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Primary Extranodal Non-Hodgkin's Lymphoma in Adults: Clinicopathological and Survival Characteristics

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Among 318 cases of non-Hodgkin's lymphoma (NHL) treated in our unit, 145 (45.6%) had primary extranodal NHL (PE-NHL). The stomach was the most common site (42.1%), followed by the PE-NHL of the head and neck region. Histologically aggressive histologies (65.5% intermediate and 20.7% high grade) predominated. 89.6% of the cases were localized (stage I_E, 51% and stage II, 38.6%) but 28% had B symptoms. CR was achieved in 82.1% of the cases. 5-years disease free survival and overall survival were both 65%. Factors that influence prognosis were stage and high grade histology. Among various primary sites the Waldeyer's ring, small intestine and testes had the worse prognosis. Compared to nodal NHL, the PE-NHL were more frequently localized, belonged more often to aggressive histologies and had more often distal extranodal relapses. CR rates and disease free and overall survival were significantly better for PE-NHL. The survival rates, however, listed according to stage and histology for nodal and PE-NHL were not different.

We conclude that although PE-NHL differed from nodal NHL in several respects, prognosis is mainly a factor of stage and histology rather than of the primary localization per se.

KEY WORDS: Lymphoma non-Hodgkin's extranodal

INTRODUCTION

Involvement of extranodal sites is a common feature during the course of non-Hodgkin's lymphomas (NHL). Moreover, a proportion of NHL is considered to originate at sites other than the lymph nodes or spleen and is referred to as primary extranodal NHL (PE-NHL). PE-NHL may occur at any organ or tissue including lungs, kidney, testes connective tissue e.t.c., though gastrointestinal tract (GI tract), tonsils and skin are the commonest sites of primary involvement.[1–8]

There are many reports describing the clinical and histological characteristics of PE-NHL of specific extranodal sites. However, few studies have reviewed the general problem of PE-NHL.[5,6,9] As a result the natural history as well as the biological behaviour of these tumors, in relation to nodal NHL, is poorly characterized.

In the present report we analyse the data of our cases of PE-NHL, diagnosed, treated and followed up in a single institution during the last 14 years. Several clinical, histological and survival parameters of PE-NHL were compared to those of nodal NHL in order to define the distinctive features, if any, of the PE-NHL.

PATIENTS AND METHODS

Between January 1978 and February 1992, 376 consecutive patients with NHL were diagnosed and treated in the Haematology-Oncology Section of the Second Department of Internal Medicine, "Evangelismos" Hospital, Athens. The clinical records of all patients were reviewed. Fifty eight patients were excluded from the study because of incomplete follow-up. Excluded from the study were cases with mycosis fungoides, Sezary's syndrome, chronic lymphocytic leukaemia, hairy cell leukaemia and multiple myeloma.

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As PE-NHL were considered those NHL which presented with disease at any organ or tissue other than lymph nodes or spleen, the symptoms at initial presentation were caused mainly from this extranodal involvement and after routine staging procedures the extranodal involvement remained the clinically dominant site of the disease.

Tonsils and Waldeyer's ring were classified as extranodal sites. Cases with bone marrow involvement were considered as extranodal on the condition that they fulfilled the definition criteria for PE-NHL. Patients were classified histologically according to the Working Formulation[10] and staged according to the Ann-Arbor system.[11] Staging was performed on the basis of physical examination, surgical reports, x-rays, biochemical profile, bone marrow biopsy, CT scan of the thorax and CT scan of the abdomen. In 88 patients bipedal lymphogram was performed. In 60 out of 71 cases of GI lymphoma and 38 of 49 cases of head and neck lymphoma upper CI tract endoscopy was performed at presentation. Median follow up time was 38 months (range 2–167 months).

