

# Ocular Adnexal MALTomas: Case Series of Patients Treated With Primary Radiation

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## Keywords

MALToma, ocular adnexa, lymphoma, radiation, conjunctiva, lacrimal gland

**Abstract:** *Background:* Ocular adnexal mucosal-associated lymphoid tissue lymphomas (MALTomas) are rare, and there are no phase III trials to guide treatment. Primary radiation therapy has been the typical management. This retrospective series reports the experience of a single institution and adds to the current literature. *Methods:* Our electronic medical record system and available paper charts were used to identify patients with MALTomas of the lacrimal gland or sac, conjunctiva, and orbital structures, including extraocular muscles. In order to determine pathology, staging, treatment information, local and distant control, salvage treatments, and late toxicity, records were reviewed. *Results:* Sixteen patients with ocular adnexal MALTomas had local radiation between 1992 and 2011 for primary or recurrent disease. Fifty percent of patients had lymphoma in the conjunctiva, 25% had lymphoma in the lacrimal sac/gland, and 25% of patients had lymphoma in the posterior orbit. Stage IAE disease occurred in 75% of patients, 6% had stage IIAE disease, and 19% of patients had a positive bone marrow biopsy. One patient received chemotherapy as part of initial therapy. The median radiation dose was 30 Gy (25.5–36 Gy) delivered with electrons (31%) or photons (69%). After a mean follow-up of 62.8 months, 2 patients had residual/progressive disease, 2 had contralateral recurrence, and 1 patient had a distant failure, for local control of 87.5% and overall disease control of 68.75%. Recurrence/progression occurred at a median of 35.45 months. Two patients with residual/progressive disease and 1 patient with a contralateral recurrence were followed, successfully salvaged, and have no evidence of disease. Fourteen patients are still alive, and there were no disease-related/toxicity deaths. Seven patients developed cataracts in the treated eye, 2 patients had radiation retinopathy, 2 had permanent dry eye syndrome, and 1 patient had severe keratopathy requiring enucleation. Six patients (3.75%) had worsening visual acuity of unclear etiology. *Conclusions:* Primary radiation therapy for ocular adnexal MALTomas with a median dose of 30 Gy led to excellent local control. Patients who did recur were successfully salvaged.

Radiation was generally well tolerated, with expected cataractogenesis, given the dose required to achieve local control (with only 1 patient developing severe keratopathy after receiving the highest dose in this series).

## Background

Ocular adnexal mucosal-associated lymphoid tissue lymphomas (MALTomas) are rare entities that comprise a small proportion of both orbital neoplasms and non-Hodgkin lymphomas (NHL). Unlike other NHL types, ocular adnexal lymphomas show little difference by sex. Incidence rates tend to be highest among Asians/Pacific Islanders, lower in whites, and lower still in blacks.<sup>1</sup> Additionally, the frequency of ocular adnexal lymphomas appears to be increasing, with annual increases of 6.2% for white males and 6.5% for white females with no evidence of peaking. By contrast, the rates for other extranodal NHLs increased at 4.3% and 4.0% per year among males and females, respectively, while the rates for nodal NHL rose less rapidly, at 1.8% and 1.3%, an increase that may partially be secondary to changes in pathologic classification.<sup>1</sup> MALTomas represent the most common subtype of ocular adnexal lymphomas.<sup>2</sup> The primary management of these tumors has generally consisted of radiation therapy with the addition of chemotherapy as indicated depending on stage. Because of the rarity of this tumor, there are no randomized phase III trials evaluating therapy and outcomes. The aim of this retrospective series is to add to the current literature regarding the management of MALTomas of the ocular adnexa.

