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Primary non-Hodgkin's lymphoma of the orbit: treatment outcomes from India

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Original Article

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Abstract

Background: Primary non-Hodgkin's lymphoma (NHL) of the orbit is rare. Orbital NHLs show good response to both radiotherapy (RT) and chemotherapy, and hence, the emphasis should be to ensure maximum cure rate with minimum morbidity. In this study, we present the clinical profile and treatment outcomes of patients with NHL who had initial presentation in the orbit.
Materials and methods: In this retrospective analysis, case records of patients with a diagnosis of NHL of the orbit were analysed from January 2005 to January 2015. Patients were worked up and staged according to the Ann Arbor system. Patients with large tumours were initially given chemotherapy with CHOP regimen (cyclophosphamide, vincristine, adriamycin and prednisolone) three weekly for 4–6 cycles. Patients with residual disease were given RT 20–30 Gy at 2 Gy per fraction. RT when given as a primary treatment consisted of 36–45 Gy at 1·8–2 Gy per fraction on either Cobalt 60 machine or linear accelerator.
Results: A total of 52 patients with diagnosis of orbital NHL were included in this study. Median age at presentation was 57 years (range 13–71). Left, right and bilateral orbit was involved in 21 (40%), 28(54%) and 3(6%) patients, respectively. Low- and high-grade pathology was seen in 39(75%) and 13(25%) patients, respectively. On immunohistochemistry, 23(44%) tumors were CD 20 positive. After staging, 33 (63%) patients had stage I disease. Median tumour size was 4·0 × 3·2 × 1·5 cm (1·7 × 1·7 × 1·4 cm to 5·8 × 4·0 × 4·7 cm). Primary RT was given to 7(13%) patients. Upfront chemotherapy was given in 45(86·5%) patients, out of which 24 had stage I disease. RT consolidation was done in 26 (50%) patients for residual disease after chemotherapy. Median follow-up was 88 months (range 29–183 months). Relapse occurred in 6(9·6%) patients; 2 local; 2 local + distant and in 2 distant alone. These patients were successfully salvaged with systemic chemotherapy and local RT. One patient died due to neutropenia. Overall survival in this series was 96%.
Conclusions: Excellent local control was achieved with initial chemotherapy followed by RT for primary orbital NHL with minimal toxicity. We recommend a dose of 36–40 Gy for definitive RT and 30 Gy for lymphoma following chemotherapy using 2 Gy/fraction for Indian patients who present with bulky tumours. RT should be incorporated in treatment of orbital NHL whenever possible as it is safe, effective and is associated with minimal complications.

Introduction

Primary lymphomas of the orbit are the most common malignant tumours of the orbit, constituting nearly 50% of orbital tumours but are rare among the lymphomas constituting only 1% of all non-Hodgkin's lymphomas (NHLs). Majority, 85–90% are low-grade B-cell lymphomas and show good response to both radiotherapy (RT) and chemotherapy. Hence, the aim of the treatment should be maximum cure rate with minimum toxicity. In our country due to the low educational and poor socio-economic status, patients present with bulky tumours at presentation (Figure 1). Upfront RT cannot be used in such patients who have severe proptosis as the eye cannot be adequately opened to stare at the beam (Figure 2), which is essential to spare the cornea and the lens from RT to prevent long term toxicity. In these patients, chemotherapy must be used to reduce the bulk of the disease to make RT delivery possible. In this study, we present the clinical profile and treatment results of patients with primary NHL of the orbit. We also examine the effect of induction chemotherapy followed by RT (which is the mainstay of treatment) in these patients. Based on our findings, we have drawn recommendations for optimum treatment in these patients for a disease which carry a favourable prognosis.