The patients were treated in the following manner:

Nodal lymphomas

Low grade:

1. In early stages (I–II) patients were usually treated with local radiotherapy.
2. In advanced stages (stages III–IV) chemotherapy was given either with single agent (chlorambucil) or combination chemotherapy (CT) with COP regimen (cyclophosphamide, vincristine, prednisone) or CIOPP regimen (chlorambucil, vincristine, procarbazine, prednisone).
3. In some cases of stage II and III patients radiotherapy was given in combination with chemotherapy.

Intermediate and high grade:

1. In early stages (I–II) CT was given with CHOP regimen (cyclophosphamide, adriamycin, vincristine, prednisone) followed by local radiotherapy.
2. In advanced stages patients were treated with CT (CHOP). In a few cases bleocin was added to CHOP, while in 8 cases the PROMACE-CytaBOM regimen[12] was given.
3. Cases with lymphoblastic or Burkitt's lymphoma were treated with acute lymphoblastic leukaemia protocols.

Extranodal lymphomas

They were treated as the nodal NHL according to their clinical stage, histology and bulk of the disease.

However, there are some special treatment considerations for the PE-NHL of specific anatomical sites. This is of particular importance in early stages of GI tract lymphomas, mainly in the stomach, when "curative" surgery was followed by postoperative CT with 6 courses of CHOP or COP regimens. Among the 71 patients with GI tract lymphoma 57 were treated with surgery and chemotherapy.

In the second large group of PE-NHL of the head and neck region, the vast majority of patients were treated with CT (CHOP or COP regimen) followed by local radiotherapy. In the small number of patients with testicular lymphoma orchiectomy was followed by CT in all cases.

Survival was calculated from the onset of therapy and disease free survival from the onset of remission. Death from whatever cause was considered the end point of survival. Actuarial survival curves and disease free of survival were considered according to the method of Kaplan-Meier. Analysis of clinical data was performed using the standard Pearson's chi-square statistics. Statistical significance of differences between survival curves was assessed using the log-rank test.

RESULTS

Among the 318 evaluable patients 145 (45.6%) had PE-NHL and 173 (54.4%) nodal NHL. The specific sites of extranodal involvement are shown in table 1. the most common site was the GI tract (49%) where the stomach was the most frequently involved organ (42.1%). Next in frequency were the PE-NHL of the head and neck region (33%) with the tonsils the most frequently involved site (15.8%).

Table 1 Extranodal NHL: Sites of Involvement (N = 145)

Head and Neck	48 (33%)	Others	20 (13.8%)
Tonsils	23	Bone marrow	4
Base of the tongue	2	Skin (other than	5
Nasopharynx	2	mycosis fungoides)	
Oral cavity	9	Bone	3
Parotis	3	Lung	3
Orbit	2	Peura	1
Larynx	2	Liver	1
Thyroid	2	Kidney	1
Nasal cavity	2	Connective tissue	1
Sinuses	1	Brain	1
Gastrointestinal tract	71 (49%)		
Stomach	61		
Small intestine	6		
Colon	4		
Testes	6 (4.2%)		

Age, sex

The age of patients with PE-NHL at presentation ranged from 18 to 84 years with a median of 56 years. Only 14.5% of the patients were less than 40 years. There were 91 males and 54 females (M:F ratio of 1.68). The age and sex characteristics of PE-NHL were not different from those of nodal NHL (table 2).

Histology

The distribution of histological subgroups of the patients with PE-NHL according to the Working Formulation is shown in detail in table 3. The vast majority of the patients belonged to the aggressive histologies (65.5% intermediate and 20.7% high grade) while the incidence of low grade subtypes was 13.8% only. Nodular histology was rare (4.1%).

The distribution of histological subtypes in PE-NHL was clearly different from that observed in nodal NHL (table 2). In the latter group the incidence of low grade histologies was higher, whereas the frequency of intermediate grade subtypes was lower than those observed in PE-NHL at a statistically significant level.

