Ocular adnexal lymphoma: A single-institution retrospective study

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Abstract:

PURPOSE: To characterize demographic, clinical, and histopathologic features of ocular adnexal lymphoma (OAL) at a single institution.

METHODS: Retrospective review of all patients with pathologic diagnosis of OAL between 2015 and 2020.

RESULTS: There were 133 patients with OAL, with a median age of 65 years (range 23–97) and a slight female predominance (male: female = 1:1.46), (n = 79, 59%). The majority of tumors were non-Hodgkin B-cell lymphomas (n = 131, 99%), most frequently Extranodal Marginal Zone B-Cell Lymphoma (EMZL, n = 93, 70%), followed by follicular lymphoma (n = 21, 16%), chronic lymphocytic leukemia/small lymphocytic lymphoma (n = 7, 5%), diffuse large B-cell lymphoma (n = 5, 4%), and mantle cell lymphoma (n = 5, 4%). The most frequently involved sites included the orbit (n = 85, 64%) and conjunctiva (n = 43, 32%). Information was available on oncologic staging in 78 (59%), treatment in 82 (62%), and follow-up in 75 (56%) patients. By the Ann-Arbor classification system, patients were classified as IE (54/78, 69%), IIE (9/78, 12%), IIIE (6/78, 8%), and IVE (9/78, 12%). The most common treatments included external beam radiotherapy (standard and ultra-low-dose) (48/82, 59%), biologics (22/82, 27%), and surgical excision with cryotherapy (14/82, 17%) (some patients had >1 therapy). Median follow-up time was 24 months (range 0–221 months). Recurrence was observed in 13% (10/75) with a median time to recurrence of 60 months (95% confidence interval 47–73 months). Excision with cryotherapy as a sole treatment modality was associated with earlier recurrence (P = 0.003).

CONCLUSION: In this largest single-center study of OAL, we found that most OAL were Ann-Arbor Stage IE EMZL, occurring in older patients with a female predominance. Early recurrence was noted in tumors treated with excision and cryotherapy alone.

Keywords: Ocular adnexal lymphoma, Ocular adnexal lymphoma pathology, ocular adnexal lymphoma recurrence, ocular adnexal lymphoma staging, ocular adnexal lymphoma treatment

INTRODUCTION

Lymphomas are malignant tumors derived from clonal expansion of B or T lymphocytes, and rarely natural killer (NK) lymphocytes. B-cell lymphomas are broadly divided into Hodgkin and non-Hodgkin subtypes and can arise in a lymph node or in an extranodal site.[1] Lymphomas are further classified according to the presumed cell of origin as defined by the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues.[1] Although pathogenesis of ocular adnexal lymphoma (OAL) is multifactorial, a major proposed mechanism is a clonal expansion of lymphocytes induced by persistent antigenic stimulation from chronic inflammation, analogous to a process that has been described in other mucosal-associated lymphoid tissue sites.[2,4]

Ophthalmic lymphomas can involve the intraocular tissues or the OA. Intraocular lymphomas are rare and include vitreoretinal diffuse large B-cell lymphomas (DLBCL) associated with central nervous system lymphoma, and choroidal...
lymphoma associated with systemic lymphoma.\(^{[5‑7]}\) OAL can be primary, arising in the eyelids, conjunctiva, lacrimal gland, lacrimal sac, extraocular muscles, and orbital soft tissue, or can involve these structures secondarily. Compared to all lymphomas collectively, OAL is rare, with an incidence of 0.28 cases per 100,000 patients and comprising only 1%–2% of all lymphomas and 8% of all extranodal lymphomas. However, it is important to note that OAL is the most common orbital malignancy in adults, accounting for 10% of all orbital mass lesions, and this percentage can increase up to 24% in patients aged 60 years or older.\(^{[8‑11]}\)

OAL predominantly affects patients in the fifth to seventh decade of life, with a median age of 65 years and female predominance, with female-to-male ratio of 1.5–2:1.\(^{[12‑15]}\) The most frequent involved site is the superior orbit (40%), followed by conjunctiva (35%–40%), lacrimal gland (10%–15%), and the eyelid (10%).\(^{[12‑14,16]}\) Demirci et al. reviewed 160 cases of orbital lymphoproliferative tumors and noted involvement of the superior orbit in 64%, inferior 9%, temporal 8%, nasal 8%, and 11% central.\(^{[11]}\) The most common presenting signs were orbital mass (67%), proptosis (54%), restriction of extraocular motility (39%), conjunctival swelling with a “salmon-patch” appearance (22%), and symptoms of irritation and tearing.\(^{[12‑14,16‑19]}\)

