients with orbital and ocular adnexal lymphoma treated in a recent 7-year period were reviewed for stage at initial examination, highest stage during the follow-up period, and recurrence-free survival.

Results: Forty-three patients were included. Nineteen patients had mucosa-associated lymphoid tissue, 9 had follicular, 9 had diffuse large-cell, 3 had mantle cell, 2 had small lymphocytic, and 1 had large T-cell lymphoma. The staging workup included chest radiography; orbital computed tomography or magnetic resonance imaging; computed tomography of the chest, abdomen, and pelvis; and bone marrow biopsy. Thirty-

six patients had total body positron emission tomography, 7 had gallium scans, and 16 had gastrointestinal endoscopy. Lymphoma stage at diagnosis was IE in 18 patients, II in 6, and IV in 19. Six of 19 patients with mucosa-associated lymphoid tissue, 7 of 9 patients with follicular, 6 of 9 patients with diffuse large-cell, and 3 of 3 patients with mantle cell lymphoma had non-stage IE disease at initial examination. The 5-year recurrence-free survival was 64.6% for the entire cohort.

Conclusions: Extraorbital involvement is present at diagnosis in more than half of patients with orbital and ocular adnexal lymphoma and warrants extensive systemic workup at diagnosis, continued surveillance, and consideration of systemic therapy.

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ORBITAL AND OCULAR ADnexal lymphoma accounts for only about 2% of all cases of non-Hodgkin lymphoma but is the most common primary orbital malignancy in adults.¹ Orbital and ocular adnexal lymphomas can involve the orbit, the eyelid, the conjunctiva, or a combination of these 3 ocular adnexal structures. The most common histologic subtype of orbital and ocular adnexal lymphoma is mucosa-associated lymphoid tissue (MALT) lymphoma; the second most common subtype is low-grade follicular lymphoma.²⁻⁴ Diffuse large-cell lymphoma, mantle cell lymphoma, and other more aggressive histologic subtypes are less commonly seen in the orbital and ocular adnexal structures.

Most investigators believe that orbital and ocular adnexal lymphomas are associated with a very low rate of systemic involvement. For this reason, most investigators do not recommend extensive staging workup at the time of initial diagnosis or during the follow-up period.^{5,6} In addition,

because of beliefs about a low rate of systemic involvement in orbital and ocular adnexal lymphoma, irradiation of the ocular adnexal structures has historically been considered standard treatment for this disease. A few studies have suggested that a detailed and accurate staging workup at diagnosis of orbital and ocular adnexal lymphoma is critical, because the presence of extraorbital disease is associated with a poor prognosis.⁷⁻¹⁰ Most studies to date, however, have focused on the initial ophthalmic signs and symptoms and have promoted local radiation therapy for low-grade orbital and ocular adnexal lymphoma without much attention to detailed staging information.^{2,5,6} Some evidence suggests that MALT lymphomas are indolent and associated with a very good prognosis^{3,5}; other evidence suggests no difference in survival between patients with MALT lymphoma and those with other low-grade forms of orbital and ocular adnexal lymphoma.⁴

The goal of our study was to determine the disease stage at initial examina-

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Table 1. Stage of Orbital and Ocular Adnexal Lymphoma by Histologic Subtype

Histologic Subtype	Patients, No. (%)			
	All	Stage IE	Stage II	Stage IV
Mucosa-associated lymphoid tissue lymphoma	19 (100)	13 (68)	1 (5)	5 (26)
Follicular lymphoma	9 (100)	2 (22)	0	7 (77)
Diffuse large-cell lymphoma	9 (100)	3 (33)	5 (56)	1 (11)
Mantle cell lymphoma	3 (100)	0	0	3 (100)
Small lymphocytic lymphoma/ B-chronic lymphocytic leukemia	2 (100)	0	0	2 (100)
Large T-cell/natural killer cell lymphoma	1 (100)	0	0	1 (100)
Total	43	18	6	19

tion and the prevalence and nature of systemic involvement at initial examination and during the follow-up period for each histologic subtype of orbital and ocular adnexal lymphoma. This retrospective study was limited to patients who underwent staging at a single tertiary cancer center, which followed a uniform lymphoma staging protocol, and whose lymphoma was diagnosed during a recent period when advanced staging tools, such as positron emission tomography, were available. Appropriate institutional review board approval was obtained for this study.

