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Radiation therapy for primary orbital and ocular adnexal lymphoma

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ABSTRACT

Objective: To report the efficacy and toxicity of External beam Radiotherapy (EBRT) as a sole treatment for MALT and Follicular Primary Orbital and Ocular adnexal Lymphoma (POOAL)
Methods: Retrospective review of all POOAL patients treated with EBRT utilizing megavoltage photon or electron beam radiotherapy between 2003 and 2015. Patient demographics, tumour extent and pathology, radiotherapy techniques, and treatment outcomes were reviewed. The actuarial rates of tumour control and radiation toxicities were calculated using Kaplan-Meier estimates.
Results: This study included 167 tumours, of which MALT lymphoma involved 149 (89 %). The conjunctiva and orbit were equally involved as the predominant site (48 %). Megavoltage photon radiotherapy was used in 60 % of predominantly orbital lymphoma and Electron beam with lens shielding in 77 % of the conjunctival lymphoma. The majority (95 %) were treated with a total dose of 25 Gy in 10 fractions. Local control rate was 98 % (CI: 93–100 %) at 5 years. The long-term RT toxicities included dry eye in 27 eyes (16 %) and cataract in 22 (13 %). None of the patients developed significant structural or functional radiation toxicity.
Conclusion: External Beam Radiotherapy, with lens shielding whenever indicated, at a dose of 20–30 Gy delivered over 10–20 fractions is an efficacious and safe primary treatment option for POOAL lymphoma, with excellent local control and low incidence of late manageable ocular toxicities.

Introduction

Lymphomas are a group of neoplasms that develop from B-lymphocytes, *T*-lymphocytes, or NK lymphocytic cell origin[1,2]. The 4th edition of the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, published in 2017, classifies the lymphoid neoplasms into 5 main categories: (1) Precursor lymphoid neoplasms; (2) Mature B-cell neoplasms; (3) Mature *T*-cell neoplasms; (4) Hodgkin lymphoma; and (5) Immunodeficiency-associated lymphoproliferative disorders[3]. The incidence of lymphoma has increased considerably in the western countries over the last decades [4–6]. Brenner et al estimated in 2020, 10,400 cases of non-Hodgkin lymphomas in Canada[7].

Primary Orbital and Ocular adnexal Lymphoma (POOAL) represents 8 % of all extra nodal lymphomas, and it is the most common primary orbital malignancy in adults[8]. Lymphomas involving the periocular tissue are in 90 % of cases of mature B-cell origin [3]. Extra nodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT) is the most common histopathological type of periocular lymphoma [9–12]. Clinically, POOAL typically presents as a diffuse lesion that involves one or more of the ocular adnexa and/or orbital structures. Conjunctival involvement typically appears as slowly growing, infiltrative, salmon-coloured lesion involving the conjunctival stroma and the underlying Tenon's capsule (Fig. 1A). In the orbit, it may involve the lacrimal gland, extra-ocular muscles, intra or extraconal spaces, or multiple periocular tissues (Fig. 1B–D). Orbital imaging reveals lymphoma as an ill-defined infiltrative mass that molds to the shape of surrounding structures[8]. This diffuse presentation excludes complete surgical excision as a suitable approach to cure extensive POOAL. However, incision biopsy of the lesion is essential for diagnosis and establishing a treatment plan.

Lymphoma treatment generally may include radiotherapy (RT), chemotherapy, immunomodulating therapy, primary antibiotic treatment, surgical excision, or combination therapy. The choice of treatment depends on systemic staging and the tumor histopathologic type at the