Of all OALs, 98% are B-cell lymphomas, with extranodal marginal zone B-cell lymphoma (EMZL) being the most common subtype (49%–64%), followed by follicular lymphoma (FL) (10%–23%), and DLBCL (8%–10%).\(^{[13,20,21]}\) The less frequent subtypes include mantle cell lymphoma (MCL) (5%–9%), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (4%–7%). T-cell lymphomas are extremely rare accounting for <2% of all OALs.\(^{[13,20,21]}\)

The objectives of this study were to analyze the distribution of OAL at our institution by demographics, location, subtype, treatment, and outcome and to compare our data with the prior literature.

**Methods**

**Study design**

A retrospective review of patients with the pathologic diagnosis of OAL managed by the Pathology, Oncology, and Oculoplastic and Orbital Surgery Services at a single tertiary care center between January 01, 2015 and January 01, 2020, was performed. The study was approved by the Institutional Review Board and followed the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability act of 1996 in the United States.

**Tissue selection/biopsy Specimens**

The pathologic diagnoses were rendered based on the integration of morphologic, immunohistochemical, immunophenotypic, and molecular genetic parameters in accordance with the current World Health Organization classification of lymphomas.\(^{[11]}\)

Immunohistochemical panels for B-cell and T-cell lymphoma included the following panel of antibodies: CD3, CD5, CD4, CD8, CD7, CD10, CD20, CD21, CD23, CD30, CD56, CCND1 (cyclin D-1, BCL-1), BCL-2, BCL-6, MUM1, CD138, kappa, lambda, c-MYC, and Ki-67. Flow cytometry was performed with standard panels for B-cell and T-cell lymphoma. Molecular genetic studies included the polymerase chain reaction for B-cell and T-cell clonality, fluorescence in situ hybridization for lymphoma subtyping, targeted next generation sequencing with a 40 gene lymphoma panel (complete list of genes available at https://www.pennmedicine.org/-/media/academic%20departments/personalized%20diagnostics/pdfs/canfy1819117epdphysicianbrochure2018updatev2.ashx?la=en) or targeted MYD88 mutation analysis.

**Clinical data**

The demographic and clinical data collected included age, sex, presenting signs and symptoms, clinical local disease extent, biopsy site, tumor laterality, results of systemic oncologic workup, management, and outcome. The patients were staged in accordance with the Ann Arbor staging system for extranodal lymphoma and the tumour node metastasis (TNM) classification for OAL specified by the American Joint Committee on Cancer (AJCC) Cancer.\(^{[22,23]}\)

The tumors were classified into 3 categories: Primary, disseminated, and secondary. Primary OAL was defined as lymphoma limited to the OA and the adjacent regional site (unilateral preauricular or sub-mandibular lymph nodes or nearby structures such as the parotid gland) and no prior history of lymphoma elsewhere. Disseminated OAL was defined OAL with concurrent involvement of lymph nodes outside of regional area or in noncontiguous tissues or organs external to the OA (submandibular gland, lung, liver, spleen, kidney, breast, and bone marrow) at the time of diagnosis. Secondary OAL was defined as known systemic lymphoma of any kind, with secondary involvement of the OA. Progression of disease was defined as transformation from a low-grade to a high-grade lymphoma or progression to a higher Ann Arbor or AJCC TNM stage after a period of remission. Recurrence of the disease was defined as lymphoma that re-manifested after successful treatment and a period of remission (no evidence of lymphoma on follow-up testing and imaging).

Oncologic workup (imaging, laboratory studies, bone marrow biopsy) and management including treatment modalities (excision and cryotherapy, systemic chemo-and/or biologic therapy, radiation, and allogenic bone marrow stem cell transplant [BMT] or combination therapies) were documented. Outcome information included recurrence status, time to recurrence, disease progression, disease-related mortality, and date of last follow-up.\(^{[24,25]}\)

**Statistical analysis**

Demographic and clinical data of patients with recurrent and non-recurrent OA lymphoma were summarized and proportions were analyzed via Chi-square test or Fisher exact test.
Results

Tissue selection/biopsy Specimens

Review of pathology records identified a total of 170 biopsies suspicious for lymphoproliferative disease between 2015 and 2020. Of these, 133 (78%) were diagnosed as OAL [Figure 1]. Histopathologic findings were supported by immunohistochemical panels in 126 (95%), flow cytometry in 57 (43%), and molecular genetic studies in 30 (22%) cases.

