A TNM-Based Clinical Staging System of Ocular Adnexal Lymphomas

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Context. The ocular adnexal lymphomas (OAL) arise in the conjunctiva, orbit, lacrimal gland, and eyelids. To date, they have been clinically staged using the Ann Arbor staging system, first designed for Hodgkin and later for nodal, non–Hodgkin lymphoma. The Ann Arbor system has several shortcomings, particularly when staging extranodal non–Hodgkin lymphomas, such as OAL, which show different dissemination patterns from nodal lymphomas.

Objective. To describe the first TNM-based clinical staging system for OAL.

Design. Retrospective literature review.

Results. We have developed, to our knowledge, the first American Joint Committee on Cancer–International Union Against Cancer TNM-based staging system for OAL (Arch Pathol Lab Med. 2009;133:1262–1267).

By definition, ocular adnexal lymphomas (OALs) arise in the conjunctiva, the orbit, the lacrimal gland, or the eyelids. These tumors can be solitary or multicentric, unilateral or bilateral. They can invade bone, sinuses, nasopharynx, and the cranial cavity. Dissemination can occur to ipsilateral and/or contralateral regional lymph nodes as well as to more distant nodes centrally and peripherally (eg, para-aortic and popliteal nodes). Ocular adnexal lymphomas are mostly extranodal non–Hodgkin lymphomas (NHLs), with the most common subtype being the extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type (1-7) according to the latest World Health Organization lymphoma classification. Although rare, T/NK-cell lymphomas also arise in the ocular adnexa. As with other extranodal marginal zone B-cell lymphomas, recurrences occur commonly within the ocular adnexa and other extra-nodal sites, such as salivary glands. Treatment is largely based on radiotherapy with or without systemic chemotherapy and/or immunotherapy, according to clinical staging and histologic subtyping. The 10-year, disease-specific mortality, which varies according to lymphoma subtype, is approximately 5% to 10%.

To date, the most widely used staging system for malignant lymphomas is the Ann Arbor staging system, which was first used for Hodgkin disease in 1971. Although its utility for the staging of other lymphomas has been challenged, the modified Ann Arbor system remains the primary means for determining clinical stage of patients with both nodal and extranodal NHL. Ann Arbor staging is essentially an anatomic assessment of disease that also takes into account any systemic symptoms. It divides the disease extent into 4 stages (stages I-IV), according to lymph node group involvement above and below the diaphragm and with or without involvement of organs, such as the spleen, liver, and bone marrow. Other staging systems have been developed for extranodal lymphomas at other sites, such as skin and gastrointestinal mucosa. In addition, other prognostic indices have been devised, taking into account features such as age, serum lactate dehydrogenase levels, and the general condition of the patient. These systems supplement the Ann Arbor staging classification to enhance treatment planning and patient stratification in clinical trials.

MATERIALS AND METHODS

The Ann Arbor staging system has a number of shortcomings, particularly when staging extranodal NHLs, such as OALs, which essentially show different dissemination patterns from nodal lymphomas. As with other locations of extranodal lymphoma (eg, gastrointestinal lymphomas), the Ann Arbor stag-
Two-thirds of Ocular adnexal lymphomas (OALs) are associated with concurrent systemic disease; in particular, lymphomas occurring in the eyelid or orbit with lacrimal gland involvement are associated with a worse prognosis.18,19 Within the subgroup of conjunctival lymphomas, systemic disease is more common in patients with lymphomas located at an extralimbal site (ie, in the fornix or midbulbar region).20 Furthermore, some evidence suggests that whether the lymphoma is located predominantly in the anterior or posterior orbit is of prognostic significance (J.R., unpublished data, 2008).21 Lymphomatous involvement of the extraocular muscles has been demonstrated by some to be a poor prognostic factor.22 Currently, all OALs confined to the ocular adnexa are categorized and recorded by the Ann Arbor system as stage IE, whatever their exact location or size. This system, therefore, does not discriminate between patients with high-risk or low-risk stage IE.

3. Extent of Primary Tumor Infiltration.—New imaging techniques enable a more precise definition of tumor extent.23,24 This feature cannot be documented adequately using the Ann Arbor staging system.

