RESEARCH COMMUNICATION

Extranodal Non-Hodgkin's Lymphomas - A Retrospective Review of Clinico-Pathologic Features and Outcomes in Comparison with Nodal Non-Hodgkin's Lymphomas

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Abstract

Objective: The primary objective of this study was to analyze the anatomic distribution, clinical features and outcome of Diffuse large B-cell lymphoma (DLBCL) patients according to the primary site (extranodal vs. nodal) with applicability of International Prognostic Index (IPI). Methodology: A retrospective review (1988 to 2004) of 557 cases of DLBC. Results: The median age was 48.7 ± 15.3 years; M:F ratio was 2:1. The distribution according to the primary site was: lymph node (N-NHL), 322 cases (58%) of which 145(44%) were stage IV, 76 (23%) stage III, 60 (18%) stage II and 47 (15%) stage I. The extra nodal sites (EN-NHL) 235 (42%) cases included gastro-intestinal tract (44%), upper aerodigestive tract (19%), bones (8%), spine (5%), and unusual sites less than 3% each as breast, CNS, testis, lungs and skin. The median survival rate was 4.8 years and 6.3 years in N-NHL and EN-NHL respectively. In the latter this varied greatly depending on the primary site and stage of disease at presentation. In the univariate analysis factors associated with good prognosis were: age less than 60 years, early stage (I-II), extranodal involvement primarily gastric or bone, 0-1 extranodal site, 0-1 performance status, lack of B symptoms and normal LDH level. In the multivariate analysis age, performance status, stage of disease and level of LDH were the main variables predicting overall survival; no nodal or extranodal site maintained their prognostic value. Conclusion: Patients with EN-NHL present more frequently with early stage disease then those with N-NHL; overall survival in both groups largely depended on IPI and not on the site of origin of the malignancy.

Key Words: Non-Hodgkin's Lymphoma (NHL) - Extranodal NHL - Nodal NHL - Karachi, Pakistan

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Introduction

Non-Hodgkin's Lymphoma (NHL) ICD-10 (International Classification of Diseases 10th Revision) categories (C82-85; 96), is a diverse group of neoplasms both in their natural history and response to treatment. They rank fifth in cancer incidence in United States, and are increasing at a rate of almost 7% per year (Zucca et al., 2000). There is large geographical variation in the incidence, histopathology and clinical behavior of NHL (Jemal et al., 2004). In Karachi NHL has been reported as the sixth most common malignancy in both genders with an incidence of 9.6/100,000 in males and 7.2/100,000 in females (Bhurgri et al., 2005). It has been reported as the most common cancer in Northern Pakistani males which may be due to a combination of environmental, infectious and genetic factors (Ahmed et al., 1992; Aziz et al., 2004).

Non-Hodgkin's lymphomas mostly arise in the lymph nodes (N-NHL), but approximately 25-40% arise in tissues other than the lymph node, and therefore termed extranodal lymphomas (EN-NHL) (Zucca et al., 1997; 1999; 2000). It has been observed that during the last two decades the incidence of lymphomas has increased, and that EN-NHL increased more rapidly than the nodal type (Harris et al., 2001; Jemal et al., 2004).

Although numerous papers dealing with EN-NHL originating in almost every organ in the body have been published, the literature on primary EN-NHL as a group is limited. Literature comparing survival and prognostic factors between N-NHL and EN-NHL as a group is scarce in our part of the world.

The definition of primary EN-NHL is a controversial issue, especially in patients where both nodal and extranodal sites are involved. Some series on primary EN-NHL have included patients with only localized disease.

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On the other hand, studies that use more liberal criteria for EN-NHL include patients with disseminated disease (Rudders et al., 1978; d'Amore et al., 1991; Krol et al., 2003; Moller et al., 2004). It has been suggested that primary site may be an important prognostic factor in terms of survival differences.

The aim of this study was to analyze the anatomic distribution, clinical features and outcome of NHL patients according to the primary site (extranodal vs. nodal) with applicability of International Prognostic Index (IPI).

