

Orbital lymphoma: Role of radiation

B S Yadav, S C Sharma

The purpose of this article is to review the literature for clinical presentation, treatment, outcome and complications of using radiotherapy for the treatment of orbital lymphoma. For this, MEDLINE, EMBASE, and the Cochrane Library were searched through January 2007 for published data on primary non-Hodgkin's lymphoma (NHL) of the orbit. The search was conducted in all document types, using the following terms "Non-Hodgkin's lymphoma, MALT (mucosa associated lymphoid tissue) and orbit". Data extracted were based on age, sex, therapeutic methods and outcome of treatment. When full articles were not available, abstracts were used as a source of information. Only those articles whose abstracts or full text were available in English were included in table. The review of reports of NHL of the orbit, in general, served as a source of information about its clinical behavior, treatment and overall prognosis. Fifty-six publications were identified, including six in languages other than English. There was no randomized trial. All the studies were retrospective. The studies were heterogeneous in patient number (3 to 112), histology, disease stage (IE to IV), radiotherapy doses used (4 to 53.8Gy), local control rates (65 to 100%), distant relapse rates (0 to 67%, from low grade to high grade) and five-year survival rates (33 to 100%). Three of the studies with a good number of patients also demonstrated clinical benefit with radiotherapy in terms of superior efficacy or less toxicity. Available data support the acceptance of radiotherapy as a standard therapeutic option in patients with low to intermediate grade orbital lymphoma. Toxicity of radiotherapy is mild if delivered precisely.

Key words: Chemotherapy, lymphoma, orbit, radiation therapy

Indian J Ophthalmol: 2009;57:91-97

Orbital lymphoma refers to a lymphoma occurring in the conjunctiva, lacrimal gland, eyelid and ocular musculature. Primary non-Hodgkin's lymphoma (NHL) of the orbit is a rare presentation, representing 8-10% of extranodal NHL^[1] and only 1% of all NHL.^[2] Generally, it has an indolent course. Orbital lymphoma in contrast to ocular lymphoma is rarely associated with primary central nervous lymphoma.

Majority of the orbital lymphomas are of low-grade variety (84%) and only 16% are of high-grade histology.^[3] Orbital lymphomas are predominantly of mucosa associated lymphoid tissue (MALT) histology (57%), but they also include other histological subtypes, such as follicular lymphomas (19%), diffuse large B-cell lymphomas (DLCL) and mantle cell lymphomas.^[4,5] Orbital lymphoma may be unilateral or bilateral and up to 20% bilateral presentation is noted.^[6] Most of the current literature consists of single institution retrospective reviews.

The purpose of this article is to review the literature for clinical presentation, treatment, outcome and complications of using radiotherapy for the treatment of orbital lymphoma. MEDLINE, EMBASE, and the Cochrane Library were searched through January 2007 for published data on primary NHL of the orbit. The search was conducted in all document types, using the following terms "Non-Hodgkin's lymphoma, mucosa

associated lymphoid tissue (MALT) and orbit". Data extracted were based on age, sex, therapeutic methods and outcome of treatment. When full articles were not available, abstracts were used as source of information. Only those articles whose abstracts or full text were available in English were included in the table. The review of reports of NHL of the orbit, in general, served as a source of information about its clinical behavior, treatment and overall prognosis. Fifty-six publications were identified, including six in languages other than English. There was no randomized trial. All the studies were retrospective. The studies were heterogeneous in patient number (3 to 112), histology, disease stage (IE to IV), radiotherapy doses used (4 to 53.8Gy), local control rates (65 to 100%), distant relapse rates (0 to 67%, from low grade to high grade) and five-year survival rates (33 to 100%). Three of the studies with good number of patients also demonstrated clinical benefit with radiotherapy in terms of superior efficacy or less toxicity. Available data support the acceptance of radiotherapy as a standard therapeutic option in patients with low to intermediate grade orbital lymphoma. Toxicity of radiotherapy is mild if delivered precisely. Several prognostic factors have been identified to decide the therapeutic strategy of this uncommon site of primary lymphoma.

Clinical Presentation

The presenting age ranges from 15 to 70 years, but majority of orbital lymphomas occur around 60 years of age.^[7] Most reports show a female predominance, three have described a slight male predominance.^[2,5,8] Majority of the patients present with a palpable mass (64%) followed by eye irritation (28%), ptosis (20%), proptosis (18%), excessive tearing (16%), blurry vision (11%) and pain in the eye (3%). The commonest site of involvement is the conjunctiva (55%), lacrimal apparatus (24%), extraocular muscles (11%) and soft tissues of the eyelid in 11% patients.^[9] Low-grade tumors are mainly localized to the orbit

Department of Radiotherapy and Oncology, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Correspondence to Dr. Suresh C Sharma, Department of Radiotherapy and Oncology, PGIMER, Chandigarh-160 012, India. E-mail: sharmasc@glide.net.in

Manuscript received: 01.05.07; Revision accepted: 10.01.08

DOI: 10.4103/0301-4738.44516 - PMID: 19237780

but high-grade tumors may extend to involve the bone, ethmoid sinuses and brain.