4. Multiple Tumors.—Ocular adnexal lymphomas can occur as multiple tumors within the same site, for example, in the conjunctiva. Large studies show that such multiple conjunctival tumors are associated with a worse prognosis.25 There is no allowance for the staging of multiple tumors in the Ann Arbor classification.

5. Lymph Node Involvement.—Recent studies indicate that conjunctival OAL with nodal involvement is associated with a worse prognosis.25 Currently, the Ann Arbor system categorizes lymph node involvement by OAL as stage II or stage III. This information, however, is vague, and could be made more precise by documenting, first, whether any regional lymph node involvement is ipsilateral or contralateral and, second, whether any distant lymph nodes are affected, as indicated below.

6. Multicentricity and Bilaterality of OAL.—Ocular adnexal lymphomas can occur in separate noncontiguous sites in the ocular adnexa (eg, concurrent but noncontiguous conjunctival and orbital tumors). Such multiple tumors can be either ipsilateral or, in up to 15% of cases, bilateral. Presently, both of these would be staged and recorded as IE, using the Ann Arbor staging system.

7. Noncontiguous Involvement of Tissues External to the Ocular Adnexa.—Commonly, OALs are associated with concurrent involvement of extranodal sites, such as the parotid and submandibular glands. Such involvement cannot be documented using the Ann Arbor classification system.

RESULTS

Under the auspices of the American Joint Committee on Cancer, we have developed a staging system to overcome the limitations of the Ann Arbor system.26 This new system uses the standard tumor, node, and metastasis (TNM) format. It is based on published evidence and the clinical experience of the authors. Our OAL staging system (Table) aims to define disease extent more precisely and to facilitate future studies identifying clinical and histomorphologic features of prognostic significance. This system is not intended for secondary lymphomatous involvement of ocular adnexa or for intraocular lymphomas. It must be emphasized that our OAL staging system should be used in conjunction with histologic subtyping according to the latest World Health Organization lymphoma classification.8

The T stage defines the lymphomatous involvement of the ocular adnexa. It essentially subdivides the stage IE of the Ann Arbor classification into finer subgroups, allowing for better documentation of disease extent. T1 categorizes conjunctival OALs according to whether they are bulbar (T1a; Figure 2), or nonbulbar (T1b; ie, confined to fornix and/or caruncle). Tumors that involve both bulbar and nonbulbar conjunctiva are placed in the T1c category (Figure 3). These categories are based on evidence indicating that nonbulbar conjunctival involvement carries a worse prognosis. Multifocal tumors are identified using

![Figure 1](https://example.com/figure1.png)
shown that the prognosis is worse with orbital involve-
not the conjunctiva is affected. Several studies have
plied to any T stage.

d Region lymph nodes, which include the preauricular (parotid), submandibular, and cervical lymph nodes.

c Eyelid involvement is said to exist when the OAL infiltrates preseptal tissues (ie, tissues anterior to the orbital septum).

b The anterior orbit is defined as the area between the orbital septum and the equator of the globe. The posterior orbit is defined as the area
posterior to the equator of the globe, extending to the orbital apex.

a Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC

Stage T2 defines any OALs involving the orbit, whether or not the conjunctiva is affected. Several studies have shown that the prognosis is worse with orbital involvement
than with lymphoma confined to conjunctiva (Figure 4).18–20 An orbital tumor is categorized as anterior and posterior,
according to its predominant location in relation to the
equator of the globe. The anterior orbit is defined as
the area between the orbital septum and the equator of the globe. The posterior orbit is defined as the area
posterior to the equator of the globe, extending to the orbital apex. This distinction is based on one of the authors’ un-
published data (J.R., 2008) and will be investigated by out-
comes analyses. Without such tentative categorization, fu-
tures investigations evaluating the prognostic value of T2
subgroups would be more difficult. Ocular adnexal
lymphomas infiltrating the nasolacrimal drainage system, but
not reaching the nasopharynx, are staged as T2d.