Materials and Methods

In this retrospective analysis, the case records between the years 2005–2015 of the patients with primary presentation with orbit swelling and a diagnosis of NHL were analysed. The diagnosis was either by fine needle aspiration cytology (FNAC) or by biopsy. They were further worked up with complete haemogram, kidney and liver function tests, serum albumin, lactate dehydrogenase, contrast enhanced computed tomography (CECT) from the base of the skull to the femoral

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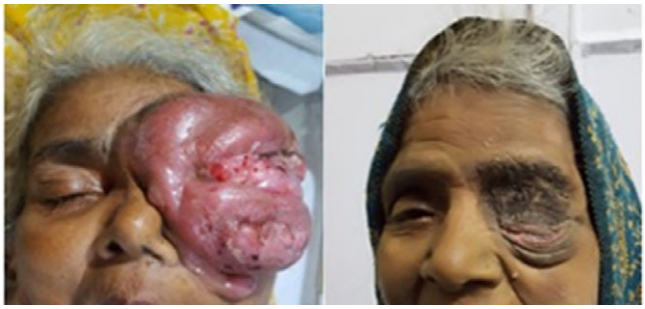

Figure 1. A patient with bulky orbital lymphoma; pre-treatment (left) and post-treatment (right).

group of lymph nodes and a bone marrow examination. Clinical examination and CECT was used to determine the size and extent of the orbital tumour. The patients were staged according to the Ann Arbor system. The treatment was based on the stage of disease, age, performance status (PS) and the size of the orbital tumour at diagnosis. Those with small tumours, low-grade disease, localised to the orbits were given primary RT. Those with advanced age and poor PS were also treated with definitive radiation. In those with stage IAE with good PS, disease localised to the orbit but with tumours of large size (where definitive RT would be technically difficult) was initially given chemotherapy with CHOP regimen to achieve chemoreduction. Those with disease elsewhere apart from the orbit were treated with systemic chemotherapy. Patients who were initially treated with chemotherapy but had significant residual disease (on clinical examination or CT scan) were given reduced dose of RT. The chemotherapy regimen given was CHOP, consisting of cyclophosphamide (750 mg/m^2), vincristine (1·4 mg/m^2), adriamycin (50 mg/m^2) and prednisolone (100 mg for 5 days) given at three weekly intervals for 4–6 cycles. Radiation when given as a primary treatment consisted of 36–45 Gy at 1·8–2 Gy per fraction. Patients who underwent radiation for residual disease after chemotherapy were given dose of 20–30 Gy at 2 Gy per fraction. Radiation was delivered on either Cobalt 60 machine or linear accelerator with 6 MV energy X-rays. The field arrangement consisted of antero-lateral fields with wedges. The response after treatment was assessed clinically as well as with a CECT. The patients were followed up by clinical examination, and those suspected of relapse were investigated with a CECT and a FNAC for confirmation. The patients who recurred were treated with second-line chemotherapy with MIME regimen consisting of mitoxantrone, ifosfamide, etoposide and mesna. The collected data were analysed with IBM SPSS statistical package 22·0 version. Frequency and percentage analysis were used for categorical variables. Mean and standard deviation (SD) were used for continuous variables. The results are reported as descriptive statistics.

Results

Fifty-two patients with orbital swelling and tissue diagnosis of NHL were analysed. Median age at presentation was 57 years (range 13–71 years). Majority, 20/32 (62·5%), were males. Left orbit was involved in 16 (50%) and right in 14 (43·75%) patients (Table 1). Bilateral disease at presentation was seen in 2(6·25%) patients. Out of the 32 patients, 25(78·12%) had low-grade NHL and 7(21·88%) had high-grade NHL. Though all were pathologically proven NHL, only 17 underwent a biopsy and the rest underwent a FNAC. Immunohistochemistry was done in patients with biopsy; all were of B-cell variety, and 12/17 (70·58%) expressed CD 20. None of the patients had B-symptoms. After staging, 21(66%) had stage I disease. Stage II, III and IV disease were present in 6(19%), 2(6%) and 3(9%) patients, respectively. Median size of the tumour was 4·0 × 3·2 × 1·5 cm (range 1·7 × 1·7 × 1·4 cm to 5·8 × 4·0 × 4·7 cm).

