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Extranodal Non-Hodgkin Lymphomas: The Impact of Different Variables on the Disease

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Abstract

Background: Extranodal non-Hodgkin lymphoma (ENL) occurs in 25-40% of non-Hodgkin lymphoma (NHL) patients. The objective of this study is to analyze the incidence, anatomical distribution, histopathological subtypes, prognostic factors, and the impact of the site on behavior and treatment response of extranodal lymphoma.

Methods: In this retrospective analytical study, 84 out of 379 NHL patients diagnosed with ENL were included. The patients were treated via predominantly chemotherapy and/or field external beam radiotherapy.

Results: The mean age of these 84 patients was 42.5 years (range 4-80 years). The leading site of ENL involvement was head and neck in 35 (41.66%) patients. Diffuse large B-cell lymphoma was the most common histological type in 46 (54.76%) patients. The median follow-up was 72.3 months (range 3.2-132.4 months). The CR was achieved in 40 patients (47.6%), PR was achieved in 22 (26.2%) patients, and NR was observed in 22 (26.2%) patients. Highest mean PFS, observed in GIT malignancies, was 68.4 months (54-82.8), overall mean progression-free survival (PFS) was 73.2 months (61.3-85.1) (P=0.369), and mean overall survival was 88.4 months (82-94.7) with a P-value of 0.014, which was statistically significant.

Conclusion: Based on the results of this study, it is concluded that extranodal NHL accounts for almost 25% of all NHL. Hence, before the initiation of treatment, all the NHL cases should be properly investigated and staged. Extranodal NHL responded well to chemotherapy as NHL. Furthermore, it was observed that treatment with field external beam radiotherapy results in an increase in the levels of progression-free survival and overall survival.

Keywords: Extranodal non-Hodgkin's lymphoma (ENL), Chemotherapy, Involved field radiotherapy, Site of involvement, Prognosis

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Introduction

The reported incidence rate of non-Hodgkin lymphoma (NHL) in India is 2-3 per 100,000 people.[1] Extranodal non-Hodgkin lymphoma (ENL) occurs in 25-40% of NHL patients.[2, 3, 4] ENL is a term referred to the NHL initiated from extranodal

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sites and confirmed after staging procedures. The ENL can arise from almost every organ in the body, except the sites that are considered as lymphoid tissues; e.g., lymph nodes, thymus, spleen, and Waldeyer's ring.[5]

Several studies have explored the association of NHL with etiological factors like occupational, environmental, chronic infections, genetic, autoimmune disorders, and immunosuppressive disorders.[6] NHLs are sensitive to radiation and chemotherapy, despite that they are cured in less than 50% of patients.

The published literature on ENL is in scarce. Most of the published studies concern head and neck, gastrointestinal, cerebral nervous system, and bone lymphoma and some are about the breast, oral cavity, skin, and gynaecologic lymphomas. Various case reports have been published about different rare presentations of extranodal lymphomas originating from every organ in the body. These studies suggest that ENL has the potential to disseminate due to its complex biological behavior.

The objective of this study is to analyze the incidence, anatomical distribution, histopathological subtypes, prognostic factors, and the impact of the ENL site on its behavior and treatment response.

Material and Methods

This retrospective analytical study was conducted at the Government Medical College of Central India. All the case records were scrutinized between the year 2007and 2016 to obtain clinical, laboratory, histopathological, and treatment data. 84 out of 379 NHL patients diagnosed as extranodal non-Hodgkin's lymphoma were included in this study. All the patients were diagnosed on the basis of histopathologic confirmation by tissue biopsy and immunohistochemistry (IHC) studies using a panel of antibodies depending on the morphology of the biopsy. Patients were classified histologically according to the revised European-American classification of lymphoid neoplasms (REAL) proposed by the International Lymphoma Study Group. Clinical stage was defined according to the Ann- Arbor classification.[7] Also, the involvement of lymph nodes, spleen, thymus and Waldeyer's ring was defined as nodal localization while the involvement of other mentioned organs was defined as extranodal. Patients were considered to be completely staged after exclusion of nodal lymphoma by adequate information of patient history, status of peripheral lymph nodes by physical examination, mediastinal lymph nodes by chest X-ray, Waldeyer's ring by ENT examination, abdominal lymph nodes, liver and spleen involvement by abdominal CT scan, and peripheral blood and bone marrow aspiration biopsy reports. Cerebrospinal fluid (CSF) analysis was done in relevant cases. All patients with gastrointestinal involvement underwent endoscopy or colonoscopy. Confirmatory staging of extranodal lymphoma was done using a CT scan of the involved site or by PET-CT scan for extensive lymphoma.