Bilateral orbital involvement is seen in about 10-25% of patients.^[10-12] This may possibly be due to the homing mechanism of MALT lymphoma cells to adhere to other epithelial or mucosal sites. This pattern of spread represents a distinct natural history compared to that observed in other, nodal low-grade lymphomas.

For local evaluation, a thorough ophthalmological examination is carried out in the beginning. Restricted ocular motility and visual impairment are the features elicited by the ophthalmologist. Systemic lymphomatous involvement may be associated in 20% of cases and thorough clinical examination of opposite orbit, oral cavity and oropharynx is mandatory along with systemic examination. In addition, symptoms of peptic ulcer disease in this patient population should be evaluated endoscopically.

Staging Workup

The staging workup for orbital lymphoma is controversial. Most of the studies had inconsistent staging tests, with the exception of two.^[13,14] Biopsy is always mandatory for stage grouping of lymphomas. The systemic workup includes complete blood counts, liver and kidney function tests, peripheral blood film, bone marrow biopsy, chest X-ray, computerized tomogram (CT) of the orbit, chest and abdomen. The CT scan will reveal a mass lesion of homogenous characteristics and rule out any bony involvement. Inflammatory pseudotumors tend to cause more enhancements with contrast than the lymphomas. Magnetic resonance imaging has been recently added as a complementary study for better visualization of soft tissue.

According to the Ann-Arbor staging system,^[15] lymphoma confined to the orbit is designated as Stage I, involvement of adjacent structures (sinuses, tonsil and nose) makes it Stage II. Stage III is abdominal nodal disease below the diaphragm and IV by definition refers to disseminated involvement of one or more extra-nodal sites (e.g. liver, bone etc) and "E" is used when there is a local extra-nodal extent (e.g. IE, IIE, IIIE and IVE). Designation A is for no symptoms and B for fever (temperature higher than 38°C), drenching night sweats, and unexplained loss of more than 10% of body weight within the preceding six months. Approximately 20% of the patients will have Stage III or IV disseminated involvement. Grading system is similar to nodal lymphomas.^[15]

Role of Antibiotics

Some infectious agents contributing to lymphomagenesis have been considered targets for new therapeutic strategies. *Chlamydia psittaci* DNA has been detected in 80% of ocular adnexal lymphomas (OAL). Ferreri *et al.*,^[16] treated nine patients with *C psittaci*-positive marginal-zone B-cell lymphoma of the ocular adnexa at diagnosis or relapse with doxycycline 100 mg, twice daily orally, for three weeks. At one month from doxycycline assumption, chlamydial DNA was no longer detectable in peripheral blood mononuclear cells (PBMCs) of all four positive patients. Objective response was complete in two patients, partial response (>50%) was observed in two patients, and minimal response (<50%) was observed in three patients. Duration of response in the seven responders

was 12+, 29+, 31+, 8+, 7+, 2+, and 1+ months, respectively. *C psittaci*-eradicating antibiotic therapy with doxycycline is followed by objective response in patients with OAL, even after multiple relapses of the disease. Grünberger *et al.*,^[17] treated 11 patients (six female, five male) of MALT-lymphoma of the ocular adnexa with doxycycline 200 mg orally daily over three weeks. After a median follow-up of nine months, none of the patients responded to 'blind' antibiotic treatment with doxycycline. Only one patient with bilateral conjunctival lymphoma reported a short lasting subjective improvement, but was referred to radiotherapy, chemotherapy, surgery due to progression and worsening symptoms after six months. These results are in contrast to other series and suggest a potential geographic difference in the role of chlamydia in OAL. Thus, antibiotic therapy without prior testing for chlamydia should be discouraged.

Role of antibiotics is not yet well defined in orbital lymphomas as for MALT of the stomach because of the different biological nature of these tumors. In a meta-analysis Husain *et al.*,^[18] suggested a striking variability in the association between *C psittaci* and OAL across geographic regions and even between studies from the same geographic regions. Antibiotics have an unproven role against OAL due to lack of objective methods of assessment of response in the majority of reports, lack of stratification of response rates based on histologic subtypes of OAL and short follow-up time. Future confirmatory, large prospective trials with standard objective response criteria and a larger follow-up period is warranted to confirm whether this fast, cheap, and well-tolerated therapy could replace other more aggressive strategies as first-line treatment against OAL.

Radiation Therapy: Techniques and Dose

For Stage I and II localized disease process, radiation therapy is the primary modality of treatment. Treatment of orbital lymphoma with radiotherapy is challenging because of the radiosensitive lens, lacrimal gland, and retina, which are located near or within the target volume. Field arrangements vary depending on the exact location of the disease.^[19,20] Three-dimensional (3D) planning should be done where the facility is available. For superficial small lesions confined to the conjunctiva or eyelid, electron beam therapy with a contact lens block can be used.^[21] Bolus should be used to treat superficial lesions to bring the isodose curve to the surface for adequate coverage. In another technique, photon beam can be used with a central hanging eye block added to shield the cornea and lens after ensuring adequate coverage. It is important, when using an external eye shield, that the lead shield to eye surface distance be 1 cm or less to reduce the contribution of scatter from the electrons collimation system to the underlying lens. The technique of central hanging eye block was reported 16 years ago and only a few centers use it nowadays. In non-experienced hands it can lead to geographical miss. Moreover, if needed, other techniques using 3D conformal therapy represent more modern alternatives. In addition, cataract is currently a relatively minor issue, as discussed below. For lesions extending to involve deeper retrobulbar tissues, photons should be used without any eye blocks.