Table 1. Patient characteristics

Characteristics	N = 52	%
Age (in years)		
<40	9	17·31
40–60	21	40·38
>60	22	42·31
Gender		
Male	32	61·5
Female	20	38·5
Laterality		
Right	21	40·38
Left	28	53·85
Bilateral	3	5·77
Stage		
I	33	63·46
II	10	19·23
III	4	7·69
IV	5	9·62
B-Symptoms		
Present	8	15·38
Absent	44	84·62

Seven patients were treated with primary RT. Eleven patients had stage II disease or beyond and were given systemic chemotherapy. The chemotherapy regimen was CHOP in all the patients except three in whom rituximab (R-CHOP) was given. A total of 25(78%) patients were started with upfront chemotherapy out of which 14(56%) had stage I disease. Consolidation radiation for presence of residual disease on clinical or radiological examination was given in 17 (68%) patients after chemotherapy.

Median follow-up was 88 months (range 29–183 months). One patient died due to neutropenia during chemotherapy with CHOP regimen. There were 6(11·5%) relapses, with 2(4%) local and 2(4%) local as well as distant, and 2(4%) distant only. Median time to relapse was 36 months (range 26–109 months). Among patients with local relapse, one had initial bulky disease and received systemic chemotherapy followed by radiation to a dose of 30 Gy while another patient was treated with chemotherapy alone. The two patients who developed local as well as distant relapse had not received radiation initially, and these patients were successfully salvaged with systemic chemotherapy followed by local RT. There were three patients who had bilateral disease; with stage III and IV in 2 and 1 patient, respectively. All three were treated with systemic chemotherapy and were without disease at the time of last follow-up. The overall survival in this series was 96%.

The results according to the Ann Arbor stage are shown in (Table 2).

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Table 2. Stage-wise treatment

Stage	n	Median Age (yrs)	Low grade	High grade	Treatment			Median Survival	NED status n (%)
					CT	CT + RT	RT		
I	33	57·5	26	7	8	16	9	88·5	33 (100%)
II	10	59	6	4	2	8	0	85·3	9 (90%)
III	4	48	3	1	4	0	0	78·6	3 (75%)
IV	5	37·5	4	1	4	2	0	75·5	3 (60%)

RT, Radiation alone; CT + RT, Chemotherapy followed by consolidation radiation; NED, No Evidence of Disease clinically or radiologically at last visit.