The treatment of all patients constituted predominantly chemotherapy and/or involved field external beam radiotherapy (IFRT).

The international prognostic index (IPI) was calculated according to the parameters described by the international non-Hodgkin's lymphoma prognostic factors project for patients in addition to the Ann Arbor stage, age, presence of B-symptoms, elevated serum lactate dehydrogenase (LDH), performance status, and a number of other extranodal sites of disease.[8]

Post-treatment response was assessed according to the report of the international workshop to standardize response criteria for NHL from the clinical and radiological response.[9] Complete response (CR) required the complete disappearance of all detectable clinical and radiological evidence of disease, the disappearance of all disease-related symptoms, and normalization of those biochemical abnormalities definitely assignable to lymphoma. Partial response(PR) required at least a 50% decrease in the sum of the products of the greatest diameters of the involved extranodal site, the response lesser than 50% was considered as a no response (NR).The overall

and median survival was calculated from diagnosis of the last follow-up or death with any cause. The Kaplan-Meier method was used for survival analysis. Prognostic factors were evaluated by the log-rank test. *P* values <0.05 were considered to indicate statistical significance. SPSS software version 22 (IBM, New York) was used for statistical analyses.

Results

The mean age of 84 patients enrolled in this study was 42.5 years (range 4-80 years). The incidence of ENL was 1.40 times more common in males than females. The peak incidence was in the patients who were in the fifth or sixth decades of their life. There was no significant difference in the patient locality such that 54% had urban and 46% had rural background (Table 1).

B-symptoms were observed in 34 (41%) patients. Lactate dehydrogenase level (LDH) was found elevated in 58% of patients. According to the Eastern Cooperative Oncology Group (ECOG), performance status score of 18% of the patients was 2 and the rest 82% were able to do their normal activity without any assistance. As per

Table1. Patient Characteristics and Clinical presentations

	Male	Female	%
No. of patients (84)	49	35	
Median Age (In years)	45	40	
Range	4-80	4-61	
<10	5	3	9.52
10-30	12	9	25.00
31-50	15	11	30.95
51-70	12	10	26.19
>70	5	2	8.33
Locality-wise			
Rural	24	15	46.42
Urban	25	20	53.57
B- Symptoms			
No	31	19	59.52
Yes	18	16	40.47
Lactate dehydrogenase level(LDH)			
Normal	21	14	41.66
Abnormal	28	21	58.33
Stage			
I	8	6	16.66
II	17	10	32.14
III	11	11	26.19
IV	13	8	25.0
ECOG Performance Status			
0	17	12	34.52
1	23	17	47.61
2	9	6	17.85