Materials and Methods

This is a descriptive study conducted on diffuse large B cell (DLBC) NHL cases registered between 1st January1988 and 31st December 2004 at the Department of Oncology, the Aga Khan University Hospital, Karachi. Lymphomas presenting in extra nodal organs with no or only minor lymph node involvement were considered primary EN-NHL. Lymphomas with clinically dominant lymph node involvement [ICD-3 (International Classification of Diseases of Oncology 3rd Revision) category (C77)], as well as those presenting at the spleen, thymus and Waldeyer's ring involvement [ICD-3 categories (C42.2, C37.9, C14.2)], were considered as primary N-NHL. Lymphomas with extensive disease involving both nodal and extranodal sites were considered N-NHL (Gatter et al., 2001; Pileri et al., 2002).

The diagnosis of NHL was based on the criteria established by WHO (Gatter et al., 2001). The panel of monoclonal antibodies included antibodies against the following antigens: CD20, CD79a, CD3, CD5, CD10, MUM1, CD138, bcl-2, bcl-6, Ki-67, p53, and p27. Clinical stage was defined according to the Ann Arbor classification (Carbone et al., 1971). Patients were considered to be completely staged when adequate information was available about history, status of peripheral lymph nodes, mediastinal lymph nodes (chest X-ray), abdominal lymph nodes, liver and spleen (abdominal CT scan), as well as peripheral blood and bone marrow status (cytology and histology). Results are expressed as mean ± standard deviation, number and percentage. Post-therapy restaging included a repetition of the previously abnormal tests and/or biopsies. Response was assessed according to conventional criteria. Complete response (CR) to treatment was defined as the disappearance of all clinical, radiological or other evidence of disease.

Categorical data were compared using Fisher's exact test for a two-sided p-value, whereas for ordinal data, nonparametric tests were used. The actuarial survival analysis was performed according to the method described by Kaplan and Meier (Kaplan and Meier, 1958). Chi-square tests were used to compare percentages in cross tabulations and the log-rank test was used to compare Kaplan–Meier survival curves (Peto et al., 1973; Cox et al., 1972). Overall survival (OS) was calculated from date of diagnosis until death (all causes) or last follow-up. Disease-free survival (DFS) was calculated for patients in complete response (CR) only, from date of CR until recurrence (failure) or last follow-up (including death in patients with CR). Cox regression analysis was used to correct for the confounding effect of differences in prognostic factors. The multivariate analysis of the variables predicting response was performed by using a logistic regression. The multivariate analysis for survival was performed by using the stepwise proportional hazards model (Cox et al., 1972).

In addition, patients were categorized into four risk groups on the basis of the number of IPI independent risk factors including age, Ann Arbor tumor stage, serum LDH, performance status and number of extranodal sites: 0–1 factor: low risk; 2 factors: low intermediate risk; 3 factors: high intermediate risk; 4–5 factors: high risk group.

Results

A retrospective review (1988 to 2004) of 711 cases of Non Hodgkin's Lymphoma (NHL) was conducted. Out of these 145 (20%) cases were excluded as they were other than DLBCL histopathology, 557 (80%) cases were analyzed for the clinico-pathologic characteristics,

Five hundred fifty-seven [358 (64%) male; 199 (36%) female) patients diagnosed with NHL between 1st January1988 and 31st December 2004 were selected for the study. Forty one (7%) cases were received during 1998-1992, 64 (12%) during 1993-96, 201 (36%) in 1997-2000 and 251 (45%) in 2001-4. The median age of the patients was 48.7 ± 15.3 years; male-female ratio was 2:1. All nodal and extranodal lymphoma were diffuse large B cell (ICD-3 category M9680).

The distribution according to the primary site was 328 (59%) cases of N-NHL and 229 (41%) EN-NHL. The overall stage was 153 (27%) cases in stage 1, 183 (33%) cases in stage 2, 76 (14%) cases in stage 3 and 145 (26%) cases in stage 4. Of the N-NHL, 47 (15%) cases were in stage I, 60 (18%) cases in stage II, 76 (23%) cases in stage III and 145 (44%) cases in stage IV. Organ involvement in EN-NHL was gastro-intestinal tract (44%), upper aero-digestive tract (19%), bone (8%), spine (5%), unusual sites less than 3% each, which were breast, CNS, testis, lungs and skin.

