

# Ocular Adnexal Lymphoma: Assessment of a Tumor-Node-Metastasis Staging System

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**Purpose:** To assess distribution, correlations, and prognostic effect of tumor (T), node (N), and metastasis (M) staging on relapse and survival.

**Design:** Retrospective clinical review.

**Participants:** Sixty-three patients diagnosed with primary ocular adnexal lymphoma (OAL) between January 1986 and November 2011.

**Methods:** Complete ocular examination and systemic evaluation were performed. Patients were staged according to the American Joint Committee on Cancer (AJCC) seventh edition tumor-node-metastasis (TNM) clinical staging system for OAL and followed every 6 to 12 months (median follow-up, 27.9 months).

**Main Outcome Measures:** Relapse defined as lymphoma recurrence in the initial site of presentation, the contralateral ocular adnexal structures, or other systemic site and overall survival.

**Results:** There were 40 men (63.5%). The median age was 65 years (range, 24–85 years). The affected site was the conjunctiva in 27 patients (42.9%), orbit in 38 patients (60.3%), and eyelid in 3 patients (4.8%). The histologic subtype was extranodal marginal zone lymphoma (EMZL) in 51 patients (81.0%). A total of 14 patients (23.3%) had T1, 42 patients (70.0%) had T2, 1 patient (1.7%) had T3, and 3 patients (5.0%) had T4 disease. A total of 48 patients (82.8%) had N0 disease, and 10 patients (17.2%) had N1–4 disease. M stage was M0 in 47 patients (81.0%) and M1 in 11 patients (19.0%). With advanced T stage, there was an increase in both N1–4 ( $P = 0.045$ ) and M1 disease ( $P = 0.041$ ). M1 disease was greater among patients with N1–4 disease compared with N0 stage (50.0% vs. 12.5%,  $P = 0.003$ ). Overall, 18 patients (28.6%) relapsed and 6 patients (9.5%) died. In Cox analysis, relapse was not associated with T stage (hazard ratio [HR], 1.14 per 1 level increase,  $P = 0.71$ ), N stage (HR, 1.47;  $P = 0.51$  N1–4 vs. N0), or M stage (HR, 1.22;  $P = 0.76$  M1 vs. M0). T stage was not associated with survival (HR, 0.86;  $P = 0.81$ ), whereas N1–4 had marginally worse survival than N0 (HR, 5.35;  $P = 0.07$ ), and M1 had worse survival than M0 (HR, 9.27;  $P = 0.008$ ).

**Conclusions:** The TNM staging system for primary OAL is useful for precise characterization of extent of local disease. Although T stage does not predict relapse or survival, N1–4 and M1 stages indicated less favorable survival.

**Financial Disclosure(s):** The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology* 2013;120:1915–1919 © 2013 by the American Academy of Ophthalmology.



Ocular adnexal lymphoma (OAL) encompasses a heterogeneous group of lymphomas, the majority of which are low-grade, B-cell, non-Hodgkin lymphomas. The majority, approximately 80%, are of the extranodal marginal zone lymphoma (EMZL) histologic subtype.<sup>1</sup> Ocular adnexal lymphoma can present as a single, localized tumor or it can be multifocal. It may affect unilateral or bilateral ocular adnexal structures. Disseminated disease involving regional, central, and peripheral lymph nodes, as well as other distant extranodal sites, also is observed. The 10-year, disease-specific mortality is approximately 5% to 10%.<sup>2</sup>

The Ann Arbor staging system currently is widely used for malignant lymphoma; however, this system has several deficiencies for characterizing OAL because it results in a disproportionate staging distribution. Two-thirds of primary OAL cases present as a localized mass, which under the Ann Arbor system are classified as stage 1E.<sup>3–9</sup> This precludes the ability to differentiate the majority of OAL cases from one another on the basis of disease extent within

the ocular adnexal structures, which may have important prognostic implications.<sup>10,11</sup>

More recently, a tumor-node-metastasis (TNM)-based staging system for primary OAL has been developed under the guidance of the American Joint Committee on Cancer.<sup>12,13</sup> This staging system addresses many of the shortcomings of the Ann Arbor system and more precisely defines disease extent. The ultimate goal of the proposed TNM-based system is to facilitate future studies aimed at identifying clinical and histomorphologic features of OAL of prognostic significance, and to assess treatment outcomes. To date, the feasibility of this system has been analyzed in only a limited capacity, comparing patients with EMZL affecting the conjunctiva alone with patients with disease extending to the orbit, eyelid, or adjacent structures.<sup>14</sup> Moreover, OAL can be a multifocal disease, and involvement of lymph nodes and distant systemic disease need not reflect metastatic spread from the primary site. Therefore, it is possible that correlations between

advanced T stage with N and M stage may merely reflect the natural evolution of multifocal disease.

The purpose of the present study was to describe the distribution of T, N, and M staging within a clinical cohort of individuals with primary OAL. In addition, correlation among T, N, and M stage was assessed to determine whether advancing T stage had an impact on N and M designation and similarly whether higher N stage affected M designation. The prognostic effect of T, N, and M stage on relapse and survival was also evaluated.

## Methods

### Patients

A total of 82 patients were diagnosed with OAL at the Cleveland Clinic between January 1986 and November 2011. Of these, 63 patients had no history of systemic lymphoma at the time of diagnosis and were therefore included in the present study of TNM-based clinical staging for primary OAL. This study was approved by the Cleveland Clinic and Case Comprehensive Cancer Center Institutional Review Boards. All research adhered to the tenets of the Declaration of Helsinki. In all cases, the diagnosis of OAL was confirmed by tissue biopsy performed at our institution or reviewed by a Cleveland Clinic staff pathologist when biopsy was performed elsewhere. The lymphoma histologic subtype also was identified on the basis of histomorphology, immunohistochemistry, or genotyping.