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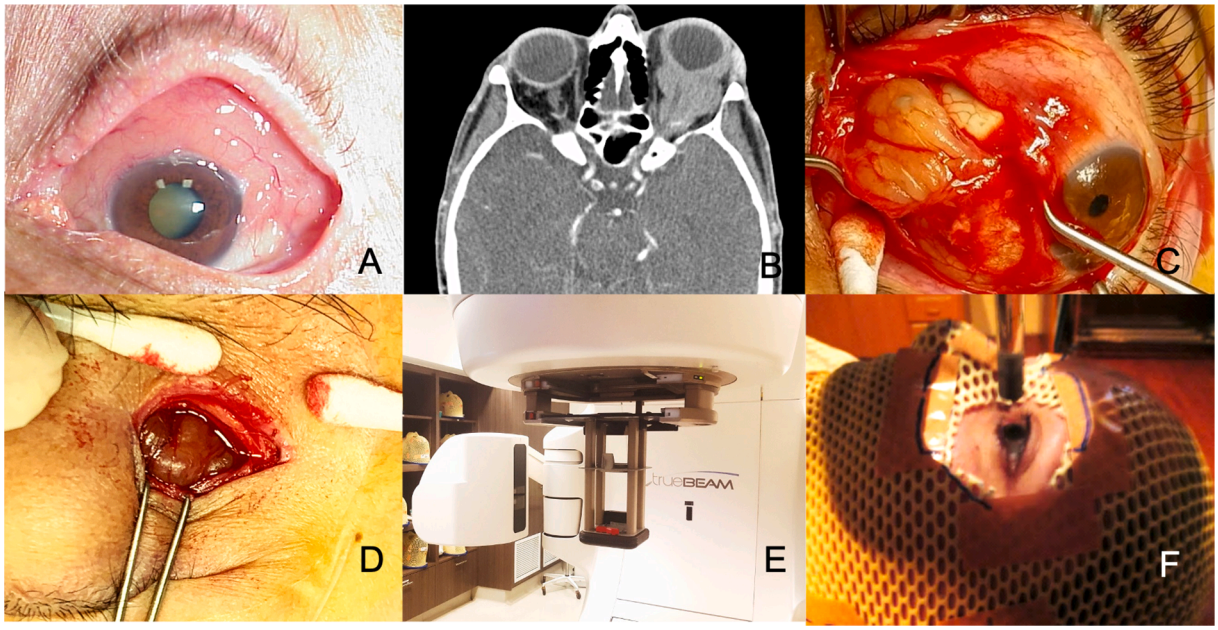

Fig. 1. Salmon patch presentation of conjunctival MALT lymphoma (A), Axial view of CT scan demonstrating lacrimal gland enlargement secondary to orbital lymphoma (B), Orbital lymphoma compromising extra-ocular muscles (C), clinical image of lymphoma involving the lacrimal gland (D). Electron beam radiation (E) Pencil shield utilized to reduce lens dose during electron beam radiation (F).

Table 1
Summary table stratified by Histology and site of tumor presentation.

Histology	Conjunctiva (48%)	Orbit (48%)	Eyelid (4%)	Total
MALT Lymphoma	74	70	5	149 (89%)
Follicular Lymphoma	8	10	0	18 (11%)
Total	84	84	6	167 (100%)

Table 2
Summary table stratified by treatment.

Covariate	Full sample (n=167)	Electrons (n=54)	Photons (n=113)
Gender			
Female	107 (64%)	36 (67%)	71 (63%)
Male	60 (36%)	18 (33%)	42 (37%)
Site			
Conjunctiva	82 (49%)	40 (77%)	42 (37%)
Eyelid	5 (3%)	2 (4%)	3 (3%)
Orbit	80 (48%)	12 (23%)	68 (60%)
Diagnosis			
MALT Lymphoma	150 (86%)	48 (89%)	102 (90%)
Follicular Lymphoma	17 (10%)	6 (11%)	11 (10%)
Shield			
No	88 (53%)	13 (24%)	75 (66%)
Yes	79 (47%)	41 (76%)	38 (34%)
Dose binary			
High dose (>=2500 Gy)	132 (79%)	20 (37%)	112 (99%)
Low dose (<2500 Gy)	35 (21%)	34 (63%)	1 (1%)

Table 3
Summary table stratified by Histology and site of tumor with distant relapse.

Histology	Conjunctiva	Orbit	Eyelid	Total
MALT Lymphoma	9	16	1	26/149 (17%)
Follicular Lymphoma	1	2	0	3/18 (17%)
Total	10	18	1	29/167 (17%)

Table 4
Comparison of the outcomes of Ocular Adnexal MALT lymphoma with systemic treatments.