Overall 289 (52%) cases presented with a high serum lactate dehydrogenase (LDH) level, 337 (61%) cases presented with B symptoms, 220 (39%) with A symptoms. One hundred and seventy nine (32%) cases presented with performance status >2 and 43 (8%) with bone marrow involvement. After sub-classification according to the primary site of the lymphoma, patients with N-NHL presented more frequently with "B" symptoms (70% vs. 47%; $p<0.001$), poor performance status (36% vs. 27%; $p=0.02$), late-stage disease (67% vs. 0%; $p=0.000$), and high serum LDH levels (65% vs. 33%; $p<0.001$) than patients with EN-NHL as shown in table 1.

Five hundred thirty-five patients were treated with CHOP regimens (cyclophosphamide, doxorubicin, vincristine, and prednisone). Combination chemotherapy with rituximab (RCHOP) was used for 21 patients. One patient was treated with high dose methotrexate (HDMTX). Intrathecal chemotherapy (ITCH) was given to 120 (22%) cases and surgery was performed on 36 (7%) cases.

Table 1. Comparison of Extra-nodal (n=229) and Nodal (n=328) Lymphomas

Factors	Diagnosis		OR* (95% CI)	p-value
	Extra Nodal	Nodal		
Gender				
Male	164 (72%)	194 (59%)	1†	
Female	65 (28%)	134 (41%)	1.7 (1.2-2.5)	0.003
Age				
≤ 60	190 (83%)	253 (77%)	1	
> 60	39 (17%)	75 (23%)	1.4 (0.9-2.2)	0.094
Stage				
Stage - I	106 (46%)	47 (15%)	1†	
Stage - II	123 (54%)	60 (18%)	1.1 (0.7-1.7)	
Stage - III	0 (0%)	76 (23%)	-	
Stage - IV	0 (0%)	145 (44%)	-	0.685
Symptoms				
A	122 (53%)	98 (30%)	1†	
B	107 (47%)	230 (70%)	2.7 (1.9-3.8)	<0.001
LDH				
≤ 520	154 (67%)	114 (35%)	1†1	
> 520	75 (33%)	214 (65%)	3.9 (2.7-5.5)	<0.001
Performance Status				
≤ 2	168 (73%)	210 (64%)	1†	
> 2	61 (27%)	118 (36%)	1.5 (1.1-2.2)	0.020
Surgery				
Not done	218 (95%)	303 (92%)	1†	
Done	11 (5%)	25 (6%)	1.6 (0.8-3.4)	0.183
Status of patient				
Alive	143 (62%)	140 (43%)	1†	
Dead	86 (38%)	188 (57%)	2.2 (1.6-3.2)	<0.001

*Odds Ratio, †Reference category

Table 2. Factors Associated with Univariate Analysis

Factor		n	Median Survival	HR* (95% CI)	p-value
Age	≤ 60	437	6.3	1†	
	> 60	113	3.9	1.8 (1.4-2.3)	<0.001
LDH	≤ 520	268	9.2	1†	
	> 520	289	3.8	2.5 (1.9-3.2)	<0.001
Stage	I	153	11.3	1†	
	II	183	6.7	1.5 (1.1-2.1)	
	III	76	5.8	1.9 (1.3-2.9)	
	IV	145	2.6	3.2 (2.2-4.4)	<0.001
Symptoms	A	220	6.8	1†	
	B	337	4.8	1.6 (1.3-2.1)	<0.001
Diagnosis					
Extranodal		229	7.2	1†	
Nodal		328	4.5	1.7 (1.3-2.2)	<0.001
Extranodal sites					
0 – 1		434	6.3	1†	
2 - 3		123	3.6	1.8 (1.4 – 2.3)	<0.001
Performance Status					
≤ 2		378	10.1	1†	
> 2		179	3.4	2.6 (2.0 – 3.2)	<0.001
Risk factor category					
Low		151	-	1†	
Low+		148	5.3	3.3 (2.0 – 5.4)	
High-		142	4.8	5.0 (31 – 7.9)	
High		116	2.6	8.1 (5.1 – 12.9)	<0.001

*Hazard ratio, †Reference category

Twenty (3.4%) cases were lost to follow-up. Of the remaining 537 cases, a complete response (CR) was achieved in 401 (74.7%) patients. A partial response was observed in 87 (15.6%) and 48 (8.9%) patients failed to respond to treatment. One patient (0.2%) had a stable disease. After a median follow-up of 2.8 years 274 patients had died. One hundred and thirty four (32%) of the CR patients eventually relapsed. The five-year relapse-free survival rate among the patients with complete responses was 60%, and the five-year overall survival among all patients was 55% (Figure 1).