Overall ocular adnexal lymphoma clinical features

OAL occurred at the median age of 65 years (range 23–97 years) with a female predominance (79/133, 59%) [Table 1]. The mean time from clinical symptoms to consultation was 12 months (interquartile range 6–45 months).

Laterality was known in 131 of 133 (98%) patients. 52 of 131 (40%) lesions involved the left OA, 60 of 131 (46%) involved right OA, and 19 of 131 (14%) demonstrated bilateral involvement [Table 2]. Presenting signs included proptosis, decreased visual acuity, “salmon-patch” mass, and tearing.

The orbit and the conjunctiva were the most frequently involved OA sites, accounting for 50% and 32% of 133 cases, respectively [Table 2].

Of 78 patients with staging information, 58 (74%) had primary OAL, 16 (21%) had disseminated lymphoma, and 4 (5%) had secondary lymphoma [Table 3]. The Ann Arbor and AJCC classification data are summarized in Table 4.

Ocular adnexal lymphoma subtypes

Of 133 lymphomas, 131 (99%) were B-cell lymphomas and the remaining 2 (1%) were T-cell lymphoma [Table 1].

Extranodal Marginal Zone B-cell lymphoma throughout EMZL was by far the most common lymphoma of the OA, constituting 93 of 133 (70%) of all cases [Table 1]. EMZL was more common in females, with a male: female ratio 1:1.2, and a median age of 64 years (range 23–92). Most EMZL lymphomas (44/52, 85%) were primary, Ann Arbor stage IE (44/53, 83%), involved the conjunctiva alone (AJCC T1, 23/52, 44%) or orbit (AJCC T2, 28/52, 54%), and had low frequency of distal nodal involvement (AJCC N3, 2/52, 3%). None of the patients with EMZL had extranodal involvement outside of OA [Table 4].

Follicular lymphoma

FL was the second most common OAL, constituting 21/133 (16%) of all cases. The majority (19/21, 90%) of FL were low-grade, with only two (2/21, 10%) high-grade (Grade 3) cases. FL was more common in females, with a M:F ratio 1:3.2 and a median age of 71 years (range 34–97) [Table 1]. Similar to EMZL, most FL were primary (10/16, 63%) and confined to the OA and regional sites [10/16, 63% stage IE and IIE, Table 4]. However, isolated conjunctival involvement was less frequent in FL (AJCC T1, 4/16, 25%) when compared to EMZL. Additionally, FL had a higher tendency for disseminated disease (5/16, 31%), higher Ann Arbor stage IIIE (4/16, 25%), and a higher potential for distal nodal metastasis (N3 6/16, 38%) and extranodal metastasis (1/16, 6%) [Table 4]. Of two high-grade FL, one was secondary FL, Ann Arbor stage IIIIE and the second high-grade FL was stage IE.
Table 1: Demographics of patients with ocular adnexal lymphoma by subtype (n=133)

| Type of lymphoma                  | n (%) | Median age (years) | Age range (years) | Male:female ratio |
|-----------------------------------|-------|-------------------|-------------------|------------------|
| Marginal zone lymphoma            | 93 (70)| 64                | 23-92             | 42:51 (0.8)      |
| Follicular lymphoma               | 21 (16)| 71                | 34-97             | 4:16 (0.3)       |
| Small lymphocytic lymphoma        | 7 (5) | 69                | 66-85             | 2:5 (0.4)        |
| Diffuse large B-cell lymphoma     | 5 (4) | 76                | 64-89             | 1:4 (0.3)        |
| Mantle cell lymphoma              | 5 (4) | 61                | 51-76             | 4:1 (4)          |
| T-cell lymphoma                   | 2 (1) | 34                | 26-41             | 0:2 (0)          |
| Total                             | 133 (100)| 65              | 23-97             | 54:79 (0.7)      |