Study	Treatment Type	# of Patients	Local Control	Median Follow-up (months)
Ferreri et al., 2005	Doxicycline 100mg bid/3w	9	22%	12
Ferreri et al., 2006	Doxycycline 3 weeks	27	22%	14
Ham et al., 2015	Doxicycline 100mg bid/3w	90	65%	40.5
Annibali et al., 2015	Rituximab 6 cycles 375mg/mq IV every 3 weeks	7	67%	29

initial presentation. Since POOAL is mostly confined to the periocular tissue, orbital RT has been mostly elected as a primary treatment. There is a lack of consensus about the optimal RT dose, and fractionation scheme [13–15]. In this study, we present our RT protocol, clinical outcomes, and long-term toxicities of RT in the management of a large cohort of MALT and Follicular POOAL.

Patients and methods

A retrospective electronic chart review was conducted for all consecutive patients that were diagnosed with MALT and Follicular POOAL and were treated with radiotherapy between December 2003 and October 2015 and followed afterwards at Princess Margaret Cancer

Table 5
Reports of radiotherapy outcome for orbital lymphoma.

Study	Radiation Dose	Type of Lymphoma	# of Patients	Local Control	Median Follow-up (yrs)	Toxicities
Fung et al., 2003	30.6 Gy	MALT (57%) Follicular (15%) DLBCL (9%) Other (12%)	98	100%	6.8	Cataract 16 (16%) Retinopathy 4 (4%) Corneal perforation 1 (1%)
Goda et al., 2010	65 pts 25 Gy 5 pts, 25-30 Gy 1 pt, 35 Gy	MALT (100%)	71	99%	7.4	NS
Goda et al., 2011	87 pts, 25 Gy 2 pts, 36 Gy	MALT (100%)	89	99%	5.9	Cataract 22 (25%) Dry Eye 22 (25%) Keratitis 3 (3%) Retinopathy 3 (3%)
Konig et al., 2016	45 pts, 36 Gy 7 pts, 4 Gy	MALT (52%) Follicular (15%) Immunocytoma (9%) Other (25%)	52	98.00%	9.9	Conjuntivitis 28 (54%) Dermatitis 24 (46%) Dry Eye 14 (27%) Cataract 11 (21%) Keratitis 1 (2%) Corneal ulcer 1 (2%)
Ohga et al., 2015	30 Gy	MALT 100%	73	100%	3.8	Cataract 31 (43%) Dry Eye 22 (30%) Keratitis 5 (7%) Conjuntivitis 4 (6%)
Parikh et al., 2015	30.6 Gy	MALT 75% Follicular (25%)	79	100%	4.1	Cataract 11 (14%) Dry Eye 13 (17%) Retinopathy 2 (3%)
Son et al., 2010	30.6 Gy	MALT 100%	46	93%	2.7	Cataract 2 (4%) Dry Eye 6 (13%) Tearing 2 (4%) Keratitis 2 (4%)
Stafford et al., 2001	27.5 Gy	MALT (60%) CLL (23%) DLBCL 4% Other 13%	48	98%	5.4	NS
Uno et al., 2003	36 Gy	MALT 100%	50	98%	3.8	Conjuntivitis 8 (16%) Cataract 6 (12%) Keratitis 1 (2%) Retinopathy 2 (4%)
Woolf et al., 2015	30 - 35 Gy	MALT (88%) Follicular (6%) T-cell 1% B-precusor Lymphoblastic 1 %	81	100%	4.4	Cataract 6 (7%) Dry Eye 3 (4%) Conjuntivitis 19 (24%) Erythema 19 (24%) Other 4 (5%)

Centre/University Health Network, Toronto, ON, Canada. The study was conducted according to the declaration of Helsinki, and the institutional research ethics board has approved it. Patients who presented with unilateral or simultaneous bilateral periocular involvement were included. Diagnosis of POOAL was based on clinical and/or orbital imaging of the lesion, in addition to histopathologic confirmation. Patients with associated systemic lymphoma (i.e., stage III/IV disease) at presentation, who required primarily systemic treatment, were excluded. Similarly, patients with incomplete pre-treatment or post treatment data, or less than 1-year follow-up were excluded.

