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Primary Extranodal Non-Hodgkin's Lymphoma of the Head and Neck

Abstract

Among 387 cases of non-Hodgkin's lymphoma (NHL) treated in our units between January 1977 and December 1990, 52 (13.4%) had primary extranodal (PE) NHL of the head and neck. The median age was 55 years with a M:F ratio of 1.9:1. The most frequent primary site was the tonsil (28 cases), followed by oral cavity, parotid gland, orbit and other sites. The aggressive histological subtypes predominate. 55.2% of the patients were in stage I and 44.8% in stage II of disease. The CR rate was high (94.2%). The 5 years' overall survival rate was 65% and it was influenced mainly by stage (stage I 82.5% vs. 48.7% in stage II). Sex, age and histology did not significantly affect survival rate. Patients with primary Waldeyer's ring involvement (WR group) did not differ significantly from the other primary sites analyzed as a group (non-WR group) in respect to median age, sex distribution, histology and CR rates. They differed, however, in: (1) stage distribution with stage II disease more frequent in the WR group; (2) overall survival and disease-free survival both of which were significantly better in the non-WR group; and (3) the high incidence of GI tract involvement as initial manifestation of relapse in the WR group.

It is concluded that the behaviour of the Waldeyer's ring PE-NHL is rather distinctive and should be considered separately from the other PE-NHL of the head and neck.

Key Words
Extranodal lymphoma
Head and neck lymphoma

Primary extranodal non-Hodgkin's lymphoma (PE-NHL) of the head and neck accounts 10–20% of all cases of NHL [1–6]. Despite their frequency, the information about the natural history and biological behaviour of these lymphomas is rather sparse in the literature. Moreover, there is still controversy whether the involvement of the Waldeyer's ring (faucial tonsils, nasopharynx and base of the tongue), which is the most common primary site of these lymphomas, should be considered as nodal or extranodal involvement.

In the present study we analyzed our cases of PE-NHL of the head and neck with reference to primary sites, stage, histology, survival and patterns of relapse. In addition, PE-NHL of the Waldeyer's ring were analyzed as separate group and compared to the PE-NHL of the other sites of the head and neck region.

Patients and Methods

Between January 1977 and December 1990, 387 consecutive patients with NHL were diagnosed and treated in the Haematology-Oncology section of the Second Propaedeutic Department of Internal Medicine, Evangelismos Hospital, Athens University, the AHEPA University Hospital, Thessaloniki, and Ioannina Uni-

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versity Hospital, Greece. Among these patients 61 had extranodal localization of lymphoma in the head and neck region and presented for evaluation because of symptoms caused mainly by this involvement. The 52 patients (13.4%) with the largest tumor located in the head and neck at presentation were included in the present study. Excluded were 9 patients with extensive disease (stage III and IV) because primary localization in the head and neck region was uncertain.

Review of the histology was performed in all cases, the diagnosis of NHL was verified in all of them and they were classified according to the Working Formulation [7]. Medial follow-up time was 30 months (ranged from 12 to 148 months). Patients were staged according to the Ann-Arbor system [8] on the basis of physical examination, chest X-rays, biochemical profile, bone marrow biopsy, CT scan of the abdomen and CT scan of the thorax. In 48 of the 52 cases upper gastrointestinal tract endoscopy was performed at presentation.

The patients were treated in the following manner: (1) local radiotherapy; (2) local radiotherapy and systemic chemotherapy, and (3) systemic chemotherapy only. The chemotherapy regimes used were either a combination of cyclophosphamide, vincristine, and prednisone (COP) or a combination of the same drugs with Adriamycin (CHOP). In a few cases bleomycin was added to the CHOP regimen. Response to treatment was assessed according to the standard criteria applying restaging procedures as required.

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 for survival. Actuarial survival curves and disease-free survival were constructed 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

Age and Sex

The age at presentation ranged from 27 to 80 years with a median of 55 years, the peak age being in the sixth decade. There were 34 males and 18 females, giving a male: female ratio of 1.9:1. Male predominance was evident in all primary sites with the exception of thyroid lymphomas.