METHODS

DATA COLLECTION

The medical records of all patients with a diagnosis of orbital and ocular adnexal lymphoma treated by the senior author (B.E.) between January 1999 and October 2006 at a single tertiary cancer center were reviewed. During this period, all patients with orbital and ocular adnexal lymphoma seen at our institution had a standard staging workup that included chest radiography; computed tomography (CT) or magnetic resonance imaging (MRI) of the orbit; CT of the chest, abdomen, and pelvis; and a bone marrow biopsy. Additional staging examinations were ordered as indicated by the patient's signs and symptoms at the physician's discretion.

For each patient, the following data were collected from the patient's medical record: age, sex, ethnicity, ocular and systemic symptoms and signs at initial examination, anatomic site of involvement (orbit, eyelid, conjunctiva, or a combination of these structures), laterality, histologic subtype of lymphoma, elements of the staging workup, stage of lymphoma at initial examination, highest stage during the follow-up period, site of systemic involvement (if any) at diagnosis of lymphoma, initial treatment modality, response to therapy, site of recurrence (if any), recurrence-free survival (RFS), follow-up time after diagnosis of orbital and ocular adnexal lymphoma, and patient's status at last contact. Patients with periorbital mycosis fungoides were excluded.

The 5-year RFS rate was defined as the proportion of patients who neither died nor had any recurrence during the first 5 years after completion of treatment for orbital and ocular adnexal lymphoma. Complete response was defined as complete disappearance of all detectable clinical evidence of disease in the orbit and ocular adnexa and disease-related symptoms if present before therapy. The response to therapy was evaluated using clinical examination and CT or MRI of the orbit. Par-

tial response was defined as at least a 50% decrease in the size of the mass in the ocular adnexal region. Stable disease was defined as less than 50% response but no progressive disease.

STATISTICAL CONSIDERATIONS

Curves describing the overall and RFS of patients were generated in accordance with the Kaplan-Meier method. The log-rank test was used to evaluate whether there were statistically significant differences between the curves for the subgroups with nodal vs extranodal systemic involvement, primary vs secondary lymphoma, each histologic subtype vs others, and complete vs partial response to treatment. $P \leq .05$ was considered statistically significant. These statistical procedures were performed with the assistance of the Statistica data analysis software system, version 7.1 (StatSoft Inc, Tulsa, Oklahoma).

RESULTS

PATIENT AND DISEASE CHARACTERISTICS AND SYMPTOMS AT INITIAL EXAMINATION

Forty-three patients with a diagnosis of orbital and ocular adnexal lymphoma were treated by the senior author (B.E.) during the study period. There were 26 women and 17 men, ranging in age from 25 to 84 years (median, 62 years). Twenty-eight patients (65%) had primary orbital and ocular adnexal lymphoma, ie, orbital and ocular adnexal lymphoma was the first and predominant site of involvement, and 15 (35%) had secondary orbital and ocular adnexal lymphoma, ie, the diagnosis of ocular adnexal involvement followed a previously established diagnosis of lymphoma. In the 15 patients with secondary orbital and ocular adnexal lymphoma, the time from diagnosis of lymphoma to diagnosis of ocular adnexal involvement ranged from 10.8 to 179.0 months (median, 52.4 months). Thirty-five patients (81%) had unilateral disease (affecting the right eye in 20 patients and the left eye in 15) and 8 patients (19%) had bilateral disease. Thirty-two patients (74%) had orbital involvement, 10 (23%) had conjunctival involvement, and 7 (16%) had eyelid involvement. Five patients had involvement of more than 1 ocular structure: 3 had involvement of the orbit and conjunctiva; 1 had involvement of the orbit, conjunctiva, and eyelid; and 1 had involvement of the eyelid and orbit.

The symptoms at diagnosis of orbital and ocular adnexal lymphoma included a palpable mass in the orbit or eyelid in 14 patients (33%), eyelid or periorbital swelling in 12 patients (28%), proptosis in 9 patients (21%), diplopia in 8 patients (19%), upper eyelid ptosis in 4 patients (9%), excessive tearing in 4 patients (9%), fever, weight loss, and/or night sweats in 4 patients (9%), and an afferent pupillary defect suggesting significant optic nerve compression due to the mass effect of orbital and ocular adnexal lymphoma in 2 patients (5%).