## Methods

We used our electronic medical record system to identify patients seen in the radiation oncology department between January 1992 and June 2011 with diagnoses involving the eye or other ocular structures, as well as those with lymphoma. These results were then reviewed to identify patients with MALTomas involving the conjunctiva, lacrimal sac or gland, extraocular muscles, or other orbital structures, excluding patients presenting with intraocular lymphoma or primary central nervous system (CNS) lymphoma. Once these patients were identified in the electronic medical record system, electronic records were reviewed for the radiation oncology and medical oncology departments. In addition, paper charts were reviewed from the radiation oncology, medical oncology, and ophthalmology departments. Data regarding pathology, dates of diagnoses and treatment completion, treatment details, follow-up, recurrence, salvage treatment, and survival were analyzed. All pathology specimens were reviewed by

**Table 1.** Patient Characteristics

Age at Diagnosis (Years)	
Median	56.9
Range	35.25–77.68
Sex	
Male	8
Female	8
Stage	
IAE	13
IV	3
Location	
Conjunctiva	7
Lacrimal apparatus	3
Orbital	4
Multiple subsites	2
Staging	
Computed tomography (chest, abdomen, and pelvis)	15
Bone marrow	13

a hematopathologist. Although staging was not standardized, the majority of patients were staged with computed tomography (CT) of the chest, abdomen, and pelvis and bone marrow biopsy. No patients were staged with positron emission tomography (PET)/CT.

Overall survival was calculated from the date of diagnosis. Freedom from progression was measured from the start of treatment until progression or relapse. Patients who died from other causes and were otherwise disease-free were censored at the time of death. Survival was verified using electronic medical records and the Social Security Death Index.

For 15 patients, dates of diagnosis were identified based on the date of biopsy. For 1 patient who was seen for recurrent disease and whose exact date of diagnosis was unavailable, the date of diagnosis was listed as July 1 of the year in which he was diagnosed. The patient did not receive any definitive treatment until 3 years after his biopsy, and so this would affect only his age at diagnosis, as follow-up and overall survival were calculated from the date of radiation completion.

## Results

Among patients who were treated from December 1992 to July 2011, 16 patients were identified with MALTomas of the orbit, conjunctiva, or lacrimal gland/sac (Table

**Table 2.** Treatment Characteristics

<b>Radiation Dose</b>	
Median	30 Gy
Range	25.2–36.0 Gy
<b>Fraction Size</b>	
Median	1.8 Gy
Range	1.7–2.0 Gy
<b>Radiation Technique</b>	
En face electrons	5
Photons	11
<b>Treatment Volume</b>	
Conjunctiva	6
Orbit	9
Both orbits	1
<b>Initial Chemotherapy</b>	
Yes	2
No	14

1). The median age at diagnosis was 56.9 years (range, 35–79 years). Half of the patients were male. Sites of involvement included the conjunctiva in 8 patients, the posterior orbit in 6 patients, and the lacrimal sac/gland in 4 patients. One patient had involvement of both the orbit and lacrimal gland, and another patient had involvement of the orbit and the conjunctiva. Disease stage was IAE in 12 patients (75%), IIAE in 1 patient who also had involvement of the parotid (6.2%), and IV in 3 patients (18.8%).

All patients were staged with biopsies. Twelve patients were staged with bone marrow biopsy and CT of the chest, abdomen, and pelvis; 1 patient was staged with chest X-ray and bone marrow biopsy; and 2 patients were staged with CT of the chest, abdomen, and pelvis alone. Of the 13 patients staged with bone marrow biopsies, 4 were positive.

Fourteen patients were treated with radiation only for their primary disease, and 2 patients were treated with chemotherapy in addition to radiation (1 of whom had disease in the parotid gland as well as positive bone marrow, and 1 of whom had disease in both orbits; Table 2). The median dose was 30 Gy (25.2–32.4 Gy) in 1.8-Gy (1.7–2.0 Gy) fractions. A lens block was used for 3 patients, and bolus was used for 6 patients. For 2 patients, the available records did not specify whether a bolus or lens block was used, and for the remaining patients, no bolus or lens block was used. The treatment volume included the conjunctiva alone in 6 patients with conjunctival-only disease; the orbit in 8 patients with extraocular disease, including 3 patients with lac-

rimal gland/sac disease; both orbits in 1 patient; and an unspecified “eye” volume in 1 patient with a conjunctival primary. One of the 8 patients treated to the orbit was also treated to the involved ipsilateral parotid and another to uninvolved preauricular lymph nodes.