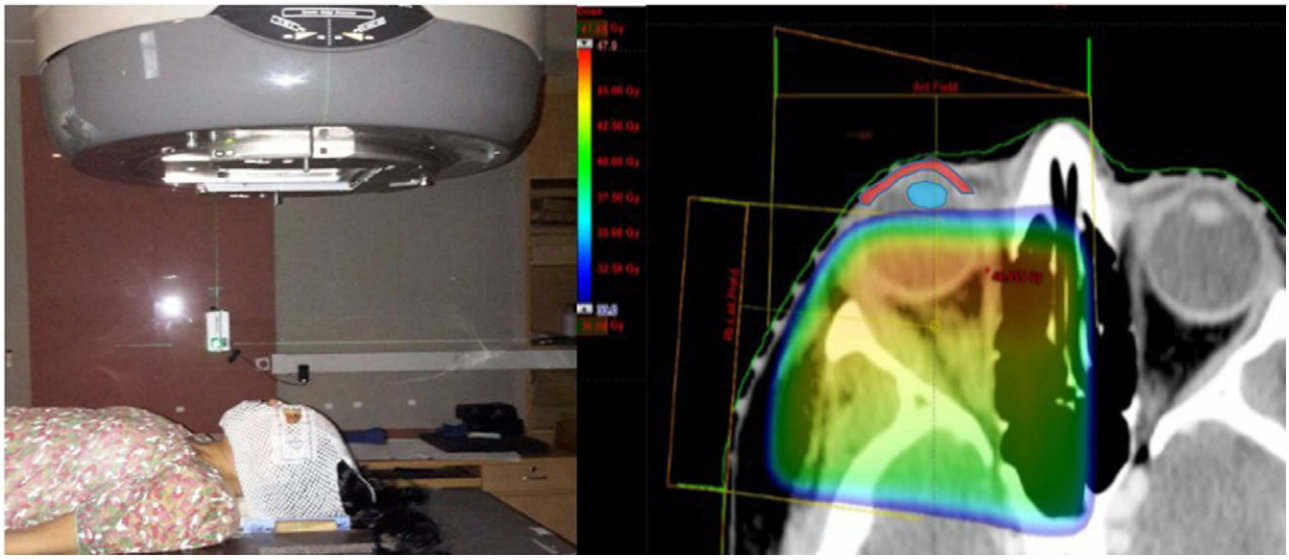

Figure 2. Radiotherapy setup for treatment of the orbital lymphoma (left) and dose distributions which spare the cornea and lens (right).

Stage I disease

There were 33 patients with stage I disease, 16 patients had involvement in the left eye, and 15 patients had disease on the right side. Low-grade and high-grade lymphoma were reported in 26 and 7 patients, respectively. The median tumour size in these patients was 3·72 cm (range-1·7–4·8 cm). Among these, 24 patients were treated initially with chemotherapy with CHOP regimen; out of these, 16 patients also required consolidation with radiation. Primary radiation treatment was given to 9 patients. None of these patients relapsed till the last follow-up. Only one patient who received CHOP followed by RT relapsed locally in the orbit and was successfully salvaged with chemotherapy (MIME). Only one patient reported decreased vision in the involved eye which was attributed to development of cataract. Median survival in these patients was 88·5 months, and all patients were disease-free at last follow-up.

Stage II and stage III disease

There were 10 patients with stage II disease in whom axillary and/or mediastinal nodes were involved. All the patients were treated with initial chemotherapy; radiation was needed to consolidate the residual orbital disease in 8 patients after chemotherapy. One patient aged 72 years developed neutropenia during chemotherapy and died. Median survival in these patients was 85 months with disease control rate of 90%.

Four patients had stage III disease; 3 were low-grade, and 1 was high-grade NHL. These were treated with systemic chemotherapy with CHOP alone. One patient developed distant relapse and died because of the disease. Median survival was 78 months with disease control rate of 75%.

Stage IV disease

There were 5 patients with stage IV disease at presentation, and 3 had bone marrow infiltration. Four were low-grade, and 1 was high-grade NHL. All of the 5 patients were treated with R-CHOP, and the one patient with high-grade disease required consolidation radiation for residual disease. The remaining two with low-grade lymphoma were disease-free at the end of chemotherapy. There were 2 relapses, one patient with low-grade lymphoma developed relapse (local and distant) after a period of 14 months and was given second-line chemotherapy with MIME regimen with adequate control of local disease but had persistent residual disease at distant site. The second patient relapsed in the opposite orbit and was salvaged with radiation alone. Median survival in these patients was 75 months with a disease control rate of 60%.

There were 9 patients with stage IAE disease. All of them had low-grade disease and were primarily treated with radiation dose of 36–45 Gy at 1·8 Gy per fraction. All the patients were clinically and radiologically disease-free at the last follow-up.

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Cataract developed in 1(2%) patient, and reduced vision was reported by 1(2%) patient. This patient had received RT dose of 45 Gy. Dry eye was reported by 3(6%) patients, and they had received ≥40 Gy of total dose. None of our patients developed corneal complications, macular degeneration and retinopathy.

Discussion

In this study, excellent local control was achieved with induction chemoreduction followed by RT for primary orbital NHL. The toxicity attributed to RT was minimal. Orbital lymphoma is a rare malignancy. As a result, most of the current literature consists of single-institution retrospective reviews. This is one of the largest single-institution experiences from India in orbital lymphoma.