Patient data

Patient data included: demographics (age at diagnosis date, gender, and laterality of involvement), the predominantly involved adnexal structure (conjunctiva, orbit, eyelid). All included POOAL tumours were diagnosed with prior tissue biopsy and were analyzed with flow cytometry and/or immunohistochemistry. The histopathologic diagnosis included: (MALT lymphoma and Follicular lymphoma). Treatment description included: type of radiotherapy (electron beam radiotherapy or megavoltage photon beam radiotherapy), treatment total dose, fractionation schedule, and the use of shielding of the crystalline lens during irradiation (used or not used). The acute treatment toxicities included, skin erythema, skin ulceration, telangiectasia, conjunctival hyperemia, and corneal ulceration. The long-term toxicities included, radiation-induced cataract, radiation retinopathy, persistent dry eyes, iris neovascularization, and neovascular glaucoma. The terminology criteria for adverse events, version 3 (CTCAE v3.0), was used to record late toxicities.

Radiation therapy

Selection of RT technique was individualized according to the extent of tissue involvement. Based on orbital imaging, Electron Beam Radiotherapy was elected for localized eyelid and/or conjunctival lymphoma, not extending beyond the globe equator. Electrons energies are typically 12 MeV to 16 MeV and covers the entire orbit. Megavoltage photon irradiation has been used for deeper lesions involving lacrimal gland, orbital soft tissue, extraocular muscles, or for bulky eyelid and conjunctival lesions that extended beyond globe equator.

Technique: on the treatment table, the patient head was immobilized using a custom-fitted thermoplastic mask; a non-contrast computerized tomography (CT) imaging of the head was executed. The target volumes (GTV where applicable, and the CTV) were contoured on the CT images, with addition of 3–5 mm margin for the PTV to account for possible day-to-day set-up errors. The planning images were then uploaded into the planning software. Treatment planning was applied, where doses are calculated and isodose distributions and dose-volume histograms were generated to the target volume and the nearby tissues. Image guidance was performed with cone beam-CT at each treatment session, and coverage adjusted for any translation error in the X, Y, and Z dimensions.

Electron beam treatment (Fig. 1E) was delivered using direct anterior beam, while megavoltage irradiation was delivered over 3–5 fields, through Intensity Modulated Radiotherapy (IMRT). A “Pencil Shield” made of Tungsten alloy and a lead head, suspended at 1 cm from cornea, was utilized to reduce lens dose during electron beam irradiation (Fig. 1F). Lens shielding was used if the target volume was beyond 3 mm from the limbus. Lesions within 3 mm from the limbus were treated without lens shielding.

The standard dose of photon radiotherapy used for MALT lymphoma was 25 Gy delivered in 10 fractions; few patients before 2005 were treated with 35–40 Gy in 20 fractions. In electron radiotherapy, with relatively higher surface dose, the dose was 20 Gy in 10 fractions to minimize ocular surface dryness.

Follow-up

Patients were examined at 4 to 8 weeks after completion of radiotherapy, to assess the initial response to irradiation including management of short-term treatment toxicities. Subsequently, patients were followed every 3 months for the first year, then every 4 to 6 monthly for 2 years, then yearly thereafter. Follow-up assessment included ophthalmic clinical examination for response of superficial lymphoma, and 6 monthly orbital imaging with CT and/or magnetic resonance imaging (MRI) scans. Complete response was defined as complete resolution of the local disease by physical examination and orbital imaging. Treatment efficacy was measured as the rate of local tumour control versus local recurrence. Treatment failure was defined as local relapse within the irradiated region. The relapse patterns (local, contralateral orbit, and distant systemic) and late toxicities were recorded based on detailed ophthalmologic evaluation.

Statistical analysis

Survival distributions for the overall time- to- local failure, as well as proportion with local control, -based on treatment parameters such as radiation energy were calculated using Kaplan-Meier estimates. Rates of complications were calculated using the cumulative distribution function for overall time to various radiation complications and for time to complications aggregated by radiation type and energy level; with or without shielding. Long rank test was used to compare the statistical significance between the survival curves. Results were considered significant if the p-value was less than 0.05.