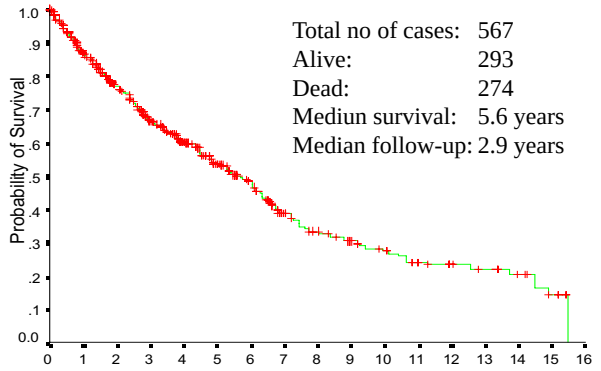

Figure 1. Overall Survival (in years)

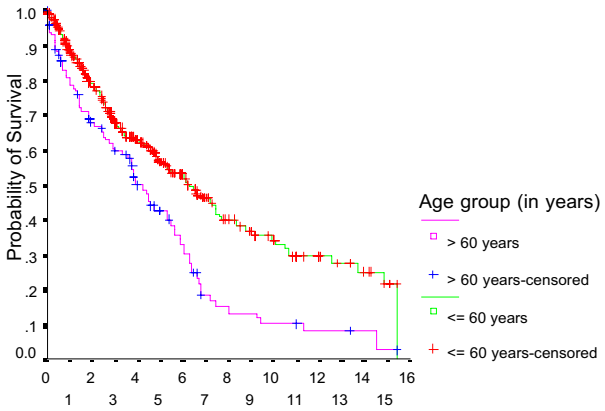

Figure 2. Overall Survival (in years) by Age Group

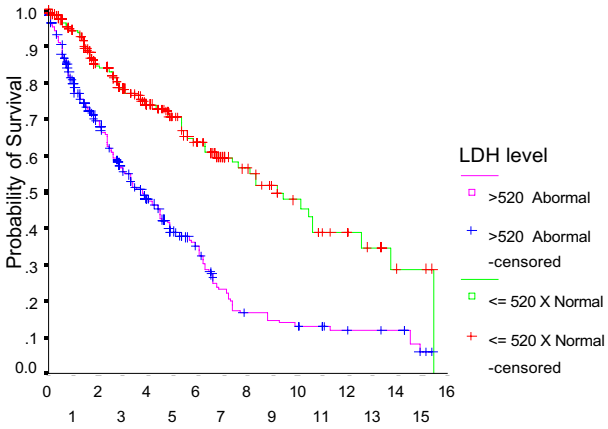

Figure 3. Overall Survival (in years) by LDH Level

In the univariate analysis, age younger than 60 years (p<0.001), ambulatory performance status (Eastern Cooperative Oncology Group [ECOG] score < 2) (p<0.001), absence of B symptoms (p=0.0002), early Ann Arbor stage [I/II] (p<0.001), extent of extranodal involvement [fewer than two sites vs. two or more sites] (p<0.001) and normal LDH levels (p<0.001) were the most important variables predicting OS. The associations between IPI factors and overall survival among those with complete responses are shown in Figures 2-7 and Table 2.