Data were collected regarding patient age at diagnosis, gender, date of diagnosis, and extent of OAL involvement (affected ocular adnexal structures and laterality). This was accomplished by complete ophthalmic examination, including measurement of visual acuity, intraocular pressure, pupillary reflex testing, external inspection for regional lymph node involvement, exophthalmometry, ocular motility testing, slit-lamp examination, and dilated fundus examination. B-scan ultrasonography was performed in addition to neuroimaging (computed tomography [CT] or magnetic resonance imaging of the orbits) to identify occult orbital involvement.

To screen for systemic lymphoma at the time of diagnosis, all patients were referred to an experienced medical oncologist at the Cleveland Clinic Taussig Cancer Institute for initial staging studies, which included a history, physical examination, and imaging with CT scan of the chest, abdomen, and pelvis. Blood work including a complete blood count and complete metabolic panel was performed in all cases. Additional hematologic studies and ancillary testing (e.g., bone marrow biopsy) were performed at the discretion of the treating oncologist.

### TNM Staging of Ocular Adnexal Lymphoma

TNM-based clinical staging was determined for each patient at the time of diagnosis according to the criteria outlined in the recently proposed American Joint Committee on Cancer seventh edition staging manual for OAL. This staging algorithm has been described in detail (Table 1; available at <http://aojournal.org>).<sup>12,13</sup> Briefly, the T stage defines the extent of lymphoma involvement of the ocular adnexal structures. Stage T1 disease characterizes conjunctival lymphoma, whereas T2 defines any OAL involving the orbit whether or not the conjunctiva is affected. Stage T3 implies involvement of the preseptal eyelid tissues (e.g., dermis, orbicularis, or eyelid skin) in addition to any conjunctival or orbital disease. Stage T4 describes lymphomatous invasion of the bony and soft-tissue structures external to the ocular adnexa, such as the periosteum, bone, nasopharynx, sinuses, and intracranial space. The N stage describes lymph node involvement in OAL. Regional lymph nodes of the

ocular adnexa include the submandibular, preauricular, and cervical nodes. Distant lymph nodes include the central nodes located in the trunk and peripheral nodes at distant sites not draining the ocular adnexa. The N stage indicates whether the involved lymph node is regional (ipsilateral: N1, contralateral or bilateral: N2), peripheral (N3), or central (N4). Stage M describes the extent of extranodal sites and bone marrow infiltration.

Patients were followed in an ophthalmic oncology clinic and by their medical oncologist every 6 to 12 months until the end of the study period in March 2012 (median follow-up 27.9 months). In addition to clinical examination, systemic surveillance with the previously mentioned imaging studies was performed to monitor for disease relapse and survival. Relapse was defined as lymphoma recurrence in the initial site of presentation, the contralateral ocular adnexal structures, or other systemic site. Survival was defined as overall survival. During the study period, 6 patients died. Of these deaths, 4 were lymphoma related.

### Statistical Analysis

The Cochran–Armitage trend test was used to assess correlations among T, N, and M staging. This statistical test determined whether patients with more advanced T stage resulted in an increase in N or M stage, or if increasing N stage correlated with advanced M stage.

Cox proportional hazards analysis was used to assess the prognostic effect of T, N, and M stage with relapse and survival. Results are presented as the hazard ratio (HR), 95% confidence interval (CI) for the HR, and the corresponding *P* value. Because of the small number of events for each outcome, T classification was analyzed as an ordinal variable rather than categorizing it into groups. Kaplan–Meier analysis also was used to assess relapse and survival outcomes compared by T stage (T1 vs. T2 vs. T3–4), N stage (N0 vs. N1–4), and M stage (M0 vs. M1?). The log-rank test was used to determine the statistical significance of differences in relapse and survival outcomes.

## Results

A total of 63 patients with primary OAL were identified between January 1986 and November 2011. There were 40 men (63.5%) and 23 women (36.5%). The median age was 65 years (range, 24–85 years). Conjunctival involvement was present in 27 patients (42.9%), orbital disease was present in 38 patients (60.3%), eyelid disease was present in 3 patients (4.8%), and uveal infiltration was present in 10 patients (15.9%). The right ocular adnexal structures were involved in 20 patients (31.7%), the left ocular adnexal structures were involved in 25 patients (39.7%), and bilateral disease was observed in 18 patients (28.6%). The majority, 51 patients (81.0%), had extranodal marginal zone lymphoma (EMZL). Other histologic subtypes included follicular lymphoma in 3 patients (4.8%), diffuse large B-cell lymphoma in 3 patients (4.8%), mantle cell lymphoma in 1 patient (1.6%), or other not specified subtypes in 5 patients (7.9%) (Table 2; available at <http://aojournal.org>).

### Distribution of T, N, and M Staging

The T stage could be assessed in a total of 60 patients. In the remaining 3 cases, orbital imaging was not performed, and therefore the T stage could not be accurately defined. The majority, 42 patients (70.0%), had T2 disease. Advanced T stage was uncommon. In our cohort, there was 1 patient (1.7%) in the T3 stage and 3 patients (5.0%) with T4 disease. The N stage could be determined in 58 patients. Most patients (48 [82.8%]), had N0 disease. N1–4 stages were observed in 10 patients (17.2%). The

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