Results

Out of 314 POOAL patient charts reviewed, 140 patients with 167 tumours met the inclusion criteria. There was no gender predilection and 112 patients (80 %) showed unilateral involvement. Clinically, the conjunctiva and the orbit were equally involved as the primary site.

The histopathology of the majority of lesions was MALT lymphoma (89 %), followed by Follicular lymphoma (11 %). Table 1 summarizes the categorization of cases with respect to the histologic diagnosis and site of involvement.

All cases were treated either with Linear Accelerator (LINAC)- based megavoltage photon radiotherapy or Electron beam radiotherapy as a primary treatment. Table 2 demonstrates the choice of treatment as stratified according to the patient gender, tumour location, histologic diagnosis, the use of shielding, and radiation type. The majority (95 %) of patients were treated with photon irradiation at a standard dose of 25 Gy or less in 10 fractions, 4 tumours were treated with 30 Gy, 3 in 20 fractions.

The median follow-up, after radiotherapy, was 6.1 years (range, 1–20 years). The actuarial local control rate was 98 % (Confidence Interval; CI: 96–100 %) at 3 years, and was 97 % (CI: 93–100 %) at 5 years. Local recurrence was observed in only 6 tumors (3.6 %) of 4 patients. All recurrent cases were MALT lymphoma, which were treated with the standard photon irradiation (25 Gy/10 fractions); in two of these patients, lens shielding was used. Time to local recurrence varied from 14 to 84 months after treatment. One patient with a large tumor showed no response.

Acute RT toxicities were observed in 80 % of patients, mainly as a mild degree of periorbital skin erythema, conjunctival injection, and excessive tearing or chemosis immediately after RT, most of which were self-limited and responded to a short course of lubricant gels or skin moisturizers.

The long-term RT toxicities included dry eye in 27 eyes (16 %) followed by cataract in 22 eyes (13 %). Serious toxicities such as neovascular glaucoma and radiation retinopathy were not observed in this cohort. The cumulative incidence at 5 years of dry eyes was 14 % (CI: 81–90 %) and of radiation induced unilateral cataract was 11 % (CI: 84–94 %). All long-term toxicities were treated with success, except for a patient with pre-existing Sjogren syndrome who developed severe dry eye.

Development of systemic disease (distant relapse) has subsequently occurred in 29 patients (20 %); 2 patients developed the disease in the contralateral untreated eye. The median time to distant relapse of lymphoma was 36 months (1–152 months). The primary histologic diagnosis of the patient with systemic relapse was MALT lymphoma in 24 patients, Follicular lymphoma in 3 patients. Conjunctiva was affected in 10 patients, orbit in 19 and eyelid in 1 patient (Table 3).

Patients were treated according to histological diagnosis of the relapse and stage of disease.

Discussion

Lymphoma is the most common primary malignant neoplasm of the orbit [16]. In this study, POOAL has equally involved each of the conjunctiva and orbit as the primary periocular site, involving 48 % of the eyes in each site.

Extra nodal MALT lymphoma is the most frequent histologic subtype of the ocular adnexal lymphoma with reported incidence ranging from 35 % to 90 %.[2,5,8] In this study MALT lymphoma represented 89 % of the tumors of the entire cohort irrespective of the primary site of origin. This higher incidence probably reflects the selection criteria of the included lymphoma patients in this study, who were treated solely with orbital radiotherapy. MALT lymphoma is a low-grade lymphoma that mostly presents as a unilateral periocular disease without concurrent systemic involvement, the patients with higher-grade lymphoma and systemic involvement at presentation, requiring treatments other than

RT, were not included.

MALT lymphoma has been reported to be associated with *chlamydia psittaci* infection, which proposed the use of doxycycline as a treatment, however the association between infectious disease and lymphoma showed geographic differences. The *C psittaci* strains found in Europe and South Florida present genotypic variance that may explain the different results seen in the literature.[9,17,18] Local control varied from 22 % to 65 % when doxycycline was used to treat ocular adnexal lymphoma [18–20] and with the use of Rituximab as sole agent in one study, the authors reported 65 % of local control [21] (Table 4). The published RT series on treatment of MALT lymphoma revealed better control rates when compared to other treatments.