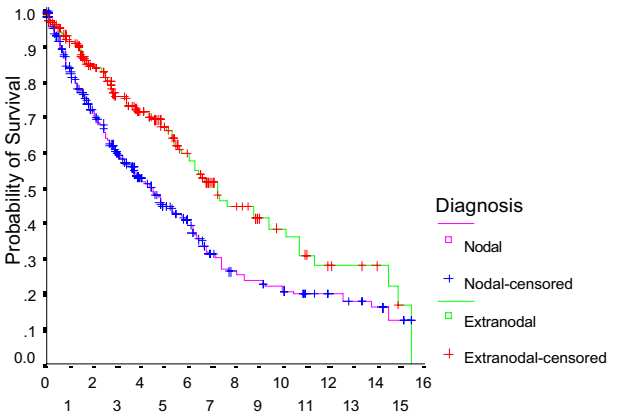

Figure 4. Overall Survival (in years) by LDH Level

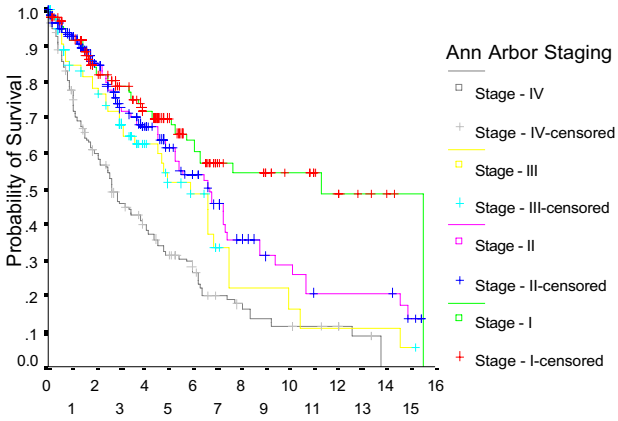

Figure 5. Overall Survival (in years) by Staging

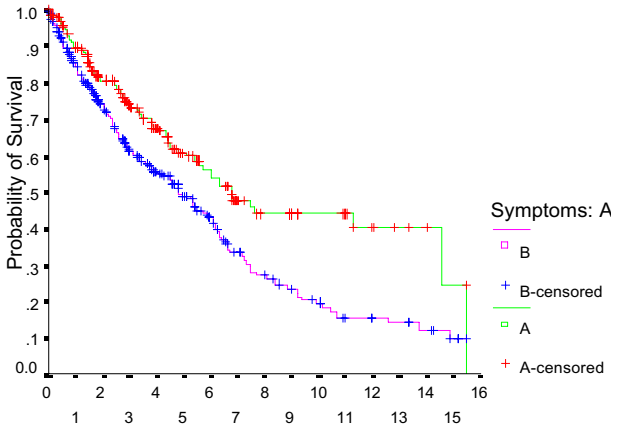

Figure 6. Overall Survival (in years) by LDH Level

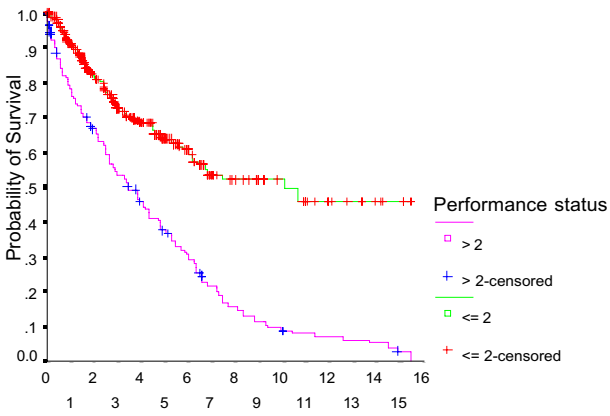

Figure 7. Overall Survival (in years) by Performance Status

Table 3. Independent Risk Factors for Mortality Identified in a Cox-proportion Hazard Model

Factor		HR* (95% CI)	p-value
Age	≤ 60	1†	
	> 60	1.3 (1.1-1.8)	0.034
Performance Status			
	≤ 2	1†	
	> 2	1.7 (1.3-2.2)	<0.001
Stage	I	1†	
	II	1.3 (0.9-1.9)	0.155
	III	1.4 (0.9-2.2)	0.120
	IV	2.3 (1.6-3.2)	<0.001
LDH	≤ 520	1†	
	> 520	1.8 (1.4 – 2.5)	<0.001

*Adjusted Hazard Ratio, †Reference category

A multivariate analysis was performed to further analyze the differences in clinical features on the basis of the primary site of presentation. All factors found to be statistically significant predictors of OS in the univariate analysis were included, namely age, B symptoms, performance status, Ann Arbor stage, number of extranodal sites involved, bone marrow infiltration, and serum LDH, along with the primary site of the lymphoma. In this model, age (p=0.034), stage (p<0.001), poor performance status (p<0.001) and serum LDH (p<0.001) maintained their prognostic value. Finally, primary site of the lymphoma (nodal or extranodal) did not maintain independent value in the multivariate analyses as shown in Table 3.