Table 2: Ocular adnexal lymphoma presentation by histological location (n=133)

| Location                        | n (%) |
|---------------------------------|-------|
| Orbital fibroadipose tissue     | 49 (37)|
| Conjunctiva                     | 43 (32)|
| Lacrimal gland                  | 18 (13)|
| Eyelid                          | 2 (2)  |
| Lacrimal sac                    | 2 (2)  |
| Extraocular muscle              | 1 (1)  |
| Mixed location                  | 18 (13)|
| Orbit, conjunctiva              | 10 (7) |
| Orbit, caruncle                 | 2 (1)  |
| Orbit, conjunctiva, lacrimal gland| 2 (1) |
| Orbit, tenon fascia             | 1 (1)  |
| Orbit, skin, extraocular muscle | 1 (1)  |
| Orbit, lacrimal gland           | 1 (1)  |
| Orbit, extraocular muscle       | 1 (1)  |
| Laterality (n=131)              |       |
| Left                            | 52 (40)|
| Right                           | 60 (46)|
| Bilateral                       | 19 (14)|

Chronic lymphocytic leukemia/small lymphocytic lymphoma

CLL/SLL was the third most common OAL, comprising 7/133 (5%) of all cases [Table 1]. CLL/SLL was more common in females, with a male: female ratio 1:2.5, and a median age of 69 years (range 66–85) [Table 1]. Of 4 patients with staging information, 3 lymphomas were primary Ann Arbor stage IE (75%). All tumors affected the orbit (T2). One patient (25%) with secondary CLL/SLL had extranodal metastasis [Table 4].

Diffuse large B-Cell lymphoma

DLBCL was the fourth most common OAL, comprising 5/133 (4%) of all cases. DLBCL was more common in females, with a male: female ratio 1:4, and a higher median age of 76 years (range 64–89) when compared to EMZL, although the difference was not statistically significant (76 vs. 64, P = 0.06). By Hans algorithm, 3/5 (60%) DLBCL were of non-germinal center B-cell (non-GCB) type and 2/5 (40%) DLBCL were of GCB type. [1] None of these high-grade lymphomas had rearrangements in MYC/BCL-2/BCL-6 genes characteristic of double-hit or triple-hit lymphoma. [1] Of 2 patients with staging information, one had primary disease and one had disseminated disease at presentation with distal nodal and extranodal metastasis [Tables 3 and 4].

Mantle cell lymphoma

MCL was the fourth most common OAL, together with DLBCL, constituting 5/133 (4%) of all lymphomas. MCL was the only lymphoma with male predilection (male: female ratio 4:1) and had a median age of 61 years (range 51–76). Of 3 patients with available staging information, all had advanced stage IVE lymphoma, presenting with either disseminated disease (2/3, 67%) or as a secondary orbital involvement of a known systemic disease (1/3, 33%) [Tables 3 and 4].

T-cell lymphoma

T-cell lymphoma was the least frequent OAL subtype, constituting 2/133 (1%) of all lymphomas. Both affected patients were females with a median age of 34 years (range 26–41) [Table 1]. One patient with known staging information had disseminated Ann Arbor Stage IV disease at the time of diagnosis [Tables 3 and 4].

Treatment, follow-up and recurrence

Treatment information was available on 82 of 133 (62%) patients [Table 5 and Supplementary Digital Content Figures 1-3]. Treatment was administered as a monotherapy in 72 patients (88%) or as a combination therapy in 10 patients (12%). The most common treatment modality was external beam radiotherapy (EBRT) (48/82, 59%), administered as a monotherapy (42/48, 88%) or in combination (6/48, 12%). The dose of EBRT varied from 24 to 30 Gy fractioned in 15 sessions or an ultra-low-dose (4 Gy) radiotherapy (ULDR), divided in two sessions (also known as “Boom-Boom” technique). [26] The second most common treatment modality was biologic agents (22/82, 27%), comprising the CD20-targeted antibody therapy (rituximab) in 21 patients and Bruton tyrosine kinase inhibitor (ibrutinib) in one patient with CLL/SLL. Fourteen of 82 patients (17%) were managed by excision with cryotherapy followed by observation. Seven of 82 (9%) patients were managed by chemotherapy [Table 5].