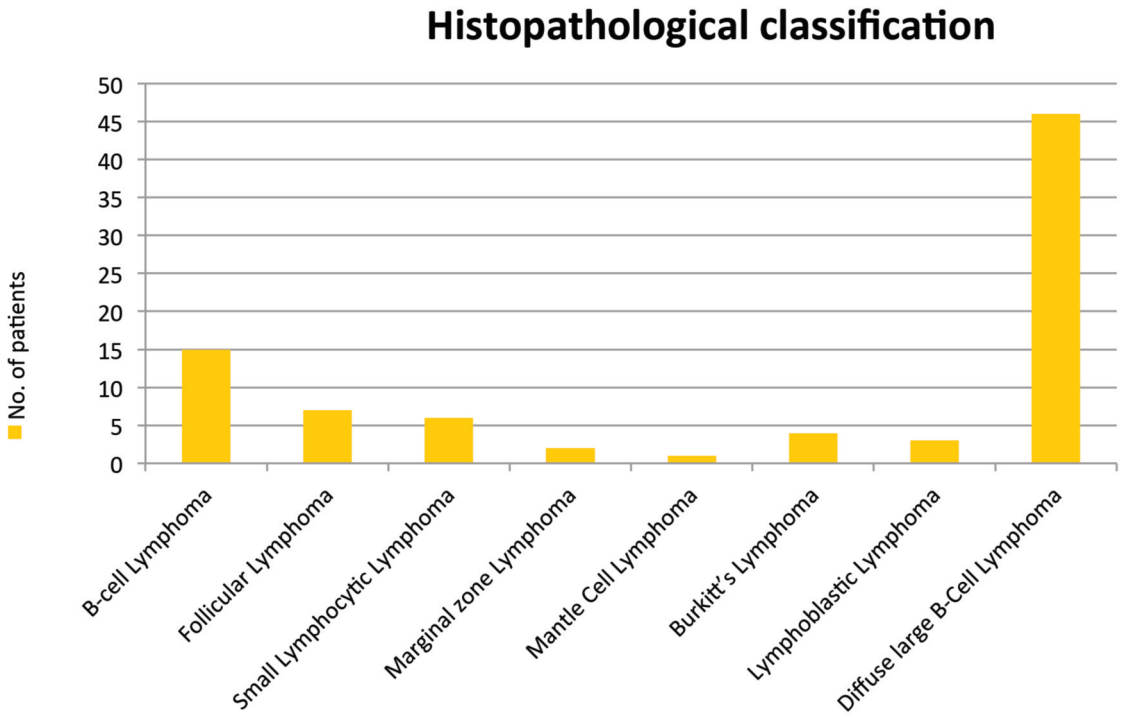

Figure 1. Histopathological classification. (CR: Complete Response; PR: Partial Response; NR: No Response).

Ann-Arbor staging, 26%, 25%, and 49%of patients presented with stage III, IV, and with the localized stage, respectively (Table 1).

The leading involvement site of ENL was head and neck in 35 (41.66%) patients followed by gastrointestinal tract (29), central nervous, and skeletal systems (13), genito-urinary (4), lung (2), and female breast (1) (Table 2).

Diffuse large B-cell lymphoma was the most common histological type in 46 (54.76%) patients followed by B-cell lymphoma in 15(17.85%) patients. Follicular lymphoma, small lymphocytic lymphoma, Burkitt's lymphoma, lymphoblastic lymphoma, marginal zone lymphoma, and mantle cell lymphoma were the histology types in the rest 28% of patients (Figure 1). As per the retrieved data, 76 (90.47 %) patients were immunophenotypically CD20 positive, 28 (33.33%) Leukocyte common antigen (LCA) positive, 13 (15.47%) CD45 positive, 9 (10.71%) Bcl2 positive, and 8(9.5%) were CD3, CD5, and CD30 positive.

The simultaneous involvement of more than one extranodal sites, surrounding and distant structures like brain, lung, liver, bone, and bone marrow were present in 39 (46.42%) patients,

Table 2. Involved site of extranodal lymphoma

Site	No.of patients	%
Head and Neck	35	41.66
Eye and lacrimal gland	5	
Nasal Cavity	6	
Nasopharynx	6	
Maxilla	7	
Parotid	1	
Tonsil	4	
Oral Cavity	4	
Thyroid	1	
Gastrointestinal	29	34.52
Stomach	5	
Small intestine	7	
Large intestine	10	
Retroperitoneum	7	
CNS &Skeletal	13	15.47
Brain	1	
Spinal cord	4	
Chest wall	2	
Extremities	3	
Bone	3	
Genito-urinary	4	4.76
Testis	2	
Ovary	1	
Kidney	1	
Others	3	3.57
Lung	2	
Female Breast	1	