HISTOLOGIC SUBTYPES OF ORBITAL AND OCULAR ADNEXAL LYMPHOMA

At initial examination, 19 patients (44%) had MALT lymphoma (**Table 1**). Nine patients (21%) had follicular lymphoma: grade I or II (low grade) in 5 patients, grade III

(high grade) in 1 patient, and an unspecified grade in 3 patients. Nine patients (21%) had diffuse large-cell lymphoma, 3 patients had mantle cell lymphoma, 2 patients had small lymphocytic lymphoma/B-chronic lymphocytic leukemia, and 1 patient had large T-cell/natural killer cell lymphoma.

STAGE OF ORBITAL AND OCULAR ADNEXAL LYMPHOMA AT INITIAL EXAMINATION AND DURING THE FOLLOW-UP PERIOD

In addition to the standard staging workup performed in every patient (chest radiography; CT or magnetic resonance imaging of the orbit; CT of the chest, abdomen, and pelvis; and a bone marrow biopsy), 36 patients (84%) underwent total body positron emission tomography, and the other 7 (16%) had total-body gallium scans. Gastrointestinal endoscopy was done in 16 patients (37%), 13 of whom (81%) had MALT lymphoma. The incidence of gastrointestinal involvement is as high as 88% in patients with mantle cell lymphoma¹¹; thus, gastrointestinal endoscopy for mantle cell lymphoma is not routinely done at our institution, and it is assumed that patients with mantle cell lymphoma have gastrointestinal involvement.

At diagnosis of orbital and ocular adnexal lymphoma, 18 patients (42%) had stage IE disease, 6 patients (14%) had stage II disease, and 19 patients (44%) had stage IV disease (Table 1). Of the 28 patients with primary orbital and ocular adnexal lymphoma, 13 patients (46%) had stage IE, 5 patients (18%) had stage II, and 10 patients (36%) had stage IV lymphoma. Table 1 presents the stage of orbital and ocular adnexal lymphoma by histologic subtype.

Of the 25 patients with non-stage IE disease at diagnosis of orbital and ocular adnexal lymphoma, 14 (56%) had extranodal systemic involvement only, 4 (16%) had nodal systemic involvement only, 7 (28%) had both nodal and extranodal systemic involvement, and 4 (9%) had bone marrow involvement. Three of the 18 (17%) patients who initially had stage IE disease developed systemic nodal disease (stage IV) during the follow-up period.

Fourteen patients with primary orbital and ocular adnexal lymphoma underwent biopsy of extraorbital sites of systemic involvement. In 3 patients, the type of lymphoma in the ocular adnexal structures was different from that at the extraorbital site. One patient had diffuse large-cell lymphoma in the eyelid but large T-cell/natural killer cell lymphoma at the extraorbital site; 1 had low-grade follicular lymphoma in the eyelid but small lymphocytic lymphoma at the extraorbital site; and 1 had follicular lymphoma in the orbit and diffuse large-cell lymphoma in the extraorbital site.

TREATMENT OF ORBITAL AND OCULAR ADNEXAL LYMPHOMA

Table 2 summarizes the treatment modalities used in our patients. Sixteen patients had radiotherapy; of these, 8 had radiotherapy in combination with other forms of systemic treatment. Fourteen patients had various forms of chemotherapy, and 20 had monoclonal antibody

Table 2. Treatment in Patients With Orbital and Ocular Adnexal Lymphoma

Treatment	No. of Patients
External beam orbital radiotherapy	8
Systemic chemotherapy	1
Ibritumomab tiuxetan	6
Rituximab	3
Radiotherapy and systemic chemotherapy	4
Radiotherapy and rituximab	2
Systemic chemotherapy and rituximab	6
Radiotherapy, systemic chemotherapy, and rituximab	2
Patient refused treatment and was observed	2
Surgical resection of orbital and ocular adnexal lymphoma and no additional treatment	2
Bone marrow transplantation after systemic chemotherapy and rituximab	1
Patient did not return for recommended treatment	6

therapy. One patient underwent bone marrow transplantation after treatment with systemic chemotherapy and rituximab. The most common combination chemotherapy was cyclophosphamide, doxorubicin, vincristine, and prednisolone, which was used in 7 of 14 patients who had systemic chemotherapy alone or in combination with other treatment modalities. Fractionated cyclophosphamide was used in 4 patients; mesna and fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone was used in 2 patients. The number of chemotherapy cycles ranged from 1 to 10 (median, 6). Twenty-five of 35 patients (71%) who completed treatment had a complete response, 6 (17%) had a partial response, and 5 (14%) had stable disease.