Treatment was generally dependent on lymphoma staging and subtype [Table 5 and Supplementary Digital Content Figures 1-3] as well as systemic involvement. Some patients received multiple therapies. The stage IE OAL was generally treated with EBRT or ULDR (32/50 (64%). The patients with stage IIIIE and IVE lymphoma underwent more aggressive therapy, including systemic biologics (6/12, 50%), chemotherapy (3/12, 25%), combination chemotherapy and allogenic BMT (1/12, 8%). One patient with stage IVE CLL/
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SLL was treated with palliative therapy because of advanced age and disseminated disease. Most patients with EMZL were treated with radiotherapy (34/59, 58%) or excision with cryotherapy followed by observation (12/59, 20%). The excision and cryotherapy as the sole therapy was a therapeutic choice in elderly, frail, and debilitated patients, who were not good candidates for other ancillary treatment modalities. Five of 15 (33%) of patients with bilateral EMZL received...
biologic therapy [Table 5]. The more aggressive lymphomas were more frequently treated with systemic therapy, such as chemotherapy in combination with either biologics or BMT in 2 of 3 MCLs and either chemotherapy or biologics in 2 of 3 DLBCLs [Table 5].

**Recurrent ocular adnexal lymphoma**

Follow-up information was available on 75 of 133 (56%) patients. Mean patient follow-up was 24 months (95% CI 15–33 months), with a range of 0–221 months. Disease progression was documented in one patient, who had bilateral conjunctival and right orbital EMZL with disseminated nodal involvement, which transformed to DLBCL 29 months after diagnosis. Local recurrence occurred in 10 patients (13%) with a median time to recurrence of 60 months [95% CI 47–73 months, Supplementary Digital Content Figure 4]. The recurrent tumors were predominantly EMZL (9/10, 90%) and less frequently, FL, Grade ½ of 3 (1/10, 10%). Recurrent lesions were localized to the orbit (5/10, 50%) and conjunctiva (5/10, 50%), with most arising at the site of primary OAL (8/10, 80%). Multiple tumor recurrences were noted in 2 patients (2/10, 20%). Recurrent tumors were initially treated with a wide range of modalities including chemotherapy and biologics (2/9, 22%), chemotherapy and radiation (1/9, 11%), biologic therapy alone (2/9%) and excisional biopsy and cryotherapy alone (1/9, 11%) Recurrent tumors were managed with biologic therapy (3/7, 43%) and radiotherapy (4/7, 57%). At last follow-up, disease remission was achieved in 5/9 (56%) and stable disease in 4/9 (44%) patients. Excision and cryotherapy as a sole treatment modality was associated with earlier recurrence (Log rank \( P = 0.003 \)).

**DISCUSSION**

**Demographics and subtype**

This retrospective study identified 133 patients with OAL at a single tertiary care center. To our knowledge, this is the largest reported single-center study analyzing clinical, pathological and treatment data in patients with OAL.

Most patients in this cohort were older adults with a median age of 65 years, with a female predominance overall (59%, female: male ratio 1.5:1). This sex distribution was present in most subtypes of lymphoma with the exception of MCL, consistent with previous studies. DLBCL had the oldest age at presentation with a median of 76 years, also in line with published literature. Autoimmune disease, which has a documented association with OAL, was noted in only one patient with EMZL in this series, which likely reflects a regional variation and an incomplete clinical data in our cohort.

Patients with OAL commonly present with a mass lesion on clinical examination or imaging, associated with proptosis, ptosis, diplopia, decreased visual acuity, “salmon-patch” mass, and tearing. The frequent mild nature of presenting symptoms may account for prolonged time to diagnosis, with an average time from symptoms to consultation of 12 months in our cohort. This is compatible with a previous study by Demirci et al. in which 160 patients were assessed and found the mean duration of symptoms at 6 months (range 0–12 months). The insidious clinical course of OAL is hypothesized to be secondary to the high tumor cellularity and low extracellular connective stroma, which allows the tumor to mold rather than distort to the globe and adjacent orbital structures.

The OAL subtype distribution in this cohort was in line with previously described series. Nearly all lymphomas were of the B-cell type (99%), with the majority being low-grade lymphomas (EMZL [70%] and FL [16%]). Although the frequency of CLL/SLL in our study was slightly higher than DLBCL (5% vs. 4%, respectively) as compared with previously published data, the frequencies for these two lymphomas are known to range between 5% and 10%, which is in keeping with our study results.

The overall distribution of OAL in this study was consistent with previously published data. Over half of OAL involved the orbital fibroadipose tissue (64%), with 37% confined to the orbital fibroadipose tissue alone, 14% involving the lacrimal gland alone, and 14% involving the orbital soft tissue and other sites. The second most common location was conjunctiva, accounting for 32% of lymphoma in our series. Bilateral involvement was seen in 14% of patients and was not associated with lymphoma subtype (\( P = 0.366 \)).