Target volume should include the entire orbit for patients with any intraorbital involvement. For superficial small lesions confined to the conjunctiva or eyelid, target volume

should include the tumor plus an adequate margin. The most common techniques for photon treatment of a single orbit used are anterior field or an anterior wedge pair field to spare the opposite orbit. For retrobulbar tumors, 3D planning is advisable; a number of fields can be used, single lateral megavoltage photon beam angled posteriorly to avoid the ipsilateral lens as well as contralateral eye, or a wedged pair of megavoltage photon beams including a lateral and a superior field again with appropriate angles on the lateral field to avoid critical structures. For patients with bilateral orbital involvement, opposed lateral fields, bilateral anterior fields or three fields (anterior and opposed lateral field) can be used based on individual patients.

Radiotherapy planning must be individualized, based on the extent of disease visualized on examination and imaging scans as well as the patient's overall general condition and clinical intent (radical versus palliative). Conformal 3D planning^[22] and intensity-modulated radiotherapy (IMRT)^[23] should be state-of-the-art radiotherapy. Provided the planning target volume (PTV) is well covered and the organs at risk well spared, what counts is individual treatment planning system (TPS)-assisted planning with individualized beam's/size, shape, angle, energy etc. Where this facility is not available photon treatment can be given with a Co⁶⁰ machine or a linear accelerator of either 4 or 6 MV. The risk of cataract should be decreased with meticulous use of the customized lens shield. The entire globe should be treated by a hinged wedge technique with or without bolus on the anterior aspect depending on the clinical findings.^[24] Dose given should be 30 to 35 Gy in 1.8 to 2 Gy per fraction over 3.5 to 4 weeks. No more than 30 Gy is required for excellent local control.^[25] The electron energy used should be 6 to 9 Mev (mega electron volt), at the dose rate of 2 to 2.5 Gy per fraction. With the use of 12-Mev electrons via an anterior portal, the dose in the region of lens (at the depth of approximately 1 cm) is 90% of the prescribed dose. With the placement of a 1 cm-thick centrally-placed eye bar suspended at 10 mm above the cornea, the dose at 1 cm falls to 5-8% of the prescribed dose.^[21]

Dose in the range of 25 to 30 Gy at 1.8 to 2 Gy per fraction can provide up to more than 95% local control.^[26] Many authors have used different dose schedules for radiotherapy from 10 Gy to 57 Gy [Table 1]. The recent trend has been to reduce the radiation doses without any reduction in the local control rate with acceptable toxicity. However, local control as well as five-year survival is poor with lower doses of radiotherapy, particularly if dose is <30 Gy.^[13] Princess Margaret Hospital reported two local failures in 30 patients with orbital MALT lymphoma after receiving 25 Gy.^[11] Other authors have also recommended a dose not <30 Gy for low-grade orbital lymphoma.^[24-28] Little data are available regarding the lower limit of effective doses for low-grade orbital lymphoma, although in one report, three of 11 patients treated with doses of <20 Gy developed recurrence compared to none of those who received >30 Gy.^[29] In another series, one of the patients who received <24 Gy developed recurrence compared to none of 14 who received >24 Gy.^[30]

Partial orbital irradiation is not recommended because of intraorbital recurrences outside the target volume or the areas of the orbit that were under-dosed. Bolek *et al.*,^[31] reported on one patient with low-grade lymphoma in the lacrimal gland that

recurred in the untreated area of the orbit. Uno *et al.*,^[32] reported one patient who developed conjunctival recurrence both under and adjacent to the shielded area of the eye. Similarly, Martinet *et al.*,^[33] reported one patient with intermediate grade lymphoma, which recurred in the orbit and was considered a geographic miss. In a recent analysis by Pfeffer *et al.*,^[34] where they used conformal partial orbital radiotherapy, they reported 33% relapse rates at the sites in ipsilateral orbits that were not included in the original target volume.

Reports in the literature reveal a local control rate of 83 to 100% and a five-year disease-free survival of 62 to 100% following local radiotherapy [Table 1]. This is true for low-grade and Stage I and II lymphoma, but distant metastases are problematic in patients with intermediate and high-grade tumors. Despite demonstrating an indolent course, extra-nodal marginal zone B-cell lymphomas are also known to recur in extra-nodal sites, including other ocular adnexal sites. The distant metastases rate for low-grade tumors is 0-23% as compared to 40-67% in patients with intermediate and high-grade tumors as shown in Table 1. These patients tend to develop distant disease soon after completion of the local therapy. Five-year survival in patients with high-grade tumors is only 30-60% [Table 1].

Patients with advanced disease should be treated with initial chemotherapy followed by localized radiation therapy to palliate symptoms and to achieve temporary disease control. Radiation dose given should be 30Gy in 10 fractions over 2 weeks or in patients with poor general condition 20Gy 5 fractions in 1 week. Supportive treatment in the form of steroids and analgesics should also be prescribed.