RFS, RECURRENCE RATES, AND MORTALITY RATES

The median follow-up time, from diagnosis of ocular adnexal lymphoma to death or last contact, for the 43 patients whose records were examined was 24 months (range, 0.3-142.1). Specific information about the chronology of initial treatment, recurrences, and mortality that was necessary for the RFS calculations was available for 36 of these patients (83.7%). For this subgroup, the median follow-up time was 27.8 months (range, 2.1-142.1). The RFS rate at 5 years for these 36 patients was 64.6% by the Kaplan-Meier method (**Figure**).

Ten patients had recurrences during the study period (median, 1 recurrence [range, 1-9]). Four patients had recurrence in the ocular adnexal structures; 3 patients had systemic recurrence; and 3 had both ocular adnexal and systemic recurrences. At last contact, 24 patients (56%) were alive with no detectable disease, 14 (33%) were alive with disease, 2 (5%) had died of the disease, and 3 (7%) had died of other causes.

Patients with primary orbital and ocular adnexal lymphoma had a higher 5-year RFS than those with secondary orbital and ocular adnexal lymphoma (79.7% vs 36.4%, respectively; $P=.01$). The 5-year RFS rate was higher for MALT lymphoma patients compared with the rest of the patients with orbital and ocular adnexal lymphoma.

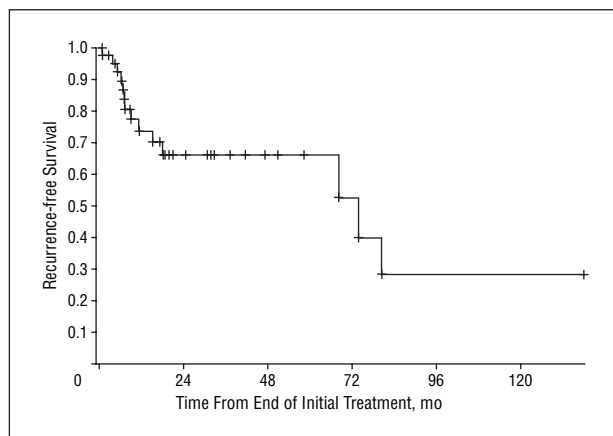


Figure. Five-year recurrence-free survival in patients with orbital and ocular adnexal lymphoma.

phoma; however, this difference was not statistically significant by the log-rank test (72.7% vs 58.8%, respectively; $P = .27$). Five-year RFS for mantle cell lymphoma was lower than the rest, but again this difference was not statistically significant ($P = .06$). There were only 3 patients with mantle cell lymphoma in this cohort. Five-year RFS was higher in patients who had extranodal lymphoma than those who had nodal lymphoma (77.9% vs 29.4%, respectively; $P = .01$).

The 5-year RFS was higher for patients who had a complete response to treatment than in those who had a partial response (82.6% vs 0%, respectively; $P = .006$). Four of the 25 patients with a complete response died at 5 years, whereas 6 of 6 patients with a partial response died at 5 years.

COMMENT

To our knowledge, this is the first report of a series of patients with orbital and ocular adnexal lymphoma treated in an ophthalmology practice fully based at a comprehensive cancer center. Because of the unique makeup of the patients and the uniform practice patterns for staging of lymphoma at our institution, this relatively large series of patients with orbital and ocular adnexal lymphoma provides some interesting new insights.

Our most significant finding was that almost half of the patients with primary orbital and ocular adnexal lymphoma had non-stage IE disease at the time of initial diagnosis. In addition, 3 of 18 patients who initially had stage IE lymphoma developed systemic nodal involvement (stage IV disease) during the follow-up period. The rates of systemic involvement in our series are higher than rates previously reported in the literature and commonly taught by most ophthalmologists and ocular oncologists.^{2,5,7,9,10,12-14} One possible explanation for the higher rates in our series is better detection of systemic disease by using uniform staging workup for each patient. Eighty-four percent of the patients in our series had total-body positron emission tomography, and 100% had a bone marrow biopsy. Perhaps there is a correlation between how extensive the staging procedures are and how often systemic involvement is found. Of the patients with non-

stage IE disease at the time of initial diagnosis, more than half had extranodal systemic involvement, about one-third had nodal systemic involvement, and about 10% had bone marrow involvement.