Ann Arbor is the most commonly used staging system for non-Hodgkin lymphoma. By Ann Arbor staging, most patients with OAL fall into IE category. The Ophthalmic Oncology Task Force of the American Joint Committee on Cancer 8th edition has proposed a new TNM staging system for OAL, which is more site-specific and allows for better delineation of the local extent of tumor. However, this differentiation is not helpful for predicting systemic prognosis and has not been widely adopted. In our study, most OAL were Ann Arbor stage IE (54/78, 69%) and T1 (27/78, 35%) or T2 (49/78, 63%), N0 (55/78, 71%), and M0 (71/78, 91%) by AJCC classification, reflecting the predominance of EMZL lymphoma [Table 4], similar to the previously published data.

**Treatment**

The management of OAL is heterogeneous, as reflected by multiple treatment regimens in this study. The level of evidence for optimal management of OAL is generally low, leading to ambiguity on the optimal treatment of these patients. Most therapeutic decisions are based on tumor size, extent, subtype, and systemic involvement. Prior studies that included data on multiple histologic subtypes of OAL or non-EMZL lymphomas documented lower local control rates, disease-free survival rates, and overall survival rates when compared with the studies focused solely on EMZL. The adverse outcomes of higher-grade lymphomas justify the need for more aggressive systemic therapy, usually as a combination therapy. In our study, high-grade lymphomas with available information (DLBCL and MCL) were predominantly treated with chemotherapy, EBRT + biologics, EBRT + chemotherapy, or chemotherapy + BMT.
For indolent and low-grade OALs, we prefer local therapies with surgical excision and/or radiotherapy, whereas if systemic involvement is present, we tend to employ systemic biologics or chemotherapy. Aggressive subtypes (MCL, DLBCL) are treated with systemic therapy, even when localized to the OA. Patients with advanced disease (stage IIE and IVE) and systemic involvement underwent more aggressive treatments for OAL, including targeted biologic therapy (33%), systemic chemotherapy (8%), and combination therapies, such as allogenic BMT (8%). However, management was overall quite heterogeneous, in part reflective of a lack of randomized clinical studies and international consensus guidelines.

The heterogeneity in OAL management also stems from the need for individualized therapy, which is based on the patient-specific variables, tumor-related factors (size, location, symptoms, histopathology, and disease extent), and treatment risk-benefit considerations, which should all be balanced to optimize results. The most important prognosticators for survival after OAL are histological subtype and the extent of systemic involvement; when evaluating treatment regimens, these two factors must be taken into consideration. Currently, a complete diagnostic workup includes tumor biopsy, computed tomography (CT) or magnetic resonance imaging (MRI), skull base to midhigh positron emission tomography (PET)/CT, bone-marrow biopsy, and hematopathology/chemistry laboratory studies.

**Excision with cryotherapy**

Adequate tumor biopsy is mandatory for accurate diagnosis. Of note, enough tissue should be excised for both histopathology/immunohistochemistry (formalin-fixed) and flow cytometry (fresh, nonfixed tissue). Although “excision” has been attempted in circumscribed and easily accessible tumors, lymphoma is an infiltrative malignancy, with potential for local recurrence (up to 25% at 4 years) following excision without adjuvant therapy. The propensity for local OAL recurrence following excision and cryotherapy as the sole treatment modality was validated in this series; adjunctive EBRT in localized, indolent cases should be considered in most cases unless the patient is of very advanced age. Furthermore, attempts at excision of diffuse lesions can lead to surgical morbidity and have been shown to have null effect on survival.

The “wait and watch” approach for indolent OAL subtypes has been evaluated in several studies. In a retrospective study by Tanimoto et al., patients with asymptomatic EMZL who were initially managed with biopsy or surgical excision alone showed results similar to those reported with immediate radiotherapy in terms of disease progression, high-grade transformation, and lymphoma-related mortality. It is therefore reasonable to consider a conservative approach with frequent follow-up in elderly, asymptomatic patients or those with severe comorbidities, since the risk of progression to higher grade lymphoma or death related to lymphoma is low.

