



## Primary Non-Hodgkin's Lymphoma of Waldeyer's Ring-A Retrospective Analysis

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### Abstract

Twenty-five newly diagnosed cases of primary Waldeyer's Ring (WR) Non-Hodgkin's lymphoma (NHL) registered from 1989-99 were analysed. These comprised 5% of total NHL cases. The most common site was tonsil (44%), followed by nasopharynx (20%), base of tongue (20%), nasal cavity (12%) and palate (4%). All the patients were staged thoroughly according to Ann Arbor staging system and 40% patients were stage I, 36% patients stage II, 4% stage III and 20% stage IV. Eighty-eight per cent patients were high grade at presentation and 12% were intermediate grade. Three patients absconded without treatment. Patients were treated with radiotherapy alone (4/22 patients), chemotherapy with CHOP regimen alone (9/22 patients) or a combination of both (9/22 patients). On comparison, complete response was recorded in 4/4 patients treated with radiotherapy alone, 5/9 patients treated with chemotherapy alone and 7/9 patients treated with combination of radiation and chemotherapy ( $p > 0.05$ ). The range of follow up period was 1-10 years with median 20 months. Overall 16/22 evaluable patients were with no evidence of disease on last follow up and the primary site was the most common site of first failure. A combined modality treatment except for stage Ia seems to be the treatment of choice for this relatively uncommon entity of Primary Waldeyer's Ring NHL.

### Key Words

Non-Hodgkin's lymphoma, Waldeyer's Ring

### Introduction

The lymphoid tissues of the nasopharynx, tonsillar region, base of tongue, and oropharyngeal wall are referred to as Waldeyer's Ring (WR). Clinical involvement of these lymphoid tissues by malignant lymphomas has long been appreciated. At the Ann Arbor Symposium in 1971, Waldeyer's Ring was acknowledged as a discrete lymphatic site for the staging of patients with lymphoma (1). Malignant lymphoma involving WR may be primary, or secondary to disseminated disease.

The frequency of involvement of Waldeyer's ring by the lymphomas varies considerably around the world. The WR is the primary site of involvement in 5% to 10% of patients with non-Hodgkin's lymphoma (NHL) in the United States (2-4). A higher incidence has been reported in European counties, probably related to the practice of routine biopsy of WR in all patients with NHL, to unique referral patterns, or to the possible influence of various etiologic or environmental factors (5,6). Most

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lymphomas of WR belong to the NHL group with Hodgkin's disease (HD) being extremely rare (7,8). The treatment of Waldeyer's Ring NHL has evolved over the years from radiotherapy alone (either involved field or extended field radiation) to chemotherapy alone and recently combined modality approach. This paper presents the rarity of presentation, clinicopathologic behaviour and comparison of response to various treatment approaches in Primary Waldeyer's ring NHL at PGIMER, Chandigarh.

### Material & Methods

Between 1989 to 1999, total of 480 biopsy proven, newly diagnosed cases of Non-Hodgkins lymphoma were registered. The involvement of Waldeyer's Ring at presentation was seen in 25/480 (5%) cases.

All the patients underwent thorough investigative work up including tissue biopsy of specific sites, laboratory investigations (complete blood counts, biochemistry), X-ray chest, CT scan abdomen and pelvis and bone marrow biopsy as essential staging procedures. Staging was done in accordance with Ann Arbor staging system (9,10) modified for Waldeyer's ring as follows: stage I, involvement limited to WR; stage II, regional (cervical) lymph node involvement in addition to that of WR; stage III, nodal involvement above and below the diaphragm (including spleen) together with WR involvement; stage IV, disseminated involvement of one or more extra-lymphatic organs or tissues in addition to that of WR. Within each stage, extension into adjacent soft tissue was denoted by "E". Each stage was subdivided into A or B categories depending on the presence or absence respectively, of fever, night sweats, and/or weight loss (10% of body weight). The morphologic classification into various grades was done according to the Working Formulation (11).