In patients with localized lymphoma, radiotherapy is usually the treatment of choice. Radiotherapy is often used as primary treatment alone for indolent lymphomas [22]. Nevertheless, there is a lack of consensus about the optimal RT type, dose, and fractionation scheme. [13] Even though the radiation dose required for eradication of disease is low to moderate, the treatment of POOAL might be technically challenging considering the proximity to radiosensitive ocular structures.

Megavoltage photon beam has been a standard therapy for a variety of deeper orbital tumours. Use of IMRT in this study, aims at optimizing energy delivery to the tumour-involved tissues whilst minimizing collateral tissue injury has been the mainstay approach. Conversely, electron beam therapy is more applicable for superficial lymphoma involving the eyelids and conjunctiva.[23]. In the latter situation, crystalline lens shielding has been used to minimize incidence of radiation-induced cataract. Therefore, tumor site and extent of orbital involvement in the study has defined the selection of radiotherapy technique.

In orbital tumours, only one patient, in 68 treated with photons had local recurrence; in conjunctival tumour 5 lesions in 42 treated with photons had local recurrence. Patients treated with electrons did not present with local recurrence.

These rates are comparable to tumour control rates in other RT series of approximate post treatment follow-up period.

Pfeffer et al compared partial orbital irradiation therapy with whole-orbit coverage and reported a high local relapse rate (33 %) in an area outside the target volume. Patients treated with whole orbit irradiation otherwise presented excellent local control.[24] Consequently, the standard treatment continues to be adequate coverage of the entire orbit. Lens shielding can be used in cases with no *retro*-orbital gross disease nor presence of the tumor too close to the limbus because of the risk of protecting the tumor from radiation.[13] The local control obtained in this retrospective cohort is compatible with the local control reported in various papers as seen in Table 5, all other studies with a smaller sample. Binkley et al reported low rates of Local failure, contralateral orbital recurrence or progression in 32 patients treated with partial orbital irradiation[25].

Ultra-low dose of radiotherapy has been utilized in some centres with a lower local control rate of 75 % at two years.[15] Fasola et al observed a complete response in 85 % of 27 sites of indolent non-Hodgkin lymphoma treated with low-dose radiation therapy, in a median follow up of 26 months[26]. Our study included two patients successfully treated using ultra low dose technique (4 Gy/2 fractions). One patient presented MALT conjunctival lymphoma and the other one had an orbital Follicular lymphoma. This is a reasonable first approach and a subsequent 20 – 24 Gy can be reserved for local failure after 4 Gy in 2 fractions.

Minor radiation toxicities were diagnosed in 29 % of the irradiated eyes. Dry eyes were the most frequent late toxicity (16 %) followed by cataract (13 %). Cataract is expected if the lens cannot be shielded. In comparison with other series of RT for POOAL (Table 5), the incidence of cataract in this cohort was similar or lower, except for Parikh et al, 2015; Son et al, 2010; and Woolf et al, 2015; all presenting lower median follow up (4.1 and 2.7 and 4.4 years). Dry eyes were more frequent in this series than the reported in the studies listed in Table 5, nevertheless, this study did not identify any case of cornea perforation, retinopathy or neovascular glaucoma, radiation retinopathy or ocular hemorrhage. A possible reason could be due to reporting practice, as patients were followed in a dedicated eye clinic at the institution.

Distant relapse is more frequent in more aggressive lymphomas as Large B-cell lymphomas. Although MALT lymphoma is a more frequent diagnosis it presents less distant relapse as well as the Follicular lymphoma, 17 % in both cases. (Table 5).

Conclusion

Despite the retrospective nature of this study, yet it demonstrates the efficacy and low toxicity of RT with a dose of 25 Gy achieved in a large cohort of Low grade (MALT and Follicular) POOAL patients who were treated with the same technique and followed at the same institution.

Radiotherapy at a dose of 20–25 Gy fractionated in 10–15 sessions with use of lens shielding whenever indicated is an efficacious and safe option for Primary Orbital and Ocular Adnexal low-grade lymphoma treatment, with excellent local control and low incidence of late manageable ocular toxicities.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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