Recurrence in Contralateral Orbit

Contralateral disease is seen in >10% of patients with orbital lymphoma.^[8,28,29,31,34-36] It is, therefore, reasonable to suggest that some patients with seemingly focal intraorbital lymphoma as seen on CT may harbor occult microscopic disease at other intraorbital sites which in due course of time progresses to manifest as recurrence. The majority of recurrences are preceded by local orbital relapse, raising the possibility that local recurrence plays a role in their origin.^[29, 31] Contralateral recurrences are managed with local radiotherapy after ruling out systemic spread of the disease.

Role of Surgery

Surgery alone is seldom used except for conjunctival lesions. There is a high relapse rate after surgery as reported by many authors.^[8] This high recurrence rate may reflect difficulty in performing a radical procedure and preserving function. Esik *et al.*,^[8] reported 0% local relapse-free survival at 10 years in patients treated with surgery alone. Local relapses after surgery alone can be effectively treated with radiotherapy leading to complete response; however, the cosmetic outcome may be worsened by two therapies. Except for biopsy, surgery has no role in this disease.

Role of Chemotherapy

The role of chemotherapy has not yet been clearly defined, probably because of the previous difficulty in distinguishing between low, intermediate and high-grade NHL. Its role in the treatment of localized low-grade disease is questioned

in many series.^[8,13,25,27] Most of the patients with low-grade tumors have disease localized to the orbit, hence are treated with local therapy limiting the systemic side-effects. As these tumors present in elderly patients, localized therapy can offer these patients the best quality of life without much side-effects. Other reason for less use of chemotherapy could be the indolent nature of the disease not responsive to chemotherapeutic drugs. It has been seen that chemotherapy

use does not have any impact on disease-free or overall survival in localized low-grade NHL. It is difficult to achieve complete response with chemotherapy even if local radiotherapy is given in local relapses which followed chemotherapy, perhaps because of selection of therapy-resistant clones.^[8,28] Primary use of chemotherapy delays the deployment of radiotherapy, so if permanent local control is not achieved within a reasonable time, recurrence and

Table 1: Literature review of early stage orbital lymphoma treated with radiotherapy

Series	No. of patients	Stage	Histology	Dose (Gy)	Local control	Distant relapse	Survival @ 5 years
Fitzpatrick <i>et al.</i> ^[2]	19	I	Low and intermediate	25-45	100%	37%	62%
Bessell <i>et al.</i> ^[3]	112	I and II	Low and intermediate	20-49	100%	Low 15% Interm 20% high 62.5%	Low 80% Interm 88% high 59%
Fung <i>et al.</i> ^{[5]*}	98	I-IV	MALT Follicular DLBCL	16.2-46	98%	MALT- 7% Follicular-36% DLBCL-25%	Stage I, 94% III-IV, 49%
Smitt <i>et al.</i> ^[6]	25	I and II	Low Intermediate and high	28-40	89%	23%	93%
Reddy <i>et al.</i> ^[10]	14	I	N/A	22.5-42.5	100%	20%	76%
Bolek <i>et al.</i> ^[11]	20	I and II	Low, intermediate and high	15-53.35	95%	Low 39% Interm and high 67%	Low 89% Interm and high 33%
Stafford <i>et al.</i> ^[12]	40	I and II	Low, intermediate and high	15-53.8	98%	25%	100%
Kim <i>et al.</i> ^[13]	25	I and II	N/A	10-36	100%	52%	78%
Chao <i>et al.</i> ^[14]	20	I	Low and intermediate	20-43.2	100%	5%	90%
Jereb <i>et al.</i> ^[25]	17	I and II	Low and intermediate	20-37.5	100%	0%	N/A
Letschertz <i>et al.</i> ^[27]	30	I	Low and intermediate	24-57	91%	20%	90%
Pelloski <i>et al.</i> ^[28]	18	I	Low Intermediate and high		100%	Low 0 Interm and high 33%	Low 92% Interm and high 100%
Platanias <i>et al.</i> ^[29]	10	I	Low and intermediate		100%	0	100%
Bhatia <i>et al.</i> ^[30]	47	I	Low, intermediate and high	20-51	100	15%	74%
Martinet <i>et al.</i> ^[33]	90	I and II	Low, intermediate and high	4.0-50.4	65%	20%	78%
White <i>et al.</i> ^[35]	11	I and II	Low	20-46	83%	23%	73%
Hardman-Lea ^[36]	3	I and II	Low	NS	100%	NS	100%
Minehan <i>et al.</i> ^[40]	22	I and II	Low and intermediate	16.9-53.8	96%	20%	75%
Zhou <i>et al.</i> ^[43]	46	I-IV	All	30.6	98-100	11%	95%
Ejima <i>et al.</i> ^[44]	42	I	MALT	30-50	100	19%	100%
Bischof <i>et al.</i> ^[45]	42	I-IV	Low, intermediate and high	20-46	80-100%	Stage-I, 5%	Stage-I, 91% II, 80% III-IV, 47%
Quyn-Thu Le <i>et al.</i> ^[46]	31	I and II	Low	30-40	100%	16%	71%
Jacobiec <i>et al.</i> ^[47]	14	I and II	Low	20-30	100%	7%	86%
Dunbar <i>et al.</i> ^[48]	12	I and II	Low and intermediate	24-30	100%	1%	83%

MALT, mucosa associated lymphoid tissue; DLBCL, Diffuse large B-cell lymphoma, *26 patients received chemotherapy. (Stage IV, 21; Stage I, high grade-5 patients)

dissemination of the disease may occur, resulting in slow systemic progression.