Patients were treated with radiotherapy alone, chemotherapy alone or combined modality depending upon the stage, bulk of tumour and grade of disease. External radiotherapy was delivered on mega voltage

teletherapy machine to a dose of 35 Gy - 40 Gy/3-4 weeks/15-20 fractions to the involved field by two lateral parallel opposed fields. CHOP regimen (cyclophosphamide - 600 mg/m<sup>2</sup> i.v., adriamycin - 40 mg/m<sup>2</sup> i.v., vincristine - 1 mg/m<sup>2</sup> i.v. on first day each and prednisolone - 40 mg/m<sup>2</sup> p.o. x 5 days) was used as the first line chemotherapy and six such courses were given at 3 weekly interval. Combined modality approach was planned for all patients with stage II b and above.

The complications of treatment were recorded according to WHO criteria. Survival data and time to first relapse measured from the date of initial treatment were analysed by life table analysis (12). The statistical significance was computed using chi square test.

### Results

#### *Patients characteristics*

Maximum 17/25 (65%) patients were 40 years and above in age (median age 52 years). Tonsil was the most common site (40%) followed by nasopharynx (20%), base of tongue (20%), nasal cavity (12%) and palate (4%). At initial staging, 10/25 (40%) of all patients were localized to the site of origin i.e. stage I a. 9/25 (36%) were stage II (II a - 8, II b - 1), 1/25 (4%) was stage III b and 5/25 (20%) were stage IV (IV a - 1, IV b - 4). 22/25 (88%) were high grade NHL and 3/25 (12%) were intermediate grade. None of our patients was of low grade histopathology (Table I).

#### *Primary treatment modality used*

Three patients absconded without treatment. Patients with stage I a intermediate grade disease were treated with radiotherapy alone (4/22 patients) and rest of the patients were treated with chemotherapy alone with CHOP regimen (9/22 patients) or a combination of both chemotherapy and radiotherapy (9/22 patients).



**Complications of treatment**

All the 22 patients successfully completed the planned treatment. 4/4 patients who received radiotherapy alone had only grade I - II mucositis. Grade I - II hematological toxicity was seen in 6/9 patients who received chemotherapy alone and no treatment delay was noticed. 2/9 patients who received combined modality treatment had grade III mucositis which delayed treatment by only a few days and this complication subsided completely with conservative treatment.

**Response, patterns of failure and survival**

Complete response was seen in 4/4 patients treated with radiotherapy alone, 5/9 patients treated with chemotherapy alone and 7/9 patients treated with combined modality. Overall 16/22 (72%) patients achieved complete remission after primary treatment, 3/22 (13%) achieved partial regression of disease whereas 3/22 (13%) achieved no response (Table 2).

The follow up period ranged from 1-10 years (median 20 months). All relapses occurred within 2 years of completing primary treatment. The median interval to complete response and relapse was 14 months. Overall 7 patients relapsed after achieving complete response with 2/7 relapses at primary site only and 5/7 at both primary plus distant sites. So, first relapses were most commonly noticed at the primary site of disease. Because of inadequate long term follow up after treatment the survival characteristics in this study are as recorded on last follow up. Failures were treated with salvage chemotherapy but none showed complete response. This series does not intend to address the role of second line therapy in Waldeyer's Ring NHL. On last follow up 16/22 patients were with no evidence of clinical or radiological disease. In the current series, actuarial disease free survival at 2 and 4 years is 77% and 46% respectively (Fig. 1).

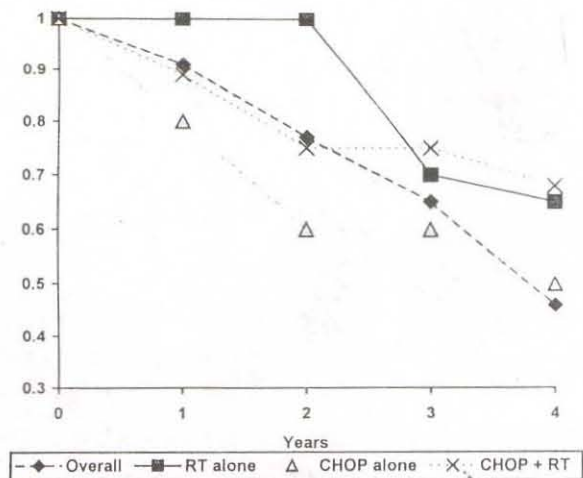
**Table 1—Patients Characteristics**

Age	11-80 years Median Age 52 years
<b>Sex</b>	
Male	20
Female	5
<b>Histopathology</b>	
High grade	22
Intermediate grade	3
Low grade	-
<b>Stage</b>	
I a	10
I b	-
II a	8
II b	1
III a	-
III b	1
IV a	1
IV b	4
<b>First Line Treatment</b>	
RT alone	4
CCT alone	9
CCT + RT	9