As a whole, primary nodal and extranodal lymphomas had a 5-year OS of 55%. The group of patients with EN-NHL showed a remarkably good OS compared to those with N-NHL (62% vs 43% OS p<0.001). However, when the analysis of OS according to the primary site (nodal v extranodal) was performed in patients with either favorable or unfavorable IPI, no significant differences were observed according to the site of presentation. Main prognostic factors for OS did not differ among the different sites of presentation (nodal or extranodal) but depended on the IPI score.

Discussion

In the present study, the five-year relapse-free survival rate among the patients with complete responses was 60%, and the five-year overall survival among all patients was 55%. These statistics are comparable with international statistics where the five-year relative survival rate for non-Hodgkin lymphoma patients have risen from 31 percent in whites in 1960-1963 to 63.8 percent for all races in 1996-2003 (Sant M et al, 2003; NHL facts and figures, 2004). Overall 5-year relative survival is reported as 56.1% in EUROCARE west, 47.1% in EUROCARE east and 56.3% in SEER (Sant et al., 2008).

Non-Hodgkin's lymphoma has a varied manner of presentation, response to therapy and prognosis. Such heterogeneity has been recognized in the REAL and WHO classification (Ahmed et al., 1992; Aziz et al., 2004). Furthermore, the site of origin of lymphoid tissue is an important determinant of lymphocyte migration patterns.

The consideration of lymphoma as primary nodal or extranodal is a controversial issue (Krol et al., 2003). Patients with purely nodal or extranodal involvement are easily classified. In some studies, only localized extranodal lymphomas have been defined as primary EN-NHL (Lossos et al., 2004). Cases with extensive disease involving both nodal and extranodal areas are difficult to categorize. In our study, these cases were included in the nodal lymphomas. However, this may represent a bias against this group.

In this study, the groups of nodal and extranodal NHL were not homogeneous from the clinical standpoint. Lymphomas arising in two specific sites (a single nodal site and primary extranodal site in the gastrointestinal track) showed very favorable features at diagnosis (e.g., early stage, absence of bone marrow infiltration, normal serum LDH, and low-risk IPI). The remaining NHL (stage III-IV nodal or other extranodal sites) presented with poorer characteristics. It is a point to note that none of the patients in the extranodal group had stage III-IV disease possibly because patients are likely to present earlier with local symptoms due to tumor mass in extranodal sites.

In terms of response to therapy, risk of relapse and OS, lymphomas at a single nodal site and GI lymphomas also showed a notably better outcome than the other groups. Thus, it is not the origin of disease (nodal or extranodal), but the stage of disease at presentation and primary disease at some specific sites that may be related to the clinicobiologic features and eventual outcome. On the other hand, with regard to the prognostic factors for OS, none of the primary sites showed an independent predictive weight when standard variables were included in multivariate analyses. In fact, IPI was the most important factor for OS, irrespective of the primary site of the lymphoma.

A few patients with bowel obstruction or cord compression lymphoma required surgery for diagnosis or relief of symptoms. There is significant difference from western data in histology, with diffuse large B cell lymphoma (DLBC) being the most common morphology in our study. Retrospective design and non-uniform treatment are the major limitations of this study. For more validated data, well designed prospective studies, with predetermined written protocol of uniform treatment and sample collection is recommended. On other hand a large number of patients and multivariate analysis of predictive factors appears to be a useful guide for selecting treatment for patients with DLBL by identifying the subsets of patients in whom intensified primary therapy may be warranted.

In conclusion, patients with EN-NHL present more frequently with early stage disease then those with N-NHL, overall survival in both groups largely depended on IPI and not on the site of origin of the malignancy.

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