Stage

The vast majority (89.6%) of patients with PE-NHL presented with early disease (51% Stage I and 38.6% Stage II). This is in contrast to nodal NHL where disseminated disease (Stage III and IV) was the most common presentation (71.1%) (table 2). B-symptoms presented with the same frequency in both groups (28.2% in PE-NHL vs 28% in nodal NHL).

Table 2 Extranodal vs Nodal NHL Clinical and laboratory findings

	No of patients (%)		
Characteristic	*Extranodal (n = 145)*	*Nodal (n = 173)*	*P*
Age			
Median	56 years	58 (years)	NS
Range	(8–83)	(16–84)	
Sex	No (%)	No (%)	
Male	91 (62.7)	111 (64.2)	NS
Female	54 (37.2)	62 (35.8)	
Clinical stage	No (%)	No (%)	0 < 0.001
I-II	130 (89.6)	50 (28.9)	
III-IV	5 (10.3)	123 (71.1)	
Histology	No (%)	No (%)	<0.001
Low	20 (13.8)	66 (38.1)	
Intermediate	95 (65.5)	64 (37)	
High	30 (20.7)	43 (24.9)	
Leukaemic picture	2(0.4)	29 (16.8)	<0.001
Monoclonal gammopathy	3 (2.1)	15 (8.7)	<0.005
Autoimmune cytopenias	4 (2.7)	18 (10.4)	<0.005
Bone marrow involvement	8(5.5)	88 (50.9)	<0.001

Other characteristics

As is shown in table 2 leukaemic picture in the peripheral blood, monoclonal gammopathies, autoimmune cytopenias and bone marrow infiltration at presentation, were rare in PE-NHL and in any case their frequency was much lower than in nodal NHL.

Response to treatment and survival

In 119 cases (82.1%) with PE-NHL complete remission (CR) was achieved while 12 patients (8.3%) had a partial response (PR). As shown in table 4 both CR and PR rates were much higher in PE-NHL than in nodal NHL, where CR and PR rates were 47.9% and 40.5% respectively. With a 38 month median follow up, disease free period at 5 years was 65% (median not reached) for PE-NHL vs 40% (median 37 months) for nodal NHL. The overall 5 years survival was 65% (median not reached) for PE-NHL and 42% (median 45 months) for nodal NHL. Both disease free period and overall survival were significantly better for PE-NHL compared to nodal NHL ($p < 0.005$ and $p < 0.001$ respectively).

Table 3 Extranodal non-Hodgkin's lymphomas: Histological Classification (Working Formulation)

Histology	*No of patients*	*(%)*
Low grade	20	(13.8)
Small lymphocytic	11	(7.6)
Plasmatocytoid	6	(3.5)
Follicular small cleaved	1	(0.7)
Follicular mixed	3	(2.0)
Intermediate grade	95	(65.5)
Follicular large cell	2	(1.4)
Diffuse small cleaved cell	8	(5.5)
Diffuse mixed	22	(15.2)
Diffuse large cell	63	(43.4)
High grade	30	(20.7)
Immunoblastic	27	(18.6)
Lymphoblastic	3	(2.0)
Total	145	

Table 4 Extranodal vs Nodal NHL: Treatment response, survival and pattern of relapse

	No of patients (%)		
	Extranodal (n = 145)	*Nodal (n = 173)*	*P*
Complete remission	119 (82.1%)	83 (47.9%)	<0.001
Partial remission	12 (8.3%)	70 (40.5%)	<0.001
Progressive disease	14 (9.6%)	20 (11.6%)	NS
Actuarial 5-year disease free period	65%	40%	<0.001
Actuarial 5-year overall survival	65%	42%	<0.005
Nodal relapse after CR	9 (26.5%)	34 (82.9%)	<0.001
Extranodal relapse after CR	25 (73.5%)	7 (17.1%)	<0.001

Prognostic factors

Survival rates were not significantly influenced by sex, age and symptoms. Stage, however, significantly affected survival which became poorer as stage advanced (Figure 1). Survival curves did not differ significantly between low and intermediate grade of malignancy but they were significantly worse for high grade cases (Fig. 2). These differences of survival, according to histology, did not change when the curves were adjusted according to stage (results not shown).