**Table 2—Response to Treatment**

Primary treatment	Complete response (CR)	Partial response (PR)	No response (NR)
RT alone (4)	4	-	-
CHOP alone (9)	5	2	2
CHOP + RT (9)	7	1	1
N = 22	16 (72%)	3 (13%)	3 (13%)

**Figure 1: Actuarial disease free survival**



## Discussion

Retrospective studies are usually unsuitable for the purpose of comparing different treatment regimens. They may often be useful, however, to expand our knowledge of the etiology and natural history of disease. The non-Hodgkin's lymphomas of Waldeyer's ring form an interesting clinical entity. Unfortunately, because of their infrequent occurrence and the presence of variables such as histologic type and stage of disease, it is difficult to draw any firm conclusions regarding the necessity of specific staging procedures or the efficacy of various treatment regimens.

In the United States, the frequency of involvement of Waldeyer's ring in the non-Hodgkin's lymphomas has been reported to be 5-10%. (2-4) Our observed frequency of 5% is compatible with the figure.

Lymphoma of WR is primarily a disease of advancing age with approximately 80% of patients being over 50 years of age at diagnosis. As in other studies of primary WR lymphoma.(5,6,13-18) the tonsil was the most common site in the current series (44%).

Anderson *et. al.* (19) found in a study of 483 patients with NHL that only 22% of patients had Stage I-II disease. In the current series despite essential staging procedures majority of patients were staged I and II.

The predominance of high grade lymphoma (88%, current series) in WR has been consistently reported in previous series (4-6,13,15,17,18,20).

In a series from Italy, 19% of patients had low-grade disease (21). A large percentage (28%) had diffuse small-cleaved cell lymphoma, an entity rarely recognized today, 76% to 85% of patients had intermediate or high-grade disease (22,23). In current series it was 88% high grade, 12% intermediate grade, no case of low grade pathology.

Patients have been treated with a variety of approaches involving radiation with or without chemotherapy for limited stage disease and chemotherapy for advanced disease. Local-regional radiotherapy may yield good results in patients with early

(Stages I and II) disease when rigorous staging procedures exclude systemic disease (24-26).

Radiotherapy treatment alone is associated with a high rate of relapse. Of patients with stage I and II disease, approximately half will relapse, mostly at distant sites (27-29). Stage I patients have generally fared well, with survival rates of 60% to 83% at 5 years. Stage II patients fared less well, with survival rates of about 30% (30). Combined modality therapy may offer better outcome than radiotherapy alone. Outcome appeared better with combined modality treatment, with a 5-year OS of 78% for stage I and 42% for stage II patients (31).

The best evidence for the effectiveness of combined modality therapy comes from a large randomized study of 316 patients with stage I disease of Waldeyer's ring (32). Patients were allocated to treatment with radiation alone, chemotherapy alone (with a cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP] or CHOP like regimen for six cycle), or a combination of chemotherapy and radiation. Complete response rates were high in all groups (>85%). Failure free survival [FFS] and OS at 5 years of follow up were significantly better in the combine modality group compared with either radiation therapy alone or chemotherapy alone (FFS, 83% v 48% v 45%; OS, 90% v 56% v 58%). The majority of patients who relapsed did so in lymph nodes or viscera below the diaphragm; only 5 of the 24 patients who relapsed manifested disease above the clavicles. Only one patient failed within the treatment volume; this was a patient with a rapidly progressive undifferentiated lymphoma. Salvage of patients who relapsed was attempted with a number of chemotherapy combinations, and was generally unsuccessful, with a 20% actuarial 5-year survival from the diagnosis of relapse.

## Conclusion

Waldeyer's Ring NHL is a relatively rare entity in our set-up. Treatment of patients with Waldeyer's ring lymphomas should be made in accordance with the histologic subtype and stage of disease. Patients with low grade lymphoma may be treated with radiation therapy. Treatment for this group of



patients should consist of doxorubicin based therapy (CHOP) for six cycles combined with radiotherapy to Waldeyer's field.

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