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Ophthalmic Technology Assessment

Treatments for Ocular Adnexal Lymphoma

A Report by the American Academy of Ophthalmology

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Purpose: To review the literature to determine the efficacy of available treatments for ocular adnexal lymphoma (OAL) and to evaluate the outcomes and complications of treatments in patients older than 13 years.

Methods: A literature search was conducted last in March 2017 in the PubMed and Cochrane Library databases for English-language original research investigations that evaluated treatment outcomes for OAL. The searches identified 307 unique citations, and 27 studies were selected according to the criteria outlined for this assessment.

Results: The 27 studies reviewed comprised 2009 patients. Seventy-five percent of the cases reported were extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT). Twenty-five studies reported results using radiotherapy with or without chemotherapy or surgery. The local control rate of MALT lymphomas with treatments involving radiotherapy averaged 95.9%. Distant and local relapses can occur, and in studies reporting only on MALT lymphomas (884 patients), the 5-year and 10-year disease-free survival rates were reported to be 86.4% and 78.7%, respectively. However, overall survival in patients receiving radiotherapy remained very good, with the 5-year and 10-year survival rates reported to be 93.8% and 84.9%, respectively. Studies that included data on multiple histologic subtypes of lymphoma or non-MALT lymphomas (988 patients) reported local control rates to be 93.1%; 5-year and 10-year disease-free survival rates to be 75.7% and 71.0%, respectively; and 5-year and 10-year overall survival rates to be 78.9% and 73.5%, respectively. Studies on the use of doxycycline for MALT lymphomas (137 patients) reported complete responses of between 4.4% and 13%. Complete and partial responses combined were between 26.7% and 65%. Disease-free survival was not reported for these 2 studies, although progression-free survival was reported to be between 55% and 60.9%. The most frequently reported complications of treatment were cataracts (12.1%) and dry eye (8.5%).

Conclusions: For MALT lymphomas, local control, disease-free survival, and overall survival are good with radiation treatment. The results of treatment of non-MALT lymphomas using radiotherapy also were good, but they were not as favorable as the treatment results of MALT lymphomas. *Ophthalmology 2017;■:1–10 © 2017 by the American Academy of Ophthalmology*

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee/Oculoplastics and Orbit Panel is to determine the efficacy of available treatments for ocular adnexal lymphoma (OAL) and to evaluate the outcomes and complications of treatments in patients older than 13 years of age.

Background

Ocular adnexal lymphoma is the most common primary orbital malignancy in adults.[1–3] Compared with other sites in the body, ocular adnexal involvement is relatively rare, accounting for approximately 8% of all extranodal lymphomas.[4] However, the incidence of OAL has been noted to be increasing, especially in the elderly, perhaps because of the longer life expectancy of the general population.[5,6] Although all subtypes of lymphoma have been reported to occur in the orbit, the most frequent histologic subtypes of OAL are extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), followed by follicular cell lymphoma.[1,7] Mucosa-associated lymphoid tissue lymphomas have been reported to account for 35% to 90% of OALs.[8–11] There are conflicting reports on the

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association between MALT lymphomas and *Chlamydia psittaci* infection, which may suggest geographic variation or a coincidental association.[3,5,12,13]

Ocular adnexal lymphoma typically presents as a slowly enlarging, painless mass that causes proptosis, but it generally does not result in decreased vision or diplopia.[5,14] When present in the conjunctiva, OAL classically has a salmon-patch appearance. In the orbit, OAL can involve the lacrimal gland, extraocular muscles, or intraconal and extraconal spaces. Orbital imaging typically shows a poorly defined mass that molds to the shape of surrounding structures without direct invasion or bony erosion.[15] In addition to orbital imaging with computed tomography, magnetic resonance imaging (MRI), or both, positron emission tomography or combined computed tomography and positron emission tomography often are performed for systemic staging of disease.[16] Biopsy of the mass should be performed to identify the histologic subtype for diagnosis, to help guide treatment, and to allow for risk stratification.

Many treatments for OAL have been reported, including radiotherapy, chemotherapy, immune modulating therapy, primary antibiotic treatment, surgical excision, or combination therapy. Most treatments generally have been reported to have good outcomes, although small patient numbers, varied histologic subtypes, and the lack of large prospective studies can make interpreting the comparative effectiveness of these treatments challenging.

Question for Assessment

The objective of this assessment was to address the following question: What are the outcomes of the various treatments for OAL with respect to local control, disease-free survival rates, overall survival rates, and complications of treatment?