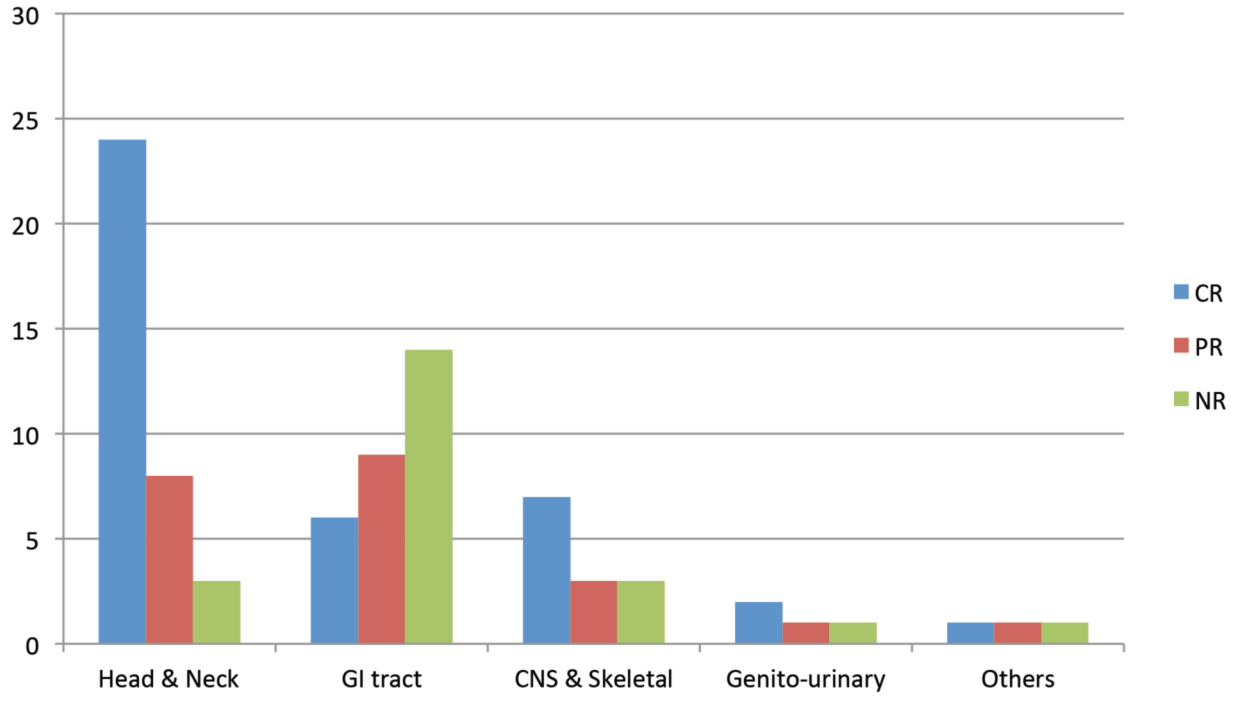

Figure 2. Site wise treatment response (CR= Complete response; PR= Partial response; NR= No response).

eminently in GI tract lymphoma, CNS, testis and lung lymphomas. The number of patients with extensive involvement of both nodal and extranodal sites were 22 (26.19%), primarily affected by their head and neck, and GI tract lymphoma.

According to the IPI, prognostic factors were calculated and the distribution of the patients was as follows: 44 (52.38%) low-risk, 18 (21.42%) low-intermediate, 9 (10.71%) high-intermediate, 5 (5.95%) high-risk, and 8(9.52%) were not assessable due to missing data.