Site of Primary Tumor

The sites of primary tumors are shown in table 1. The most common primary site was Waldeyer's ring (59.6%) where the tonsils were mainly involved (53.8%).

Stage

There were 29 patients with stage I and 23 patients with stage II disease. Seven patients had B symptoms, fever being present in all of them.

Histology

Table 2 shows the histologic classification of the patients according to the working formulation. The majority of the cases belonged to the intermediate (55.7%) and high-grade (30.8%) lymphomas while the incidence of low-grade lymphomas was 13.5% only. Nodular lymphomas comprises 13.4% of the cases.

Table 1. Sites involved at presentation

Tonsils	28
Nasopharynx	3
Paranasal sinuses	1
Hard palate	4*
Gums	1
Floor of mouth	1
Larynx	2
Parotid	3
Thyroid	2
Orbit	3
Mandible	4

* Two extended to soft palate.

Table 2. Histological classification of the PE-NHL of the head and neck (according to the International Working Formulation System)

Low grade		6 (13.5%)
Small lymphocytic	1	
Follicular small cleaved	–	
Follicular mixed	5	
Intermediate grade		30 (55.7%)
Follicular large cell	2	
Diffuse small cleaved	5	
Diffuse mixed	6	
Diffuse large cell	17	
High grade		16 (30.8%)
Large cell immunoblastic	14	
Lymphoblastic	1	
Small cell non-cleaved	1	

Treatment and Response

The 52 patients were treated as follows: (1) 10 (19.2%) patients local radiation to the primary site ($\pm$ regional lymph nodes); (2) 24 (46.2%) patients local radiation and systemic chemotherapy (COP in 14 cases and CHOP in 10 cases); and 18 (34.6%) systemic chemotherapy (COP in 7 and CHOP in 11 cases) only. Thus, in 42 (80.8%) patients treatment included therapy in the involved sites. In 49 cases (94.2%) complete remission (CR) was achieved. Three patients (5.8%) showed a partial response.

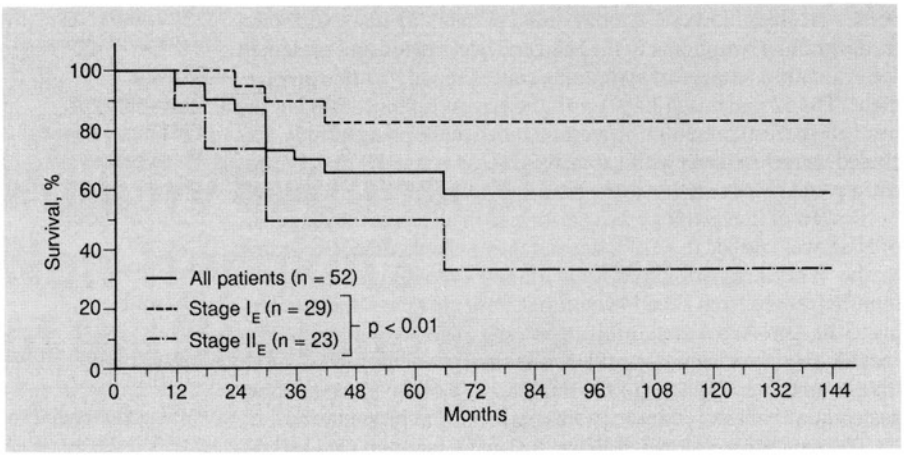

Fig. 1. Overall survival and survival by stage of the PE-NHL of the head and neck.

Survival

The overall 5-year survival rate for the 52 patients was 65% (fig. 1). The corresponding disease-free 5-year survival rate was 51.1%. Survival rates were not significantly influences by sex and age. When the patients were classified according to the working formulation the 5-year survival rates for those with low, intermediate and high-grade histologic subtypes were 83.3, 70.3 and 51.6%, respectively. These differences were not statistically significant. By contrast, the 5-year overall survival and disease-free survival rates differed according to stage. The 5-year survival rate for patients with stage I disease was 82.5% compared to 48.7% for patients with stage II disease (fig. 1). This difference was statistically significant ($p < 0.01$). The disease-free 5-year survival rates were better for stage I (80.5%) than that for the patients with stage II disease (30.2%) ($p < 0.05$).