The average volume of adult orbit is ~30 cc which is compactly filled with the eyeball, muscles and fat allowing very less space for a neoplastic process which would then produce immediate proptosis. Hence, early presentation is common and existing literature can categorise as to which sub-site of origin of lymphoma (e.g., conjunctiva, eyelids, lacrimal glands)[1] and little does tumour size determine patient treatment. However in our country, due to lack of awareness and lack of access to medical facilities, presentation with larger tumours and at later stage is a common feature (Figure 1) and the associated chemosis makes it difficult to precisely indicate the sub-site of tumour origin. In the present study, the average volume of the tumour was 19·20 cc, which can cause local symptoms such as proptosis, swelling, bleeding, ulceration and visual impairment. Post-treatment, it can lead to sequel which may need surgical interventions to restore eye functions.

In the present study, all the patients were of B-cell variety with majority (75%) being low-grade lymphomas. Extra-nodal marginal zone lymphoma is the most common histology reported in literature.[2] The incidence was higher in the males, and the median age at presentation was 57 years. These findings are similar to those reported in previous studies.[3–7] CECT was used for measuring the dimensions of the lesion which is justified by the fact that orbital lymphomas are usually homogeneous masses of relatively high enhancement and sharp margins.[3]

Radiation has been the oldest modality to treat orbital malignancies including lymphomas.[4,5] Previously, when RT was used in doses exceeding 40 Gy, the complication rates were high though local control rates were excellent.[6] With reduction in the dose of RT, it was possible to maintain excellent local control.[7–10] In a study by Stafford et al., they recommended a dose of <35 Gy, particularly for low-grade lymphomas,[7] and was confirmed by others as well.[8–10] The current recommended dose of RT in low-grade NHL is 24 Gy in 12 fractions over 2·5 weeks. We used a higher dose in our patients because most of our patients had bulky disease and 25% of the patients had high-grade histology.

Chemotherapy alone has been less explored in localised orbital lymphomas[11] with a complete response rate of 79% compared to nearly 100% response rates with radiation. Some studies have reported relapse rates as high as 29% after CHOP chemotherapy alone.[12] After local radiation, the primary concern is systemic failure,[1,8] and hence, meticulous staging is necessary before embarking on local radiation.[13,14] Our workup protocol consisted of chest X-ray, CT scan of the orbits, CT scan of the chest and abdomen, and bone marrow biopsy. In this study, 21% (11/52) were upstaged to stage II which changed the treatment strategy. The median time to relapse was 36 months (range 26–109), suggesting that relapse at distant sites were not present at the initial diagnosis. Considering the significant number of patients who were upstaged and the low incidence of distant relapses which have occurred after a reasonably long period, the present staging workup may be optimal in the resource constraint countries for orbital NHL. The role of Positron Emission Tomography/Computed tomography (PET/CT) is evolving[15] and may be considered as a better alternative to CECT[16] as a part of meticulous staging, but its availability is an issue in developing countries. In NHL, relapses may occur even after10 years[7] which suggests that late relapses may be related to etiological factors like chlamydia or immune reactions in the eye to foreign antibodies. Hence, long-term outcome may be determined by the inciting factors for lymphomagenesis.

Table 3. Literature review

Author	No.	Treatment	Follow-up	Local control (%)	RFS (%)
Bolek[1]	20	RT	5 years	95	89
Reddy[5]	14	RT	5 years	100	76
Stafford[6]	48	RT	10 years	98	66
Letschert[7]	33	RT	10 years	91	80
Martinet[8]	90	RT	5 years	65	78
Minehan[9]	22	RT	5 years	96	75
Bhatia[18]	47	RT	5 years	100	65·5
Zhou[19]	46	RT	46 months	98–100	89
Present study	52	RT + CT	88 months	96	90·62

Abbreviations: RT, radiotherapy; CT, chemotherapy; RFS, relapse-free survival.

