

# Extranodal diffuse large B-cell lymphoma: Experience from a tertiary care oncology center in South India

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## ABSTRACT

**Aims:** Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL) with frequent extra nodal (EN) presentation. The overall occurrence of lymphomas has been increasing; however, those of EN-NHL have been increasing much more rapidly. There is limited data found on EN-DLBCL in the Indian population and hence we carried out this retrospective observational study of primary EN-DLBCL at our center in Southern India. **Materials and Methods:** A total of 90 consecutive cases diagnosed as EN-DLBCL (according to the standard criteria) by tissue biopsy confirmed by immunohistochemistry between 2007 and 2011 were included. Staging workup including computed tomography of neck, thorax and abdomen and pelvis, bone marrow aspiration and biopsy was done and International Prognostic Index (IPI) calculated. Staging was according to Cotswold's modification of Ann Arbor. The actuarial survival analysis was performed by Kaplan-Meier. Data were analyzed using the SPSS (version 16) statistical software. **Results:** The median age in this study was 49 years (18-88) with results showing EN-DLBCL to be 1.36 times more common in males. Advanced stages were seen in 15 subjects (16.6%) and bulky disease in 13 subjects (14.4%). CD20 was positive in 89 (98.8%) while 32 had high serum lactate dehydrogenase. According to the IPI most were low-risk-56 (66.6%). Overall response rate for the various combination chemotherapies was 85.7% with complete response in 62.3%. The overall survival range spanned from 2 to 123 months. Univariate analysis showed only bulky disease was associated with inferior survival. **Conclusions:** EN-DLBCL was present at an early age compared to nodal DLBCL, present more often in early stage and low IPI score. Chemoimmunotherapy with radiotherapy to the EN or bulky site is the standard treatment at present.

**Key words:** Diffuse large B-cell lymphoma, extra nodal, India, nodal

## INTRODUCTION

The global burden of non-Hodgkin's lymphoma (NHL) has been steadily increasing over the last 2 decades and India is no exception with NHL causing significant morbidity and mortality.<sup>[1]</sup> Around one quarter of NHL arises in tissues other than the lymph node, spleen, Waldeyer's ring and thymus, and are referred to as primary extra nodal NHL (EN-NHL). It has been observed

that the incidence of EN-NHL has increased more rapidly in comparison to the nodal type.<sup>[1,2]</sup> Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL worldwide and is an aggressive lymphoma with a rapid onset and progression. About one-third of DLBCLs have a primary EN origin.<sup>[3]</sup>

Since the incorporation of rituximab (anti-CD20 chimeric monoclonal antibody) in the anthracycline based chemotherapy in lymphomas, a significant improvement in outcome has been demonstrated in patients with nodal DLBCL; however, the efficacy of rituximab in patients with EN-DLBCL is still debatable.<sup>[4]</sup> Although EN lymphomas have been studied in detail, there is limited data available on EN-DLBCL from the Asian subcontinent. The aim of this study was to analyze the main clinical-biological features of patients diagnosed with EN-DLBCL at our center in South India.

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## MATERIALS AND METHODS

This was a retrospective observational study done at Kidwai Memorial Institute of Oncology, Bengaluru, a tertiary care center in Southern India. All consecutive cases aged 15 years or more were included in this study. These cases were diagnosed as DLBCL by appropriate lymph node or tissue biopsy and confirmed by immunohistochemistry (WHO classification) between January 2007 and December 2011.

Informed consent was obtained from all patients. Demographic, clinical, and treatment details along with investigations were recorded and analyzed. Staging included patient history and physical examination, which entailed complete hemogram and serum biochemistry including lactate dehydrogenase (LDH); human immunodeficiency virus (HIV), HBS-Ag and echocardiography or MUGA scan. Computed tomography (CT) scan of chest, abdomen, and pelvis or Positron emission tomography (PET)-CT scan in affordable and chest X-ray/ultrasound abdomen/pelvis in not affordable patients was done as per the institutional protocol. All patients underwent bone marrow aspiration and biopsy from the iliac crest as part of the staging workup. Cerebrospinal fluid (CSF) analysis was done in relevant cases. Patients were staged according to Ann Arbor staging as modified by Cotswold's and International Prognostic Index (IPI). Patients with nodal  $\pm$  bone marrow involvement, indolent lymphoma with subsequent transformation into a DLBCL, and primary central nervous system lymphoma were excluded from the study. The responses were assessed according to standard criteria according to the International Working Group response criteria and the patients were treated as per the institute protocol. The clinicopathological factors were statistically evaluated for poor survival.