Survival curves of PE-NHL and nodal NHL listed according to stage and histology were not different for early (I–II) stages (Figure 3). Such a comparison was not possible for advanced (III–IV) stages since the number of advanced stages cases of PE-NHL was small.

Pattern of relapse

Among the 119 CR patients in the PE-NHL group 34 (28.5%) have relapsed. The sites of relapse were exclusively or included distant extranodal sites (GI tract, lungs etc.) in 25 cases (73.5%). On the contrary, distant extranodal involvement in the relapsed 41 (49.4%) cases of nodal NHL was observed in only 7 cases (17%). The difference in extranodal involvement between relapsed extranodal and nodal NHL was statistically significant ($p < 0.001$).

DISCUSSION

In the present series of 318 cases of NHL treated in a single unit, the PE-NHL constitute 45.6% of the cases. In the reported studies from various countries the incidence of PE-NHL varied from 15% to 48%.[1,4–6,13–15] These differences in incidence may be the consequence of variation in definition of primary extranodal involvement or may be the result of staging procedures and referral policy. It is of interest in this respect that in two recently published studies, reported data of population based registries, a high incidence of PE-NHL was found. In the first of them from Netherlands, among 580 cases of NHL the occurrence of PE-NHL was as high as 41%.[5] In the other study from Denmark of a total of 1257 cases of NHL registered, 37% were classified as PE-NHL.[6] In the latter study, however, NHL of the Waldeyer's ring (8% of the whole series) were recorded as nodal NHL. It appears that in more than one third of NHL cases, the disease presents with extranodal localization as the clinically major site of involvement. Furthermore the incidence of PE-NHL is expected to increase in the following years, since PE-NHL appear with increasing frequency in AIDS patients[16] as well as in patients with iatrogenic immunosuppression after organ transplantation.

The distribution of PE-NHL in the various anatomical sites varies considerably in the reported studies. In the present series stomach was the most common site of involvement followed by the primary involvement of the tonsils. Although this distribution, with considerable variation in the relative frequencies, is not dissimilar to the reported by others,[1,5,6] special attention should paid to the small number of patients with intestinal lymphomas of the

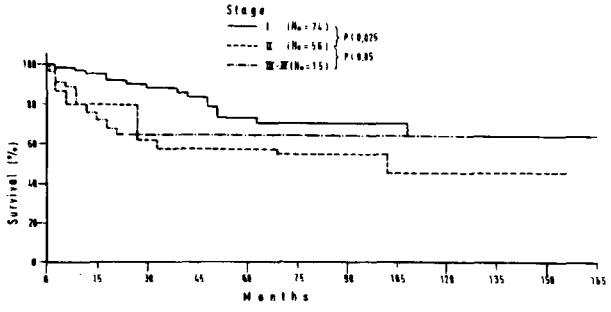

Figure 1 Survival for patients with primary extranodal lymphomas by stage according to the Ann Arbor.

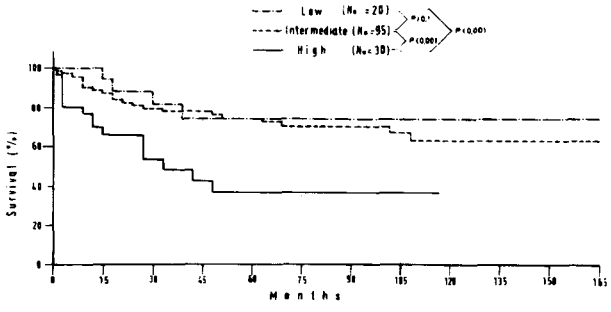

Figure 2 Survival for patients with primary extranodal lymphomas by grade of malignancy according to the Working Formulation.