Local control reported in a retrospective analysis with chemotherapy was only 42% as compared to 100% with radiotherapy alone.^[8] Thus, the overall survival may be worse after primary chemotherapy (even with salvage radiotherapy) than when radiotherapy is given as initial treatment. Because of this and the potential side-effects of chemotherapy in elderly patients there is no indication for primary chemotherapy, in early stage localized low-grade disease. However, it has a definitive role in high-grade tumors or those with systemic manifestations of low grade and intermediate lesions.

High-grade tumors should be treated with standard combination chemotherapy, cyclophosphamide, adriamycin, vincristine and prednisone (CHOP). The current treatment of choice for elderly patients with DLCL is that of CHOP chemotherapy with rituximab (an anti CD-20 monoclonal antibody) or the rituximab cyclophosphamide adriamycin (vincristine) oncovin prednisolone (R-CHOP) regimen. This is based on a recent European study^[37] which studied CHOP vs. R-CHOP in elderly patients with DLCL and showed significant prolongation of event-free survival and overall survival in the group that was treated with R-CHOP without additional toxicity. On complete response, radiotherapy dose of 30 Gy is adequate. A dose of 40 Gy should be given after partial remission. In a recent study, Avelis *et al.*,^[38] reported similar complete response rates in both arms: 98% in the radiotherapy arm, and 100% in the combined therapy group. At a median follow-up of 16.4 years, event-free survival was 94% and 85% respectively. Overall survivals were: 96% and 91% respectively. No statistical differences were found. Acute and late toxicities were mild. They concluded that addition of chemotherapy was of no further benefit, as the results did not differ, thus, radiotherapy can be considered as the treatment of choice in primary orbital malignant lymphoma patients. Long-term follow-up with six-monthly examinations are therefore recommended. However, in high-grade histologies, it may be useful to follow the patients at closer intervals once they have achieved complete remission after the treatment.

Prognostic Factors

Major prognostic criteria for orbital adnexal lymphomas include anatomic location of the tumor; stage of disease at first presentation; lymphoma subtype as determined using the revised european american lymphoma (REAL) classification;^[39] immunohistochemical markers determining factors such as tumor growth rate; and the serum lactate dehydrogenase level (LDH).^[4] In a rare cancer network study of 90 patients by Martinet *et al.*,^[33] the statistically significant factors on univariate analysis were younger age, low grade, normal erythrocyte sedimentation rate, absence of muscular infiltration, complete response to treatment, conjunctival localization, and normal LDH for overall survival, disease-free survival and freedom from treatment failure. In multivariate analysis, the favorable factors were younger age and low grade for overall survival and disease-free survival; a favorable response, conjunctival localization, and complete staging were highly significant for disease-free survival and freedom from treatment failure. On the contrary, Minehan *et al.*,^[40] reported that prognostic factors reflecting the importance of tumor volume are muscular

infiltration, ptosis, and plegia. The International Prognostic Index (IPI)^[41] was developed by 16 institutions and cooperative groups in the United States, Europe and Canada as a prognostic factor model for aggressive NHL. This includes the age (<60 or >60), performance status by (Eastern Cooperative Oncology Group (0 to 1 vs. 2 to 4), Ann -Arbor stage (I-II vs. II-IV), extra-nodal sites (<1 vs. >1), and LDH level (normal or above normal).

Complications

Acute effects of radiation are mild and can be managed symptomatically. Acute conjunctivitis is the most common type and should be treated with artificial tears. Excess use of antibiotics should be avoided because these can worsen symptoms by causing more conjunctival irritation.

The most common late toxicity is cataract formation. Doses of 2 Gy in a single fraction and 4.4 to 5.5 Gy in fractionated course have been reported to produce cataract, however, the lens tolerance is 10 to 12 Gy when fractionated radiotherapy is used. Other risk factors such as age, diabetes mellitus, familial predisposition and drugs should be ruled out. As orbital lymphoma is seen in older patients they tend to develop cataract even without radiation. Lens opacities usually appear three to nine years after radiotherapy. Posterior subcapsular cataracts are a typical location for radiation-induced cataracts.^[12]

On literature review, it was seen that cataract occurred more in patients treated without lens shielding than with shielding. Its incidence varies from 0-38% with lens shielding as compared to 9-100% in patients treated without lens shielding as shown in Table 2. Bessel *et al.*,^[3] reported cataract development in three of seven patients treated without shielding, and in five of 52 patients treated with shielding. Smitt *et al.*,^[6] noted that cataract developed in two of 31 eyes when eyes were routinely shielded. Others have also reported similar findings. In a series by Bolek *et al.*,^[31] cataract occurred in seven of 21 patients treated without lens shielding, but in none of the 17 patients