Of 84 patients, 31 underwent surgery followed by chemotherapy and IFRT in their stomach (3), small intestine (5), large intestine (7), tonsil (2), nasal cavity (2), parotid (1), thyroid (1), maxilla (2), breast (1), spine (1), bone (2), testis (2), ovary (1) and kidney (1). 46 patients received chemotherapy alone and 38 patients received both chemotherapy and IFRT. Anthracycline-based chemotherapy was applied in all patients, 45 patients received CHOP regimen (cyclophosphamide, doxorubicin, vincristine, prednisolone), 15 R-CHOP (Rituximab), 10 CEOP (epirubicin), 9 CHOP with pegylated liposomal doxorubicin, and 5 patients received CNOP (mitoxantrone) regimen.

The median follow-up was 72.3 months (range 3.2-132.4 months).The CR were achieved in 40 patients (47.6%), PR were achieved in 22(26.2%) patients, and 22(26.2%) patients showed NR. In head and neck, 32 patients responded to treatment, while in three patients, no response were observed (P=0.0315). In patients with GI tract lymphoma, 15 patients responded while 14 patients showed no response (P=0.0277). Among CNS and skeletal lymphoma,10 patients responded and three patients showed no response (P=0.811). Three patients with genitourinary lymphoma responded to treatment and one had no response (P=0.957). However, at other sites, two of the patients showed response and one patient did not respond to treatment (P=0.782) (Figure 2).

When treated with chemotherapy and IFRT, head and neck patients with nodal involvement responded better than GI tract ENL. The OS and PFS in the pediatric age group patients were better compared to older ones. In this regard, the highest mean PFS was observed in GIT malignancies, i.e., 68.4 months (54-82.8), overall mean progression-free survival (PFS) was 73.2 months (61.3-85.1) (P=0.369) (Figure 3), and mean overall survival was 88.4 months (82-94.7) with a P value of 0.014, which is statistically significant (Figure 4).

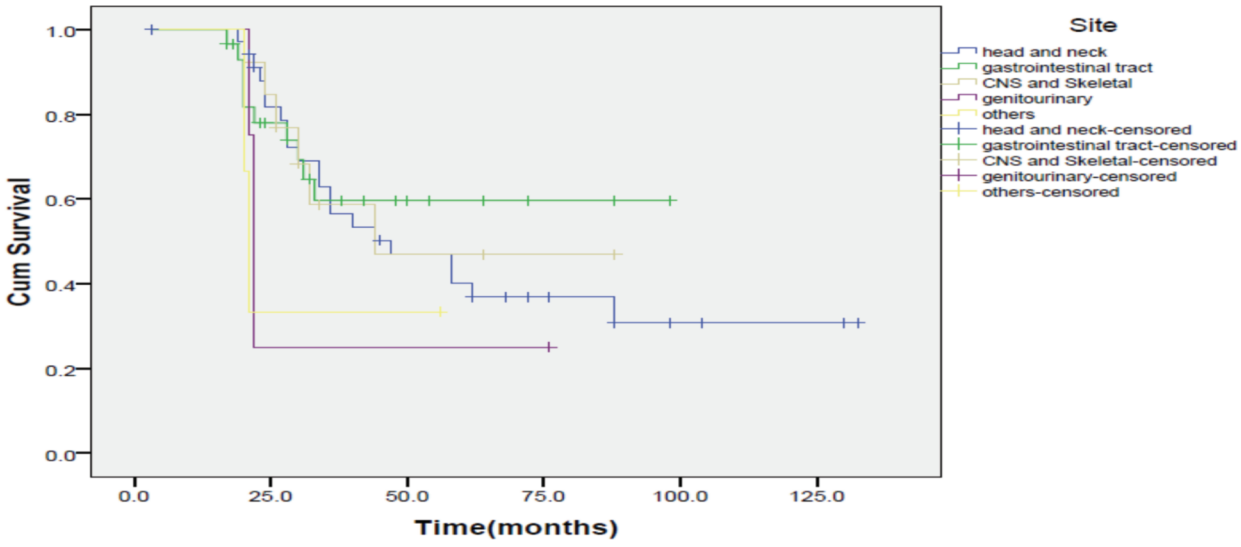

Figure 3. Progression-free survival.