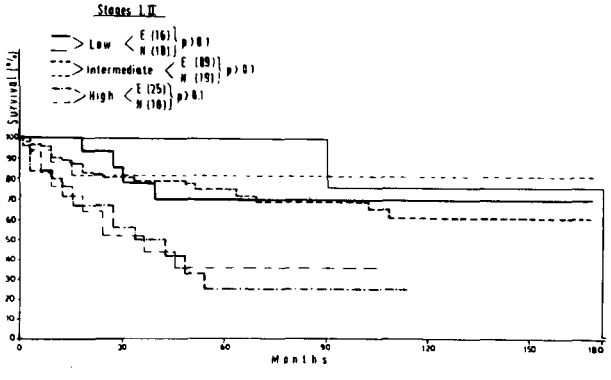

Figure 3 Survival for patients with extranodal and nodal NHI by stage and grade of malignancy (early stages): E: Extranodal, N: Nodal.

present series. In a recent population-based analysis of NHL[17] of GI tract the incidence of intestinal NHL is higher. As it has been shown[18] intestinal lymphomas occur more frequently in children and young adults. Therefore the low incidence of these lymphomas of the present study could be attributed to the fact that patients with small ages are not included.

The major clinicopathological differences between PE-NHL and nodal lymphomas in our study, were differences in histology and stage. In general the vast majority of PE-NHL were localized (stage I or II) and belonged to intermediate and high grade malignancy. Other features of PE-NHL such as the low incidence of leukemic picture in the peripheral blood, bone marrow infiltration, monoclonal gammopathies and autoimmune cytopenias may be related to the striking low incidence of low grade histology and advanced disease at presentation in these tumors.

The response to treatment of PE-NHL cases in our series was high, reflecting the fact that the majority of them were localized tumors. Two main prognostic factors influence survival, the stage and histology. The prognostic significance of stage is a universal finding (5,6) despite differences in the details of classification as well as staging procedures. Histology in the present study discriminates high grade lymphomas from low and intermediate grade, a finding similar to that reported by D'Amore *et al* (6). Others, however, found that all three grades of malignancy obtained by the Working Formulation influence survival.

PE-NHL in the present study showed, compared to nodal NHL, a much better disease-free and overall survival. However, this probably reflects differences in stage and histology rather the primary extranodal or nodal localization per se. In fact survival curves listed according to histology and stage for the two groups were comparable at least for the localized disease (stage I and II) which represented the majority of our cases. This analysis of PE-NHL, as a group, does not exclude the possibility that specific sites of PE-NHL has no prognostic significance. It has been reported that the overall survival of stage I PE-NHL of the Waldeyer's ring is significantly shorter than the Stage I PE-NHL of the other sites of head and neck region (7). The exact significance, however, of extranodal presentation of NHL as well as the significance of every specific extranodal site, as an independent factor, influencing survival can only be solved in prospective clinical studies.

A distinctive feature of PE-NHL compared to nodal NHL was the high frequency of extranodal relapses after achieving CR. The predilections for extranodal (particularly solitary extranodal) relapses in this group of tumors is of great interest. The reason for extranodal recurrences is not clear but it is likely that is closely linked to the homing process regulated by homing receptors on the lymphoid cells (19). This tropism for specific sites has been particularly noticeable with tonsils and stomach (7,20) testes and nasopharynx (17,21). In this respect of great interest is the concept of lymphomas arising from the mucosa associated lymphoid tissue (MALT) of the GI tract (22–24). It appears that there is a wider group of extranodal B-cell lymphomas of MALT origin, apart from GI tract ones, such as lymphomas arising in conjunctiva, salivary glands, Waldeyer's ring, thyroid gland, breast, lungs and others. These concepts may explain the tendency of PE-NHL to remain localized and when they disseminate to spread to anatomical sites other than peripheral lymph nodes.

From the analysis of our data it appears that PE-NHL differ from nodal lymphomas in some very important respects, such as histology, stage at presentation and pattern of relapse after CR. These differences may explain the better CR rates and disease-free and overall survival time seen in PE-NHL.

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