Table 2: Incidence of cataract formation

Series	With lens shielding (%)	Without lens shielding (%)
Smitt <i>et al.</i> ^[6]	-	2
Esik <i>et al.</i> ^[8]	0/10 (0)	11/11 (100)
Reddy <i>et al.</i> ^[10]	-	2
Bolek <i>et al.</i> ^[11]	0/17 (0)	7/21 (33)
Stafford <i>et al.</i> ^[12]	5/33 (22)	3/25 (12)
Chao <i>et al.</i> ^[14]	3/8 (38)	4/12 (33)
Letschertz <i>et al.</i> ^[27]	-	58%
Pelloski <i>et al.</i> ^[28]	0/9 (0)	3/12 (25)
Bhatia <i>et al.</i> ^[30]	2/19 (13)	28/103 (27)
Martinet <i>et al.</i> ^[33]	7/29 (24)	6/20 (33)
Pfeffer <i>et al.</i> ^[34]	1/12 (8)	1/11 (9)
Minehan <i>et al.</i> ^[40]	-	3
Hasegawa ^[42]	1/8	11/21
Zhou <i>et al.</i> ^[43]	0/17 (eyes)	9/39 (20)
Ejima <i>et al.</i> ^[44]	10%*	100%*
Bischof <i>et al.</i> ^[45]	4/42 (9.5)	-

*Probability of developing Grade 3 cataract at 3.5 years

treated with lens shields. Minehan *et al.*,^[39] reported cataract formation in seven of 21 patients treated without shielding and none of the patients treated with shielding. Recent series by different authors^[42-45] have also reported variable incidence of cataract formation as shown in Table 2. However, with current surgical techniques, the treatment of cataract is quick, safe and efficient. So the risk of missing the lymphoma overweighs the inconvenience of the cataract. So it can be concluded from these findings that routine lens shielding should be avoided and the PTV should encompass the entire orbit, in most cases, to avoid a geographical miss.

Late lacrimal gland toxicity is usually mild; this is due to the tolerance of the gland to the doses used for lymphoma. Fitzpatrick *et al.*,^[2] reported one corneal ulceration in 23 patients. Bessel *et al.*,^[3] treated 112 patients with radiotherapy for orbital lymphoma, only five patients required artificial tears. He established a dose-response correlation, none of the patients had late toxicity at a dose of <30 Gy, but 4.5% developed toxicity at 30 to 39 Gy, and 23% at 40 to 49 Gy. Corneal ulcer was seen in two patients who received a dose of >40 Gy. Because of this steep dose-response relationship, care should be taken to avoid dose inhomogeneity between the prescribed tumor dose and the dose received by the lacrimal apparatus. Smitt *et al.*,^[6] reported one of 25 patients who developed significant corneal damage.

Corneal toxicity is very rare if the patients are instructed to look into the beam during treatment. The tolerance dose of cornea is 50 Gy in conventional fractionation, which is hardly given in lymphoma. Some have indicated 30 Gy if larger than the conventional fractionation is used.^[32]

Retinal toxicity is minimal at the doses used for patients with lymphoma. This finding has been confirmed by Bessel *et al.*^[3] In a series by Quyn-Thu Le *et al.*,^[46] two of 12 patients developed retinopathy who received a retinal dose of >34 Gy. According to literature, radiation-related retinopathy has been observed at doses as low as 35 Gy, although its incidence is very low at doses of <45 Gy.^[47-49]

Conclusions

Lymphomas of the orbit are uncommon and may involve any site in the orbit. Full staging work up is mandatory for proper management. Radiotherapy is an excellent treatment modality for primary orbital lymphoma. Radiation doses of 30 to 35 Gy are adequate for low-grade tumors. Intermediate grade lymphomas should be treated with chemotherapy followed by radiation dose of 30 Gy for complete responders and 40 Gy for partial responders using conventional fractionation to achieve maximum local control with relatively low morbidity. Partial orbit volume irradiation leads to unacceptable incidence of intraorbital recurrence and is not recommended. Role of surgery is limited to biopsy only. Several prognostic factors have been identified; those should be considered while managing this uncommon site of primary lymphoma. Radiation toxicity can be minimized by meticulous planning and proper dose prescription.