Another possible explanation for the higher than previously reported rate of non-stage IE orbital and ocular adnexal lymphoma in our series may be the selection bias for more aggressive lymphomas at our tertiary cancer center. As expected, stage IE disease was most common among patients with MALT lymphoma, but even within this histologic classification, 6 of 19 patients had non-stage IE disease at initial examination (Table 1). Seven of 9 patients with follicular lymphoma and all 3 patients with mantle cell lymphoma also had non-stage IE disease at initial examination.

The distribution of histologic subtypes of orbital and ocular adnexal lymphoma in our series was similar to that previously reported in the literature in the sense that MALT lymphoma was the most common histologic subtype.^{9,12-14} Almost half of the patients had MALT lymphoma, about 20% each had follicular lymphoma and diffuse large-cell lymphoma, and 7% had mantle cell lymphoma. The remaining patients had rare histologic subtypes, such as small lymphocytic lymphoma and large T-cell/natural killer cell lymphoma. The proportion of MALT lymphoma reported in previously published cohorts of patients with ocular adnexal lymphoma ranges from 50% to 87%.^{4,9,12} In a recently published report from Korea, 87% of all cases of orbital and ocular adnexal lymphoma were MALT lymphoma.¹⁵ Geographic variations may contribute to the differences in the distribution of the histologic subtypes of orbital and ocular adnexal lymphoma.

Another interesting observation in our cohort is the treatments chosen for orbital and ocular adnexal lymphoma. Only 16 patients (37%) had orbital radiotherapy as the primary treatment modality; more than half of these patients received chemotherapy or monoclonal antibody therapy in combination with radiotherapy. More than half of the patients in this cohort were treated with monoclonal antibodies directed against CD20 (rituximab or ibritumomab tiuxetan). This recent trend of using monoclonal antibodies or monoclonal antibodies with a radioactive ligand (radioimmunotherapy) for treatment of orbital and ocular adnexal lymphoma is a reflection of the overall trend in management of non-Hodgkin lymphoma.^{1,16-18} This trend represents a departure from classic practice among ophthalmologists and ocular oncologists, who have traditionally considered orbital radiotherapy the gold standard for treatment of orbital and ocular adnexal lymphoma.^{2,6,10,13} Several previous reports have focused on the efficacy and potential benefits of targeted immunotherapy.^{1,18}

The 5-year RFS for our cohort was 64.6%. This compares favorably with that reported in the literature.¹³ As expected, we found that RFS was higher in patients with primary orbital and ocular adnexal lymphoma than in those with secondary orbital and ocular adnexal lymphoma and that RFS was higher in patients with extranodal systemic disease than in those with nodal systemic disease. Our data also suggested a higher RFS for patients who have complete initial response to therapy

compared with those who only achieved partial response. This highlights the importance of posttreatment imaging and also the recent role of positron emission tomography for assessment of response to treatment of orbital and ocular adnexal lymphoma.

On the basis of our data, we recommend a thorough staging workup, including a workup for systemic disease for all patients with primary or secondary orbital and ocular adnexal lymphoma. This staging workup should include total-body positron emission tomography, a bone marrow biopsy, and—for patients with some histologic subtypes of orbital and ocular adnexal lymphoma, such as MALT lymphoma and mantle cell lymphoma—gastrointestinal endoscopy. For most patients with orbital and ocular adnexal lymphoma, systemic targeted treatments, such as monoclonal antibody therapy or radioimmunotherapy, should be considered, because close to half of patients with primary orbital and ocular adnexal lymphoma at initial examination are found to have systemic involvement on careful staging. Even among the lowest risk histologic type of lymphoma (MALT), there was close to one-third incidence of non-stage IE disease at initial examination. The efficacy of targeted monoclonal antibody therapy for local control of orbital and ocular adnexal lymphoma needs to be compared with the efficacy of radiotherapy. In fact, the value of these treatment modalities for orbital and ocular adnexal lymphoma are currently being evaluated in prospective trials. Monoclonal antibody therapy may not only be as effective as orbital radiotherapy for local control of orbital and ocular adnexal lymphoma but also may offer better overall systemic control of lymphoma, as it is a systemic form of treatment. It may also be potentially less toxic to the orbital and ocular adnexal tissues compared with orbital radiotherapy.

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