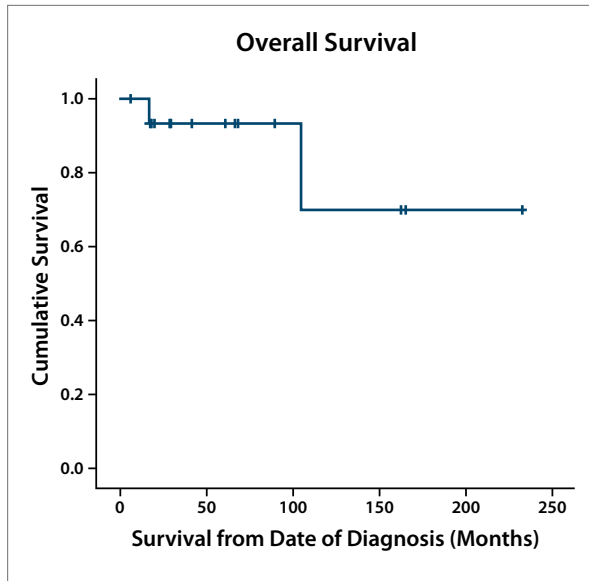
Complete response was observed in 14 of 16 patients (87.5%). After a mean follow-up of 62.8 months, local control was achieved in 12 patients (75%), with 2 patients having residual disease requiring further treatment that was effectively salvaged. One patient failed in the ipsilateral orbit, and 1 patient failed in the contralateral orbit (after having been treated to both orbits). Only 1 patient failed distantly. Of those who failed locally (with either residual disease or recurrence), 1 patient was controlled after resection followed by further radiation, another patient was controlled after repeat irradiation followed by chemotherapy, and 1 patient was controlled with rituximab (Rituxan, Genentech/Biogen Idec) alone. The fourth patient had to discontinue care at our institution due to a change in insurance. The 1 patient with a distant failure was treated at an institution closer to home. Of the 16 patients, there were 2 deaths (1 due to metastatic colon cancer and the other due to an unclear cause), but both patients had control of their disease as of 8 months prior to death at last follow-up. Three of the patients who underwent local salvage are currently disease-free, and the other 2 patients with failure are alive, although their disease status is not known as they were followed at other institutions. Median survival was not reached, and median disease-free survival was 102 months. Figure 1 demonstrates overall survival and Figure 2 shows disease-free survival.

### Lacrimal Gland

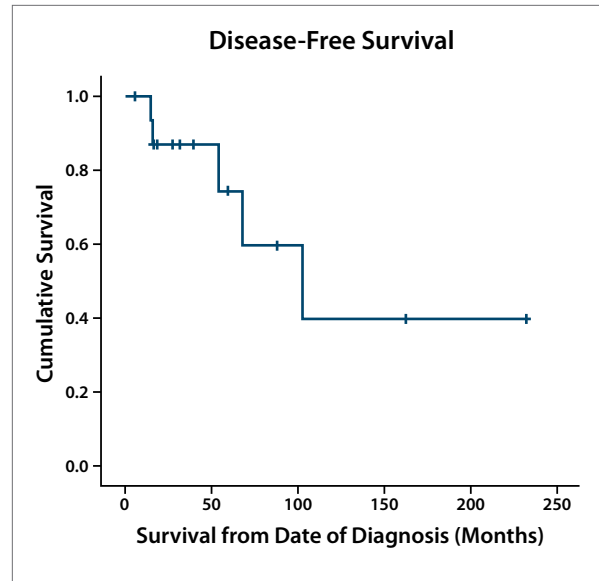
Four patients with lacrimal sac/gland MALTomas were treated. All of these patients were treated to the entire orbit with photon treatment. One patient ultimately had a distant recurrence. Another patient had residual disease treated with resection and rituximab, and is currently disease-free at 20.3 months after completing primary radiation therapy.

### Conjunctiva

Eight patients with conjunctival MALTomas were treated. Six patients were treated to the conjunctiva alone. One patient was treated to the entire orbit due to involvement of the inferior rectus, and another patient's volume is listed as “eye.” Only 1 patient failed, in the contralateral conjunctiva, but had to transfer care to another institution secondary to insurance changes shortly after recurrence, so no follow-up is available.