Stage T3 indicates OAL infiltration of preseptal eyelid
tissues (ie, tissues anterior to the orbital septum, such as
dermis, orbicularis muscle, or eyelid skin) as defined pre-
viously (Figure 5).27 There is much evidence showing that
preseptal eyelid involvement is associated with a worse
prognosis than disease confined to conjunctiva and/or/orbit.1,3,5,15,18,19,28 Tumors are categorized as T3 irrespective of
any such conjunctival and/or orbital involvement.

Stage T4 refers to tumor invasion of bony and soft-tis-
ture structures beyond the ocular adnexa, including the
perioseum, bone, nasopharynx, the adjacent sinuses, and
the intracranial cavity (Figure 6). These advanced stages
are usually seen with high-grade lymphomas, which be-
have aggressively (eg, diffuse large B-cell lymphomas,
mantle cell lymphomas, and T/NK cell lymphomas).9,10,29,30

Lymph node involvement of OAL at diagnosis is docu-
mented using the N stage. The regional lymph nodes of
the ocular adnexa include the submandibular, preauricu-
lar, and cervical lymph nodes. Distant nodes include “cen-
tral” nodes, located in the trunk (eg, mediastinal and
para-aortic nodes) and “peripheral” nodes at other distant
sites not draining the ocular adnexa (eg, popliteal lymph
nodes). The different substages of N indicate whether the
lymph node involvement is local (ipsilateral, contralateral,
bilateral), central, or peripheral.

The M stage documents involvement of an extranodal
site distant to the ocular adnexa as well as bone marrow
infiltration (Figure 7). The most common metastatic sites
of OAL include salivary glands, gastrointestinal tract,
lung, and liver. Lymphomatous infiltration of these organs

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### TNM Clinical Staging for Ocular Adnexal Lymphomas (OALs)*

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Tumor extent</th>
<th>T0</th>
<th>No evidence of lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>Bulbar conjunctiva only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>Palpebral conjunctiva ± fornix ± caruncle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1c</td>
<td>Bulbar and nonbulbar conjunctival involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Lymphoma with orbital involvement ± any conjunctival involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>Anterior orbital involvement but no lacrimal gland involvement (± conjunctival disease)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>Anterior orbital involvement with lacrimal gland involvement (± conjunctival disease)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2c</td>
<td>Posterior orbital involvement (± conjunctival involvement ± any extraocular muscle involvement)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2d</td>
<td>Nasolacrimal drainage system involvement (± conjunctival involvement but not including nasopharynx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Lymphoma with preseptal eyelid involvement27,30 ± orbital involvement ± any conjunctival involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Orbital adnexal lymphoma extending beyond orbit to adjacent structures, such as bone and brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>Involvement of nasopharynx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Osseous involvement (including perioseum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4c</td>
<td>Involvement of maxillofacial, ethmoidal ± frontal sinuses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4d</td>
<td>Intracranial spread</td>
<td></td>
<td></td>
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<tr>
<td>Lymph node involvement (N)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Involvement of lymph nodes not assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>No evidence of lymph node involvement</td>
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<td></td>
</tr>
<tr>
<td>N1</td>
<td>Involvement of ipsilateral regional lymph nodesa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>Involvement of contralateral or bilateral regional lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td>Involvement of peripheral lymph nodes not draining ocular adnexal region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N4</td>
<td>Involvement of central lymph nodes</td>
<td></td>
<td></td>
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<tr>
<td>Distant metastasis (M)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MX</td>
<td>Dissemination of lymphoma not assessed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>No evidence of involvement of other extranodal sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>Lymphomatous involvement in other organs recorded either at first diagnosis or subsequently</td>
<td></td>
<td></td>
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<tr>
<td>M1a</td>
<td>Noncontiguous involvement of tissues or organs external to the ocular adnexa (eg, parotid glands, submandibular gland, lung, liver, spleen, kidney, breast)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1b</td>
<td>Lymphomatous involvement of the bone marrow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1c</td>
<td>Both M1a and M1b involvement</td>
<td></td>
<td></td>
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</tbody>
</table>


*b The anterior orbit is defined as the area between the orbital septum and the equator of the globe. The posterior orbit is defined as the area posterior to the equator of the globe, extending to the orbital apex.

c Eyelid involvement is said to exist when the OAL infiltrates preseptal tissues (ie, tissues anterior to the orbital septum).

d Regional lymph nodes, which include the preauricular (parotid), submandibular, and cervical lymph nodes.
Figure 2. Bulbar conjunctival ocular adnexal lymphoma (OAL) with a TNM stage of T1a.