References

- Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. *Cancer* 1972;29:252-60.
- Fitzpatrick PJ, Macko S. Lymphoreticular tumors of the orbit. *Int J Radiat Oncol Biol Physics* 1984;10:333-40.
- Bessel EM, Henk JM, Wright JE, Whitelocke RA. Orbital and conjunctival lymphoma: Treatment and prognosis. *Radiation Oncol* 1988;13:237-44.
- Coupland SE, Hummel M, Stien H. Ocular adnexal lymphomas: Five case presentation and a review of literature. *Surv Ophthalmol* 2002;47:470-90.
- Fung CY, Tarbell NJ, Lucarelli MJ, Goldberg SI, Linggood RM, Harris NL, *et al.* Ocular adnexal Lymphoma: Clinical behaviour of distinct world health organization classification of subtypes. *Int J Rad Oncol Biol Phys* 2003;57:1382-91.
- Smitt MC and Donaldson SS. Radiotherapy is successful treatment for orbital lymphoma. *Int J Radiat Oncol Biol Physics* 1993;26:59-66.
- Mittal BB, Deutch M, Kennerdell J, Johnson B. Paraocular lymphoid tumors. *Radiology* 1986;159:793.
- Esik O, Ikeda H, Mukai K, Kaneko A. A retrospective analysis of different modalities for treatment of primary orbital non-Hodgkins lymphoma. *Radiation Oncol* 1996;38:13-8.
- Tsang RW, Gospodarowicz MK, Pintilie M, Wells W, Hodgson DC, Sun A. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. *J Clin Oncol* 2003;21:4157-64.
- Reddy EK, Bhatia P, Evans RG. Primary orbital lymphomas. *Int J Radiat Oncol Biol Phys* 1984;10:1013-9.
- Bolek TW, Moyses HM, Marcus RB Jr, Gorden L 3rd, Maiese RL, Almasri NM, *et al.* Radiotherapy in the management of orbital lymphoma. *Int J Radiat Oncol Biol Phys* 1999;44:31-6.
- Stafford SL, Kozelsky TF, Garrity JA, Kurtin PJ, Leavitt JA, Martenson JA, *et al.* Orbital lymphoma: Radiotherapy outcome and complications. *Radiation Oncol* 2001;59:139-44.
- Kim Y, Fayos J. Primary orbital lymphoma: A radiotherapeutic experience. *Int J Radiat Oncol Biol Phys* 1976;1:1099-105.
- Chao CK, Lin HS, Devineni VR, Smith M. Radiation therapy for primary orbital lymphoma. *Int J Radiat Oncol Biol Phys* 1995;31:929-34.
- Lister TA, Crowther D, Surcliffe SB, Glatstein E, Canellos GP, Young RC. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 1989;7:1630-6.
- Ferreri AJ, Ponzoni M, Guidoboni M, Conciliis De C, Resti AG, Mazzi B, *et al.* Regression of ocular adnexal lymphoma after chlamydia psittaci-eradicating antibiotic therapy. *J Clin Oncol* 2005;23:5067-73.
- Grünberger B, Hauff W, Lukas J, Wohrer S, Zielinski CC, Streubel B, *et al.* 'Blind' antibiotic treatment targeting Chlamydia is not effective in patients with MALT lymphoma of the ocular adnexal. *Ann Oncol* 2006;17:484-7.
- Husain A, Roberts D, Pro B, McLaughlin P, Esmali B. Meta-analysis of the association between Chlamydia psittaci and ocular adnexal lymphoma and the response of ocular adnexal lymphoma to antibiotics. *Cancer* 2007;110:809-15.
- Freire JE, Brady LW, Shields JA, Shields CL. Eye and orbit. In: Perez CA, Halperin EC, Schmidt-Ullrich RK, editors. Principles and practice of radiation oncology. Philadelphia: Lippincott Williams and Wilkins; 2004. p. 888.
- Freire JE, Brady LW, Shields JA, Shields CL. Non-Hodgkin's lymphoma. In: Perez CA, Halperin EC, Schmidt-Ullrich RK, editors. Principles and practice of radiation oncology. Philadelphia: Lippincott Williams and Wilkins; 2004. p. 2096.
- Donaldson SS, Findley DO. Treatment of orbital lymphoid tumors with electron beams. *Front Radiat Ther Oncol* 1991;25:187-200.
- Purdy JA. Three-dimensional conformal radiation therapy: Physics, treatment planning and clinical aspects. In: Principles and practice of radiation oncology. Philadelphia: Lippincott Williams and Wilkins; 2004. p. 283-313.