Discussion

Extranodal NHL is a heterogeneous disease with complex biological behavior.[10, 11] The factors that differentiate these from NHL are geographical divergence, anatomical localization, etiological, morphological heterogeneity, and prognosis.[12] The incidence of ENL is high where the total NHL prevalence is high. Studies from Western and Asian countries reported the incidence of ENL as 25-40%and 45-62%, respectively. A study from North India reported an incidence of 44% and another study from South India reported the incidence of 22%. The ENL incidence rate in our study was 22.16%, which is comparable to the study from South India.[13, 14]

The median age of the patients was 42.5 years with a peak ENL incidence at the 5th and 6th decades of their life; this result is comparable with the results of other studies. Our study showed male preponderance, which is comparable to the data from South India.[14] The most common site of the presentation was head and neck followed by GI tract lymphoma in our study, which is in line with the study of Singh et al. The literature suggested that the incidence of GI tract lymphoma has been increasing throughout the world. The studies from India, China, and Pakistan reported GI tract as the most common site followed by head and neck.[13,14,15,16,17] DLBCL and B-cell lymphoma were the most common histological variants comprising 72% of the cases in our study; this result is consistent with the results of other studies from India.[13,14] A study by Biagi et al. reported that the follicular lymphoma, small lymphocytic lymphoma, and anaplastic large cell lymphomas are the histologic variants commonly seen among nodal NHL, while they were not seen at extranodal sites due to the geographic region variations in molecular expression profiling of lymphoma.[18]

About 60% of ENL patients achieved CR, of which 70% belonged to head and neck group irrespective of prognostic factors and extensive disease involvement. All the patients received chemotherapy with or without IFRT. Studies from other parts of the world suggested that ENL have a favorable prognosis and better treatment response with chemotherapy + IFRT. Loco-regional treatment can be curative in 40-50%of patients with localized disease because of the favorable prognosis factors.[19] Primary extranodal DLBCL happens to localized at extranodal sites and they are considered different entities with different natural histories. They supported the

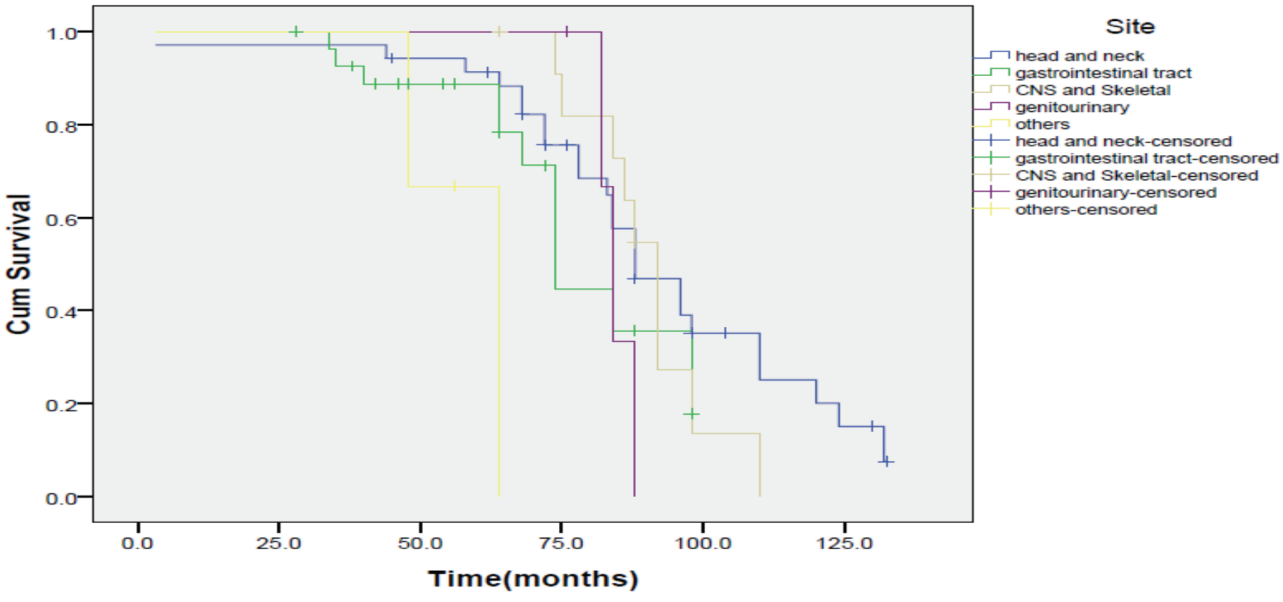

Figure 4. Overall survival.