**Figure 1.** Overall survival among 16 patients with mucosal-associated lymphoid tissue lymphomas.



**Figure 2.** Disease-free survival among 16 patients with mucosal-associated lymphoid tissue lymphomas.

### Posterior Orbit/Extraocular Muscles

Four patients had involvement of the posterior orbit. All were treated to the entire orbit, including 1 patient who was treated to the bilateral orbits. One patient had local progression which has been controlled with rituximab. The patient who was treated to the bilateral orbits also received 4 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) after initial radiation. This patient then had a contralateral recurrence at 67 months post radiation, which was treated with 4 cycles of high-dose methotrexate and 4 cycles of intrathecal methotrexate followed by palliative radiation to the posterior involved orbit. This patient is currently disease-free at 45.4 months after completing palliative radiation.

### Bone Marrow Biopsy

Thirteen of the 16 patients had bone marrow biopsies. Of those, 4 patients (30.7%) were positive and 9 patients were negative. Of the 4 patients with positive bone marrow, only 1 patient received any chemotherapy as part of the initial treatment. Of the remaining 3 patients, only 1 patient failed, in the contralateral conjunctiva. Because of insurance changes, follow-up for that patient was at another institution after recurrence.

### Late Toxicity

Regarding long-term adverse effects, 7 patients developed a cataract in the treated eye, 2 patients developed

retinopathy, 6 patients had worsening of visual acuity, and 2 patients had dry eye syndrome. Of the 9 patients followed longer than 30 months, 7 (77.8%) developed cataracts. One patient with dry eye syndrome developed severe radiation keratopathy in the affected eye requiring a keratoprosthesis, sclera patch graft, and lateral tarsorraphy, and ultimately underwent enucleation due to pain. Of note, that patient had 3 prior surgeries before he underwent radiation to both eyes to the highest dose in this series (at an outside institution), all of which may have contributed to the severity of his dry eye syndrome.

### Discussion

MALTomas of the ocular adnexal structures are infrequent, and the workup and management of these tumors are still evolving. The median age of our patients at diagnosis was 56.8 years, which is within the age range reported in most series.<sup>3-8</sup> In our series, 81.2% of patients were stage IAE and 18.8% were stage IVAE, which is consistent with most series, where 80–100% of patients are stage IAE.<sup>3,7,9,10</sup> The most common subsite was the conjunctiva (43.75%), 25% of cases involved the orbital structures, 18.75% involved the lacrimal duct or sac, and 12.5% involved more than 1 orbital subsite; these rates are similar to those reported nationwide, but with a slightly lower incidence of orbital disease.<sup>1</sup>

In our series, treatment with radiation alone led to 85% complete remission and 75% local control. In the 2 patients with persistent disease after primary radiation, both were effectively salvaged: 1 patient with rituximab

alone and the other with resection and maintenance rituximab. Those patients with either local or distant failure for whom follow-up is available were effectively salvaged, and no patients in this series died of their disease.

Radiation to a dose of 25.2–32.4 Gy is generally well tolerated in these patients and is a very effective primary treatment when compared with multiple analyses of primary cytotoxic chemotherapy, which show local recurrence in up to 40% of patients, a much higher rate than in our series and other published data regarding radiation alone.<sup>11,12</sup> In addition to chemotherapy, antibiotics have also been examined in patients with ocular adnexal MALToma. Reports from Europe and Korea have identified a strong association between *Chlamydia psittaci* infection and the development of ocular adnexal MALTomas, with an incidence of 13–78%.<sup>4,13–15</sup> Similar analyses have not confirmed this association in the United States, where approximately 6% of patients test positive for *C. psittaci*.<sup>9,14,16,17</sup> There is likely a difference in etiologies associated with different populations, although disparate techniques in polymerase chain reaction (PCR) methodologies may also relate to the difference in apparent incidence. The efficacy of doxycycline in *C. psittaci*-positive patients appears to be lower than primary radiation, with 4 of 11 patients (36%) in 1 series recurring at the primary site within 1 year of follow-up. However, many patients in the series were treated with doxycycline after relapsed disease and therefore may have been at an increased risk for relapse.<sup>4</sup> Doxycycline was associated with a 48% overall response rate in the Italian trial, including patients with *C. psittaci*-negative disease.<sup>4</sup> In a series by Tanimoto and associates involving 36 asymptomatic patients with localized ocular adnexal MALToma who were observed with a watch and wait policy (9 of whom had complete resection while the remainder underwent subtotal resection or biopsy), 42% of patients had recurrence or local progression of their disease over 7.1 years.<sup>18</sup> Only 31% of observed patients had symptoms requiring treatment, as compared with a local recurrence rate of 36% in patients treated with doxycycline in the Italian series. This suggests that doxycycline may not be much more effective than observation, although this is a comparison across series, rather than a randomized comparison.<sup>4,18</sup>