**Radiotherapy**

Adjuvant therapy can help control local recurrence in low-grade lymphomas. EBRT is the treatment of choice for the vast majority of localized low-grade OAL, with a potential for local disease control as high as 100% and a low recurrence rate that does not exceed 15%. The reliance on EBRT is seen in our series, with half of the patients managed with this therapeutic modality. According to the current National Cancer Center Network consensus guidelines, the suggested radiation dose is 20–30 Gy. Early radiation toxicity is manageable and typically consists of cutaneous or conjunctival inflammatory reactions, while long-term complications are observed in 50% patients and include cataract formation (30%–50%) and xerophthalmia (20%–40%). The two main radiation doses in our study were standard-dose radiation, which varies from 24 to 30 Gy fractioned in 15 sessions, and an ULDR, which consists of (4 Gy) in 2 sessions. Some literature suggests that complete response to ULDR may be initially achievable in the near term, but long-term implications for recurrence and survival have yet to be determined. Although a debate exists about the optimal dose, the small sample size of the cohort with recurrent lymphoma precluded statistical comparison of these two radiation schemes.

**Biologic therapy**

Rituximab (Mabthera/Rituxan, Roche, Basel, Switzerland) is a chimeric IgG1 monoclonal antibody directed against CD20 surface antigen on B lymphocytes, thought to mediate its anti-lymphoma effect through antibody and complement-dependent cytotoxicity and inducing apoptosis. Twenty seven percent of patients in our study received rituximab, either as monotherapy (17%) or in combination (10%) with other treatments. Patients with bilateral lymphoma in this cohort were more likely to receive rituximab when compared to those with unilateral disease (38% vs. 10%, respectively, $P = 0.0709$). Single-institution studies have shown response rates in the range of 30%–87% with rituximab monotherapy for the treatment of OAL, although long-term local control may be less than with regional radiotherapy.

Ibrutinib (Imbruvica, AbbVie, North Chicago, USA), is an irreversible, small-molecule inhibitor of Bruton tyrosine kinase, which stimulates pathways essential for B-cell survival and proliferation. Initially approved as a first-line therapy for CLL/SLL and as a therapy for relapsed/refractory MCL, ibrutinib has been shown to have efficacy in other B-cell lymphomas, including lymphoplasmacytic lymphoma, EMZL, and FL. In our cohort, one patient with CLL/SLL was managed with ibrutinib as a first-line therapy with excellent response.

**Chemoimmunotherapy**

The level of evidence supporting the use of chemoimmunotherapy as a treatment for OAL is low and limited to small prospective studies of patients that did not respond to local therapy. In our study, the lack of consensus guidelines was evidenced by the high variability in the treatment regimens of these patients. The frequently used chemotherapy regimens include CHOP (cyclophosphamide, adriamycin, procarbazine, and prednisone), COP/CVP (cyclophosphamide, vincristine
and prednisone), C-MOPP (cyclophosphamide, vincristine, pro-carbazine and prednisone) and chlorambucil.[26,36,57,58] The most preferred agent is chlorambucil, as it can be used in combination with other agents, causing low toxicity.[17] A recent IELSG19 trial, the largest randomized trial for EMZL lymphoma, compared chlorambucil vs. rituximab‑chlorambucil combination.[56] This trial demonstrated a higher complete remission rate in the combined arm (78% vs. 65%) and better 5‑year event‑free survival (68% versus 50%), suggesting that combination therapy is more effective.[56]

**Conclusion**

In this 5‑year retrospective single‑institution study, we characterized orbital and ocular adnexal lymphomas in terms of the clinical presentation, histopathologic findings, management, and outcomes. The vast majority of OALs were low‑grade B‑cell lymphomas with a low risk of dissemination or high‑grade transformation. Most tumors were successfully treated with local therapies, such as EBRT, while higher grade or higher stage lesions required more aggressive systemic treatments, including biologics, chemotherapy or immunotherapy, highlighting the individualized approach in OAL management. Finally, long‑term follow‑up of indolent OALs is necessary to monitor for local recurrence, systemic spread, or transformation to a high‑grade histopathology. Excision and cryotherapy as sole treatment modalities were associated with shorter interval to recurrence in this analysis.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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Supplementary Digital Content Figure 1: Management of ocular adnexal lymphoma by lymphoma subtype

Supplementary Digital Content Figure 2: Management of ocular adnexal lymphoma by treatment type

Supplementary Digital Content Figure 3: Management of ocular adnexal lymphoma by Ann Arbor stage

Supplementary Digital Content Figure 4: Recurrence-free survival of patients with orbital and ocular adnexal lymphomas