Figure 3. An ocular adnexal lymphoma (OAL) involving both bulbar and nonbulbar conjunctiva is placed in the T1c category.

Figure 4. Magnetic resonance imaging of an ocular adnexal lymphoma (OAL) involving the lacrimal gland and extending into the posterior orbit (pT2c).

Figure 5. Clinical picture of an ocular adnexal lymphoma (OAL) involving the eyelid and periorcular skin (pT3).

Figure 6. Magnetic resonance imaging of an extensive ocular adnexal lymphoma (OAL) with involvement of eyelid, orbit, and periosteal tissues, representing pT4.

Figure 7. Bone marrow infiltration of neoplastic lymphocytes arising from the same B-cell clone of a primary ocular adnexal lymphoma (OAL; pT1pN0pM2) (hematoxylin-eosin, original magnification ×40).
can be recorded at either the time of first diagnosis or subsequently, in which case the term M1 is used. Bone marrow infiltration occurs in up to 30% of patients with OAL. This infiltration can occur in different patterns (eg, micronodular, paratrabeicular, or diffuse interstitial) and should be documented as M2.

**COMMENT**

This is the first TNM staging system for OAL. It describes such tumors more precisely than the Ann Arbor system. The stages we have defined are based on published evidence, much of which has been corroborated by multiple, independent studies, some with large patient numbers. The T2a and T2b stages, documenting the extent of orbital involvement, are not based on published evidence, but rather, on extensive experience, but should facilitate future evaluation of these categories. Intuitively, one would expect that more extensive orbital involvement would reflect more aggressive or more advanced disease and, hence, a worse prognosis.

A weakness of our staging system is that it has not been validated on a large cohort of patients; however, such studies—both retrospective and prospective—are in progress. Encouragingly, our proposed TNM staging system for OAL has been ratified by both the International Union against Cancer and the College of American Pathologists (K. T. Bradley, D. A. Arber, M. Brown, et al, unpublished data, 2008).

It must be emphasized that this proposed staging system is for primary OAL only and is not intended for intraocular lymphomas. It is acknowledged that controversy does exist about some patients with extensive systemic disease as to whether the lymphoma manifestation in the ocular adnexa is primary or secondary. Careful analysis of the clinical history and ascertaining the presence or absence of any previous evidence of lymphomatous disease elsewhere usually enables clarity in such cases.

Future plans include the incorporation of nonclinical data with the aim of identifying biomarkers of prognostic relevance. Such data might include histomorphologic lymphoma subtyping, immunohistochemical indicators of cell proliferation (eg, Ki-67), as well as cytogenetic and molecular genetic information. Clinical data, such as age, general condition, and serum markers (eg, lactate dehydrogenase level) will be merged with our TNM scores to derive prognostic indices, providing more predictive information for the individual patient.

**CONCLUSIONS**

Current staging systems for NHL are not useful for the clinical staging of OALs. A user-friendly staging system for OAL would improve communication about the stage of disease, selection of appropriate management, standardization of enrollment and response criteria in clinical trials, and collection/analysis of prospective survival data. The proposed American Joint Committee on Cancer—International Union Against Cancer staging system for OAL is the first specialized TNM-based staging system of ocular lymphomas. It allows for analysis of site-specific factors not addressed by previous systems. The TNM OAL staging system is currently an anatomic documentation of disease extent but will, in the future, incorporate additional prognostic information (eg, clinical, biologic, and molecular biologic data).

We sincerely thank Stefan Seregard, MD, and James O. Armitage, MD, for their involvement in the design of, and discussions about, the TNM staging system for OAL as well as proofreading the TNM chapter in the 7th edition of the AJCC's Cancer Staging Handbook (in press).

**References**