### Definitions

Patients with EN involvement with or without regional lymph nodes were included. Waldeyer's ring, spleen, liver, and extensive lymph node involvement were defined as primary nodal DLBCL and were excluded.

### Statistical analysis

Calculation of median and the range was done using Microsoft excel, and overall survival (OS) was calculated from diagnosis to the last follow-up or death due to any cause. The actuarial survival analysis was performed according to the method described by Kaplan-Meier and the univariate analysis was performed for each parameters mentioned. *P* values 0.05 were considered to indicate statistical significance. Data were analyzed with the Statistical Package for the Social Sciences SPSS (version 16) statistical software.

## RESULTS

### Demographic profile

A total of 286 patients [Table 1] were diagnosed to have DLBCL over 5 years and among these, 90 patients (31.4%) had primary EN-DLBCL. The median age was 49 years (range: 18-88 years) and was shown to be 1.36 times more common in males than females [Figure 1]. B symptoms were present in 18 (20%) patients and the gastrointestinal tract (GIT) was the most common site [Figure 2]. The median size of the mass was 5 cm (1-15 cm).

### Staging

Advanced stage with more than one EN site (Ann Arbor IV) was observed in 15 patients (16.6%) and bulky disease in 13 (14.4%).

### International prognostic index

With the available data, 32 patients presented with high serum LDH levels and CD20 to be positive in 89 cases (98.8%). HIV, hepatitis B, and CSF were positive in one case each. The distribution according to the IPI was as follows: Low-risk-56 (66.6%), low-intermediate 17 (20.2%), high-intermediate 8 (9.5%), high-risk 3 (3.5%) (among the assessable) and 6 (7.1%) were not assessable [Figure 3].

### Treatment and outcome

Of the 90 patients, 77 (85.5%) received treatment (minimum three cycles) with either combination of rituximab (375 mg/m<sup>2</sup>), cyclophosphamide (750 mg/m<sup>2</sup>), adriamycin (50 mg/m<sup>2</sup>), vincristine (1.4 mg/m<sup>2</sup>) and prednisolone (100 mg/d)

**Table 1: Baseline characteristics of patients in comparison with study by Song *et al.***

Characteristics	Moo-kon Song <i>et al</i> (n=96)	Present study (n=90)
Median age, years (range)	61 (20-80)	49 (18-88)
Gender, male/female	55/41	52/38
IPI factors		
Age>60 years	51 (53.1)	27 (30)
Stage IE	23 (24.0)	49 (54.5)
Stage IIE	73 (76.0)	22 (24.4)
Stage IV	-	14 (15.5)
LDH elevated	44 (45.8)	32 (35.5)
ECOG PS $\leq$ 2	36 (37.5)	85 (94.4)
Involved extranodal site		
GIT	31 ( 32.3)	25 (27.7)
Head and neck	25 (26.0)	20 (22.22)
Pleural, pericardial	3 (3.1)	2 (2.2)
Breast	4 (4.2)	3 (3.3)
Bone	-	21 (23.3)
Testis	-	7 (7.7)
Thyroid	-	3 (3.3)
Ovary	-	2 (2.2)
Soft tissue mass	-	6 (6.6)
Overall response rate	85.4%	85.71%
Complete response	81.3%	62.33%

E- extranodal; ECOG PS: Eastern co-operative oncology group performance status, GIT: Gastrointestinal tract, IPI: International prognostic index, LDH: Lactate dehydrogenase.