Description of Evidence

A literature search was conducted last in March 2017 in the PubMed and Cochrane Library databases and was limited to English-language abstracts and citations from 2001 onward. To ensure consistency in comparing the various studies, the decision was made to exclude abstracts dating before 2001, because that was the year the World Health Organization Classification of Tumours was first implemented. The search terms used were as follows:

1. ((*eye* OR *orbit* OR *orbital* OR *ocular*) AND (*Lymphoma*, *Non-Hodgkin*[Mesh]) OR (*Lymphoma*, *B-Cell*, *Marginal Zone*[Mesh] OR *Lymphoma*, *B-Cell*[Mesh] OR *t-cell lymphoma* OR *Lymphoma*, *T-Cell*[Mesh] OR *Lymphoma*, *Follicular*[Mesh] OR *Lymphoma*, *Mantle-Cell*[Mesh] OR *Orbital lymphoma*[Supplementary Concept] OR *Orbital Neoplasms*[Mesh] OR *orbital lymphoma* OR *orbital neoplasm* OR *orbital neoplasms*)) AND ((*Protons/therapeutic use*[Mesh]) OR *Photons/therapeutic use*[Mesh]) OR *Electromagnetic Radiation/therapeutic use*[Mesh] OR *X-Ray Therapy*[Mesh]) OR *Radiotherapy*[Mesh] OR *X-Rays/therapeutic use*[Mesh] OR (*Drug Therapy*[Mesh] OR *drug therapy*[Subheading] OR *Drug Therapy*, *Combination*[Mesh] OR *Immunotherapy/therapeutic use*[Mesh] OR *Immunologic Techniques/therapeutic use*[Mesh] OR *Tetracyclines/therapeutic use*[Mesh] OR (*orbital radiation*[tiab] OR *chemotherapy*[tiab] OR *radiotherapy*[tiab] OR *irradiation*[tiab] OR *immunotherapy*[tiab] OR *x-ray*[tiab] OR *xray*[tiab] OR *xrays*[tiab] OR *x-rays*[tiab])) AND (*random**[tiab] OR *RCT*[tiab] OR *cohort studies* OR *cohort study* OR *outcomes research* OR *case control* OR *case series* OR *Clinical Trial*[Publication Type] OR *Comparative Study*[Publication Type] OR *Multicenter Study*[Publication Type] OR *Randomized Controlled Trial*[Publication Type]) OR (*Treatment Outcome*[Mesh]) NOT ((*Infant*[Mesh]) OR ((*Child*[Mesh]) OR *Child*, *Preschool*[Mesh])) AND ((*Adult*[Mesh] OR *Young Adult*[Mesh] OR *Aged*[Mesh] OR *Aged*, *80 and over*[Mesh] OR *Adolescent*[Mesh]))
2. (*eye* OR *orbit* OR *orbital* OR *ocular*) AND ((*Lymphoma*, *Non-Hodgkin*[Mesh]) OR (*Lymphoma*, *B-Cell*, *Marginal Zone*[Mesh] OR *Lymphoma*, *B-Cell*[Mesh]) OR *t-cell lymphoma* OR *Lymphoma*, *T-Cell*[Mesh]) OR *Lymphoma*, *Follicular*[Mesh]) OR *Lymphoma*, *Mantle-Cell*[Mesh]) OR (*Orbital lymphoma*[Supplementary Concept] OR *Orbital Neoplasms*[Mesh] OR *orbital lymphoma* OR *orbital neoplasm* OR *orbital neoplasms*))
3. *primary ocular adnexal lymphoma* OR *primary ocular adnexal lymphomas*
4. ((*Protons/therapeutic use*[Mesh] OR *Photons/therapeutic use*[Mesh]) OR *Electromagnetic Radiation/therapeutic use*[Mesh] OR *X-Ray Therapy*[Mesh] OR *Radiotherapy*[Mesh] OR *X-Rays/therapeutic use*[Mesh]) OR (*Drug Therapy*[Mesh] OR *drug therapy*[Subheading] OR *Drug Therapy*, *Combination*[Mesh])) OR *Immunotherapy/therapeutic use*[Mesh]) OR *Immunologic Techniques/therapeutic use*[Mesh] OR *Tetracyclines/therapeutic use*[Mesh] OR (*orbital radiation*[tiab] OR *chemotherapy*[tiab] OR *radiotherapy*[tiab] OR *irradiation*[tiab] OR *immunotherapy*[tiab] OR *x-ray*[tiab] OR *xray*[tiab] OR *xrays*[tiab] OR *x-rays*[tiab])
5. (*random**[tiab] OR *RCT*[tiab] OR *cohort studies* OR *cohort study* OR *outcomes research* OR *case control* OR *case series*) OR (*Clinical Trial*[Publication Type]) OR *Comparative Study*[Publication Type]) OR *Multicenter Study*[Publication Type]) OR *Randomized Controlled Trial*[Publication Type]) OR (*Treatment Outcome*[Mesh])
6. ((*eye* OR *orbit* OR *orbital* OR *ocular*) AND (*Lymphoma*, *Non-Hodgkin*[Mesh]) OR (*Lymphoma*, *B-Cell*, *Marginal Zone*[Mesh] OR *Lymphoma*, *B-Cell*[Mesh])) OR t-cell lymphoma) OR *Lymphoma*, *T-Cell*[Mesh]) OR *Lymphoma*, *Follicular*[Mesh]) OR *Lymphoma*, *Mantle-Cell*[Mesh]) OR (*Orbital lymphoma* [Supplementary Concept] OR *Orbital Neoplasms*[Mesh])) OR *orbital lymphoma* or *orbital neoplasm* or *orbital neoplasms*)).