Regarding the use of bone marrow biopsy in staging these tumors, the incidence of relapse did not appear to be any higher in patients with a positive bone marrow biopsy. The majority of our patients were staged with a bone marrow biopsy, and only 4 patients had involvement. This is consistent with the incidence of bone marrow involvement seen in multiple reports.<sup>2,3,8,19,20</sup> Only 1 of 4 patients with a positive bone marrow biopsy received chemotherapy, and of those 4 patients, there were no sys-

temic failures. One of the 4 patients who did not receive chemotherapy did have a local failure, and any subsequent treatment was at an outside hospital. In this limited series, a positive bone marrow biopsy did not seem to be associated with any increased risk of distant failure.

Cataractogenesis is a well known and anticipated long-term adverse effect of radiation to the orbit/conjunctiva, and was present in 77.8% of patients with a follow-up longer than 30 months. Several series have seen an incidence of cataracts in 16–58% of patients.<sup>21,22</sup> Follow-up notes did not specify whether there was any evidence of formation in the posterior subcapsular region consistent with radiation cataractogenesis, and 2 of these patients had bilateral cataracts despite unilateral treatment, so this number may overstate the incidence of cataracts secondary to treatment. Lens blocks were used in only 3 of the 6 patients who were treated to the conjunctiva only, and 1 of those patients (33%) developed cataracts despite lens shielding. The remaining 6 patients were treated to the entire orbit, and adequate lens shielding would have impaired coverage of the orbit. In a series by Stafford and colleagues of 48 patients, lens shielding had been used in 30 (62.5%), and 8 (16.7%) developed cataracts.<sup>21</sup> One-third of patients with lens shielding developed cataracts compared with only 12% of patients without shielding.<sup>21</sup> In our series, 1 patient (who was treated to 36 Gy after undergoing at least 3 unspecified surgical procedures) developed severe keratopathy requiring enucleation after multiple interventions. Two series have shown a marked increase in the severity of adverse events above 34 Gy and 36 Gy.<sup>5,23</sup> A dose of 30 Gy appears sufficient to provide local control, and there appears to be little additional benefit but a greatly increased risk of severe adverse events above 30 Gy.<sup>23</sup>

Limitations of this study include the smaller number of patients compared with several other series, as well as the weaknesses inherent in any retrospective analysis. Although available notes describe the incidence of cataracts in these patients, because of the age of these patients at presentation and the fact that several of them developed bilateral cataracts, clear attribution to radiation is difficult. Because of the lack of phase III data for the management of ocular adnexal MALToma however, our data add to the available literature on management and outcomes.

## Conclusion

Radiation continues to be an effective treatment modality to provide long-term control. Retrospective series have shown upfront chemotherapy alone and antibiotics to be less effective in control than radiation alone. Although no dose response was seen in our study, with all local failures occurring at a dose of 30–30.6 Gy, given the toxicity at higher doses and the good control with doses



in other series, we recommend treating the conjunctiva or the orbit to a dose of 30–30.6 Gy for the primary management of ocular adnexal MALTomas. Given the low incidence of systemic failure and the slow-growing nature of this malignancy, however, it may be acceptable to attempt antibiotic use in patients who test positive for *C. psittaci*, with radiation used for salvage in nonresponders or in patients who are negative. Additionally, in patients whose staging workup is otherwise negative, bone marrow biopsy has a low incidence of positivity, and even when positive, does not appear to correlate with the risk of systemic failure.

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