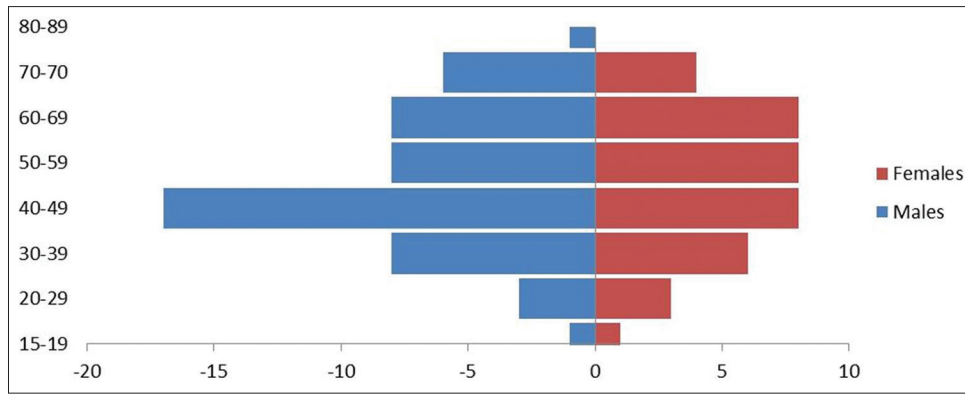


Figure 1: Age and sex distribution of patients

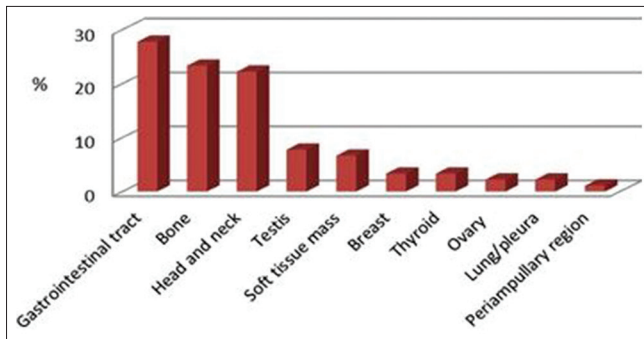


Figure 2: Various sites of involvement

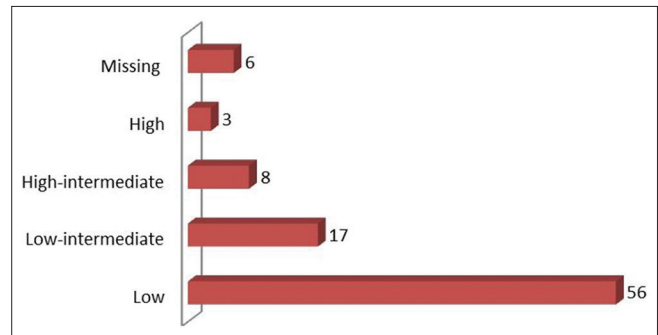


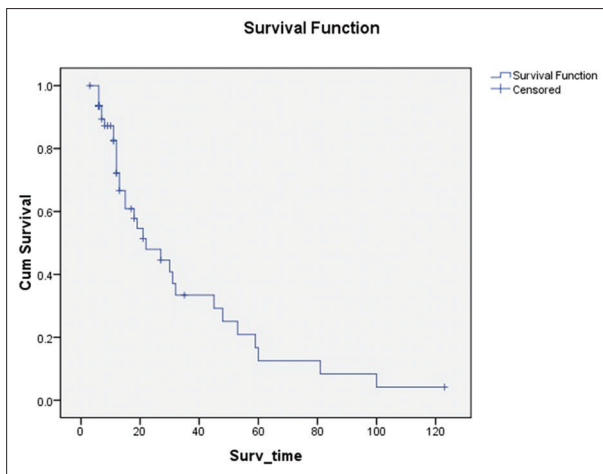
Figure 3: International prognostic index for patients

for 5 days (R-CHOP) (in 14 patients) or R-COP (in 1) or CHOP (in 57) or COP (in 3) or chlorambucil/prednisolone (in 2). 20 (25.9%) patients received local radiotherapy. Overall response rate was seen in 66 patients (85.71%) with complete response in 48 (62.33%). 30 patients were alive with no disease, 5 were alive with disease, 2 died and 40 patients lost to follow-up with no disease in 17 patients at the time of data collection. Relapses were recorded in 13 patients (16.8%). The OS ranged from 2 to 123 months with a median being 9.5 months [Figure 4]. Among the clinic-pathological factors such as age, sex, B symptoms, bulky disease, performance status, elevated LDH, stage, and IPI, only bulky disease ( $P = 0.034$ ) was associated with statistically significant poor survival on a univariate analysis.

## DISCUSSION

Diffuse large B-cell lymphoma is the most common type of NHL accounting for 40% of all NHL cases. It is a high grade BCL with varied clinical manifestations, morphology, immunophenotype, genetic and molecular alterations.<sup>[1]</sup> Consideration of a lymphoma as primary nodal or EN is controversial and hence two schools of thought have evolved to define this entity. According to some authors, primary EN-NHL is defined as involvement of other organs with no or minor lymph node involvement while extensive involvement is defined as the involvement of both EN and nodal sites. Few other suggest that involvement of an EN