Systemic chemotherapy is recommended from stage IIAE onwards. Depending on the histology, CHOP/ R-CHOP/ bendamustine + rituximab have been recommended.[17] A series reported good response rates with oral chlorambucil alone.[7] Systemic chemotherapy may be considered as a viable treatment option for initial chemoreduction in stage I disease presenting with large tumours as seen in India and may be in other low-middle-income countries as well (Figure 1). Meriting important consideration is the fact that patients from our country are poor and nutritionally compromised. Though chemotherapy must be used according to the stage of the disease, it must be judiciously used in true stage I patients and radiation must always be incorporated in the treatment of stage IAE of the orbits to achieve excellent disease control. Rituximab has also been recommended in low-grade, stage I NHL with CD 20 expression, but its availability and cost is a limiting factor for low-middle-income countries. In such situation, radiation plays an important role for the local disease as systemic chemotherapy alone may not bring about complete clinical or radiological remission. In our series, all patients who underwent primary radiation were completely disease-free till last follow-up. Patients who were started with upfront chemotherapy due to large disease at presentation had clinical or radiological residual disease requiring consolidation with radiation in 50% of the cases.

Local control with RT for orbital lymphoma is excellent,[17–19] ranging from 89% to 100%, with a distant relapse rate of 0–25% (Table 3). In our study, the local control was 92% with initial treatment. With salvage chemotherapy for orbital relapse and local RT, the local control could be achieved in 100% of patients. Our experience showed that 8% of patients developed distant relapse, which is consistent with previously reported studies.[1,7,19]

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The study from the University of Florida[1] showed high distant relapse rates of 39% and 67% for low- and intermediate-/high-grade tumours, respectively. In this study, 2/3 of patients who relapsed were of low-grade NHL with only 6·25 % distant relapse rate for low-grade tumours.

In a literature review by Yadav et al., local control rate of 65–100%, distant relapse rate of 0–67% (from low grade to high grade) and five-year survival rate from 33% to 100%[20] was observed. High-grade tumours have higher risk of relapse.[21] The issue of bi-laterality in orbital lymphoma is interesting in our study, 3 (6%) of 52 patients had bilateral disease. These patients had stage III/IV disease. So, bilateral orbital involvement must prompt an astute search for disease elsewhere.

Toxicity rates were acceptable in our study and were within those reported in the literature.[19] In a study by Bolek et al.,[1] lens sparing techniques showed lower incidence of cataract formation and hence lens sparing techniques are recommended. However, the large size of tumours at presentation in our patients precludes the use of lens sparing techniques, so initial chemotherapy use may be justified in these cases. Cataract developed in 2(4%) patients in our study, one was age-related and the other because of RT. Only one (2%) patient developed impairment of vision as he had received a dose of 45 Gy with cobalt machine, which is obsolete now, and such a high dose is not delivered with modern RT techniques which are practised presently.

There are certain limitations of our study. It was a retrospective and single-institutional study, so certain treatment bias may not be ruled out. Some of our patients with low-grade disease received RT dose of >35 Gy, which is not the current standard in these patients but these patients had bulky disease at presentation.

Conclusion

The results of our study demonstrated excellent local control with induction chemoreduction with CHOP regimen followed by RT for primary orbital NHLs. We recommend a dose of 36–45 Gy for definitive RT and 30 Gy following chemotherapy; 20–30 Gy for low-grade lymphoma and 30–36 Gy for high-grade lymphoma using 2 Gy/fraction with orbital involvement. These are based on the patients who present with bulky tumours in our country. A small proportion of patients with early-stage disease will have systemic relapse, and identification of this subset of patients is needed. The toxicity attributed to RT was minimal, and we recommend incorporation of RT into treatment whenever possible as it is safe, effective and is associated with minimal complications.

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Ethics Statement. Approved by department ethics committee on 29·08·2015.

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