genetic differences between nodal and extranodal DLBCL. Rao et al. suggested that there are also some genetic differences between extranodal DLBCL of different sites; it is conceivable that extranodal DLBCL could encompass several entities. Bcl2 overexpression is associated with adverse clinical outcome in follicular cell lymphoma and DLBCL. In our study, only 40% of GI tract ENL patients achieved CR, which is in line with the results of these studies.[20,25]

Many studies have reported that intestinal lymphoma had poorer survival than gastric lymphoma, probably due to a higher proportion of aggressive histology such as DLBCL and T-cell lymphoma seen in these sites.[31] A study of 1575 cases by Moller et al. supported our results. They found that DLBCL made up of 33% of all NHL cases. The incidence rate was 2.9 per lac population annually. The extranodal disease was common among DLBCL patients with 40% presenting with the extranodal disease as the dominating disease manifestation. They support the Danish LYFO study group that simplified a staging system that discriminates between localized and disseminated lymphoma.[2] They observed the poor performance of locoregional treatment compared with systemic therapy with anthracycline-based chemotherapy. Although anthracycline-based chemotherapy with or without IFRP is considered the gold standard for DLBCL.[22,23,24]

A study by Fuller et al. on 128 cases of stage I and II extranodal lymphomas of the head and neck revealed a 90% incidence of diffuse lymphomas. The peak age for male and female patients with extranodal lymphomas of the head and neck was in the seventh decade of their life. 37 patients were between 60 and 70 years of age. 31 patients were over age 70 years. In the M.D. Anderson Institute's study, primary extranodal presentations in 58% of stage I and stage II patients with diffuse non-Hodgkin's lymphomas was observed. In 61 % of these cases, the extranodal sites were limited to the head and neck. In our study, 50% of the patients were stages I and II.[26]

In a retrospective analysis of 45 previously untreated patients of primary lymphoma of bone with Ann Arbor stage IE and IIE, the patients received radiotherapy at least 40 Gy and doxorubicin-based chemotherapy. Histologically, 90% of cases were diffuse large B-cell lymphoma. International Index scores were assessed on 43 patients. 36 patients were treated with chemotherapy and radiation; five patients were treated with radiation alone; and four patients were treated with chemotherapy alone. The uni variable analysis revealed significantly improved 5-year overall survival for those patients who had international index scores of 0 vs scores of 1 or 2 (85 vs. 53%, respectively). The outcome of patients with chemotherapy and radiotherapy is favorable for bone lymphoma. The dose of radiation in the range of 46 Gy provides optimal local control with an acceptable rate of complications.[27]

Radiotherapy has remained an integral part of the management of lymphomas. Newer radiotherapy techniques such as 3D conformal RT and intensity-modulated RT can significantly reduce radiation doses to the surrounding normal tissues.

This study revealed that ENL accounts for almost 25% of all NHL. Hence, before the initiation of treatment, all the NHL cases should be properly investigated and staged. Head and neck, testis, ovary, bone, brain, lung, and breast lymphoma responded better to chemotherapy plus radiotherapy (IFRT) because they are limited to the organ disease. Gastrointestinal lymphoma presented with extensive disease involvement and high-grade tumor histologically treated with chemotherapy alone resulted in the poor outcome. Extranodal NHL responded well to chemotherapy similar to NHL and it was observed that treating the patients with IFRT results in enhanced levels of progression-free survival and overall survival.

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Conflicting Interest

None declared.

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