23. Mohan R, Low D, Chao KS. Intensity-Modulated radiation treatment planning, quality assurance, delivery and clinical application. In: Principles and practice of radiation oncology. Philadelphia: Lippincott Williams and Wilkins; 2004. p. 314-36.
24. Foster SC, Wilson CS, Tretter PK. Radiotherapy of the primary lymphoma of the orbit. *Am J Roentgenol Radium Ther Nucl Med* 1971;111:343-49.
25. Jereb B, Lee H, Jackobiec FA, Kutcher J. Radiation therapy of conjunctival and orbital lymphoid tumors. *Int J Radiat Oncol Biol Phys* 1984;10:1013-9.
26. Kamath SS, Marcus RB Jr, Lynch JW. The impact of radiotherapy dose and other treatment-related and clinical factors on in-field control in stage I and II non-Hodgkin's lymphoma. *Int J Radiat Oncol Biol Phys* 1999;44:563-8.
27. Letschert JG, Gonazales Gonazales D, Oskam J, Koornneef L, van Dijk JD, Boukes R, *et al.* Results of radiotherapy in patients with stage-I orbital non-Hodgkin's lymphoma. *Radiation Oncol* 1991;22:36-44.
28. Pelloski CE, Wilder RB, Ha CS, Hess MA, Cabanillas FF, Cox JD. Clinical stage IEA-IIIEA orbital lymphomas: Outcomes in the era of modern staging and treatment. *Radiation Oncol* 2001;59:145-51.
29. Palatias LC, Putterman AM, Vijayakumar S, Recant W, Weichselbaum RR, Bitran JD. Treatment and prognosis of orbital non-Hodgkin's lymphomas. *Am J Clin Oncol* 1992;15:79-83.
30. Bhatia S, Paulino AC, Buatti JM, Mayr NA, Wen BC. Curative radiotherapy for orbital lymphoma. *Int J Radiat Oncol Biol Phys* 2002;54:818-23.
31. Bolek TW, Moyses HM, Marcus RB Jr. Radiotherapy for primary orbital lymphoma. *Int J Radiat Oncol Biol Phys* 1995;31:929-34.
32. Uno T, Isobe K, Shikama N, Nishikawa A, Oguchi M, Ueno N, *et al.* Radiotherapy for extranodal marginal zone, B-cell lymphoma of mucosa-associated lymphoid tissue originating in the ocular adnexa: A multi-institutional retrospective review of 50 patients. *Cancer* 2003;98:865-71.
33. Martinet S, Ozsahin M, Belkacemi Y, Landmann C, Poortmans P, Oehlere C. Outcome and prognostic factors in orbital lymphoma: A Rare Cancer Network study on 90 consecutive patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys* 2003;55:892-8.
34. Pfeffer MR, Rabin T, Tsvang L, Goffman J, Rosen N, Symon Z. Orbital lymphoma: Is it necessary to treat the entire orbit? *Int J Radiat Oncol Biol Phys* 2004;61:527-30.
35. White WL, Ferry JA, Harris NL, Grove AS Jr. Ocular adnexal lymphoma: A clinicopathologic study with identification of lymphomas of mucosa associated lymphoid tissue type. *Ophthalmology* 1995;102:1994-2006.
36. Hardman-Lea S, Kerr-Muir M, Wotherspoon AC, Green WT, Morell A, Isaacson PG. Mucosa associated lymphoid tissue lymphoma of the conjunctiva. *Arch Ophthalmol* 1994;112:1207-12.
37. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. *N Engl J Med* 2002;346:235-42.
38. Avilés A, Neri N, Calva A, Huerta-Guzmán J, Cleto S, Nambo MJ. Addition of a short course of chemotherapy did not improve outcome in patients with localized marginal B-cell lymphoma of the orbit. *Oncology* 2006;70:173-6.
39. Harris NL, Jaffe ES, Stein H. A Revised European-American classifications of lymphoid neoplasms: A proposal from International Lymphoma Study Group. *Blood* 1994;84:1361-92.
40. Minehan KJ, Martenson JA Jr, Garriy JA, Kurtin PJ, Banks PM, Chen MG, *et al.* Local control and complications after radiation therapy for primary orbital lymphoma: A case for low dose treatment. *Int J Radiat Oncol Biol Phys* 1991;20:791-6.
41. A predictive model for aggressive non-Hodgkin's lymphoma: The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993;329:987-94.
42. Hasegawa M, Kojima M, Shioya M, Tamaki Y, Saitoh JI, Sakurai H, *et al.* Treatment results of radiotherapy for malignant lymphoma of the orbit and histopathological review according to the WHO classification. *Int J Radiat Oncol Biol Phys* 2003;57:172-6.
43. Zhou P, Andrea K, Silver B, Li S, Hua L, Mauch PM. Radiation therapy for orbital lymphoma. *Int J Radiat Oncol Biol Phys* 2005;63:866-71.
44. Ejima Y, Sasaki R, Okamoto Y, Maruta T, Azumi A, Hayashi Y, *et al.* Ocular adnexal mucosa-associated lymphoid tissue lymphoma treated with radiotherapy. *Radiation Oncol* 2005;78:6-9.
45. Bischof M, Karagiozidis M, Krempien R, Treiber M, Neuhof D, Debus J, *et al.* Radiotherapy for orbital lymphoma outcome and late effects. *Strahlenther Onkol* 2007;183:17-22.
46. Quyn-Thu Le, Stephen ME, Tracy IG, Richard H, Warnke RA, Donaldson SS, *et al.* Primary radiotherapy for localized orbital malt lymphoma. *Int J Radiat Oncol Biol Phys* 2002;52:657-63.
47. Jakobiec FA, Iwamoto T, Patell M, Knowles DM 2nd. Ocular adnexal monoclonal lymphoid tumors with a favorable prognosis. *Ophthalmology* 1986;93:1574-7.
48. Dunbar S, Linggood R, Doppke K, Duby A, Wang CC. Conjunctival lymphoma: Results and treatment with a single anterior electron field, A lens sparing approach. *Int J Radiat Oncol Biol Phys* 1990;19:249-57.
49. Gordon KB, Char DH, Sangerman RH. Late effects of radiation on the eye and ocular adnexal. *Int J Radiat Oncol Biol Phys* 1995;31:1123-39.

Source of Support: Nil, **Conflict of Interest:** None declared.

Announcement

INDIAN JOURNAL OF OPHTHALMOLOGY
and
P.D.HINDUJA HOSPITAL & MEDICAL RESEARCH CENTRE,
Announces

The Vth Workshop on Science & Art of Research & Medical Writing
On 30th and 31st May 2009

Turn to Page 173 for details of the same.