site with or without regional lymph node involvement is primary EN-NHL.<sup>[2]</sup> Particular clinical and biologic characteristics have been suggested for DLBCLs arising in the lymph node versus those in EN sites, including variations in genes BCL-2, BCL-6, CMYC, REL and FAS. All these suggest a heterogeneous pattern and a separate genetic origin for nodal and EN lymphomas.<sup>[3]</sup> The peak incidence for DLBCL occurs in the 6<sup>th</sup> and 7<sup>th</sup> decade of life.<sup>[4-6]</sup> In our study, the peak incidence was within the 5<sup>th</sup> decade with a male preponderance. This was earlier compared to other studies and was shown to be more common in males. Most of our patients had low IPI scores, which was an important factor to predict survival in patients treated with chemotherapy. HIV-associated lymphomas are more commonly associated with EN involvement, but in our study HIV was positive in only one case.<sup>[7]</sup> There is limited literature on EN-DLBCL with special reference to the clinical-biological profile from the Asian subcontinent. Song *et al.* recently highlighted the clinical profile in EN-DLBCL patients.<sup>[8]</sup> In comparison with this study, the median age of the presentation was a decade earlier with a similar male:female ratio (1.36 vs. 1.26). Most patients were in a good performance status (early stage and low IPI score) in our study compared to a similar study done by others. The most common site was the GIT (32.3%) followed by bone (23.3%) and head and neck areas (22.2%) in our study. In the study by Song *et al.*, the most common site was the GIT (32.3%), followed by the head and neck region (26%).<sup>[8]</sup>



**Figure 4:** Overall survival in our patients

The overall response rate was similar, but less complete responses and OS in our study. This could be attributed to various reasons. The regimens used were varied and fewer patients could afford rituximab based therapy. Moreover, the treatment was incomplete in many patients due to poor follow-up and compliance. The Southwest Oncology Group (37% had EN) and Eastern Cooperative Oncology Group (47% had EN) randomized controlled trials have shown that addition of radiotherapy to abbreviated anthracycline-based chemotherapy improved the progression free survival (PFS) and OS, but there were more late relapses in the combined modality arm.<sup>[9,10]</sup>

Later, the combination of chemotherapy plus rituximab was the standard treatment in DLBCL. The addition of rituximab has shown an improvement in response rate, PFS, and OS (up to 15-20%) in many randomized controlled trials. The MabThera International Trial with 75% of patients in early stage and 33% with EN disease, randomized patients between six cycles of CHOP and six cycles of R-CHOP. Radiation was included for patients with bulky or EN disease at presentation. The results showed a significant benefit in the long term survival with the addition of rituximab to chemotherapy in young patients.<sup>[11]</sup>

Phan *et al.* in their study of 469 patients with DLBCL, 30.2% of the patients received radiation therapy (RT) following complete response with R-CHOP. Patients who received six to eight cycles of R-CHOP with stage I or II disease and all stages indicated that RT improved OS (hazard ratio [HR], 0.52 and 0.29, respectively) and PFS (HR, 0.45 and 0.24, respectively) compared with no RT. This study showed significant improvements in OS and PFS among patients who received consolidation RT after R-CHOP chemotherapy for DLBCL.<sup>[12]</sup>

However, the effect of rituximab in primary EN lymphoma was not assessed separately in the above studies single

institution experience using chemoimmunotherapy found no improvement in the outcome in EN-DLBCL compared to chemotherapy in historical nodal DLBCL controls; however, it needs to be confirmed in a randomized controlled trial.<sup>[13]</sup>

Subgroup analysis of several studies have shown that rituximab improved survival only when BCL-2 and p21 are over expressed and in BCL-6 negative subgroups of DLBCLs.<sup>[14-16]</sup> EN and bulky disease may affect the prognosis of patients undergoing R-CHOP therapy for DLBCL especially in nongermlinal center type.<sup>[17]</sup>

At present, abbreviated R-CHOP chemotherapy plus involved-field radiotherapy is an excellent therapy for patients with low-risk, nonbulky early stage DLBCL. Patients with poor prognostic features, such as advanced stage, tumor bulk, or high LDH, may benefit from additional systemic therapy or clinical trials involving novel agents. Current trials are evaluating the role of PET imaging as response-directed therapy.

The strengths of the study include a large number of patients from a single institution with EN-DLBCL. However, there were quite a few limitations - not randomized, varied regimens and poor follow-up in our study. There is sporadic data on EN-DLBCL at present and hence this study can add to the understanding, clinic biological characteristics and outcome of patients with EN-DLBCL in Asian subcontinent.

## CONCLUSIONS

Extra nodal-diffuse large B-cell lymphoma presents at an early age compared to nodal DLBCLs more often in early stage and low IPI score. The chemoimmunotherapy with radiotherapy to the EN or bulky site is the standard treatment at present. Hence, EN-DLBCL is a heterogeneous disease and is distinct from nodal DLBCLs with regard to clinicopathologic behavior and response to chemoimmunotherapy. The gene expression profile classification may facilitate future research to evaluate patients for novel or experimental therapies in EN-DLBCL.

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