Patterns of Relapse

Among the 49 patients who achieved CR, 15 (30.6%) subsequently relapsed. In 3 of them local recurrence was the first manifestation of relapse. In 2 of them local radiotherapy was included in the front-line treatment. In 12 cases the first sites of relapse were outside the head and neck region. In 3 of them distant spread was only nodal (1 retroperitoneal, 1 inguinal and 1 generalized), in 2 only extranodal (1 lung, 1 stomach), and in 7 cases disseminated with nodal and extranodal sites involved. Within the last group of patients there were 5 cases with clinically manifested GI tract, 1 with lung and 1 with CNS involvement. Thus, GI tract was the most frequent site of extranodal relapse with the stomach involved in 3 cases, the small intestine in 1 case and the colon in 2 cases.

Comparison between Waldeyer's Ring PE-NHL and the Other Sites of PE-NHL of the Head and Neck

For further analysis the 52 patients were divided into two groups: the Waldeyer's ring group (WR group) included the 31 patients with PE-NHL of the tonsils (28 cases) and nasopharynx (3 cases), and the non-WR group included the 21 patients with PE-NHL of all other sites of the head and neck. As shown in table 3, sex distribution, median age, distribution in histological subtypes and response to initial treatment were similar in both groups. In contrast, major differences were found in stage distribution of presentation, survival and pattern of relapse. Patients with stage II disease were more frequent in the WR group than in the remainder ($p < 0.01$). The 5-year survival rate for patients with WR PE-NHL was 51.4% compared to 83.6% for patients with non-WR PE-NHL. This difference was statistically significant ($p < 0.05$). Differences in the 5-year disease-free survival were similar: 39.2% in the WR group and 88.2% in the non-WR group ($p < 0.05$). Analysis of survival rates in stage I patients showed similar differences (fig. 2). Both survival and disease-free survival rates were significantly better for the stage I WR group than for the non-WR group of patients with stage I disease ($p < 0.01$). Another difference between the two groups, which did not attain statistical significance, was the involvement of GI tract as a manifestation of initial relapse. It was present in 6 of the 12 WR patients but in none of the 3 non-WR patients with PE-NHL of the head and neck.

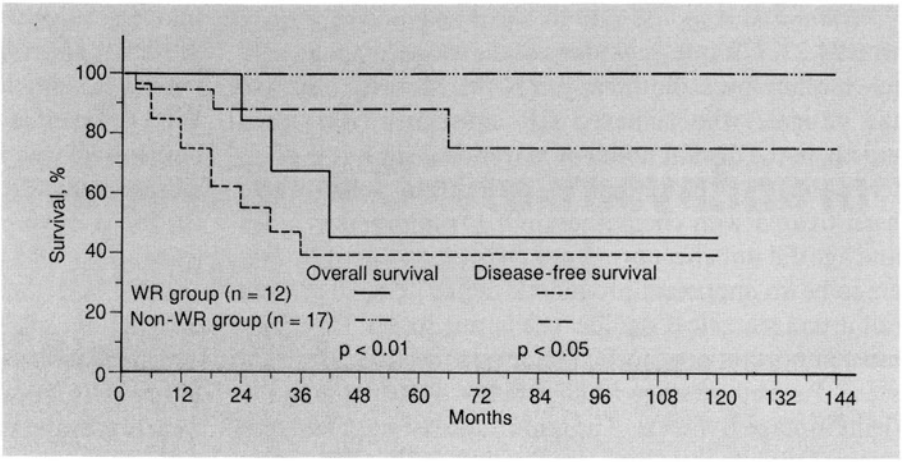

Fig. 2. Survival and disease-free survival for the patients with stage I primary WR and non-WR PE-NHL of the head and neck.

Table 3. Characteristics, survival and GI tract involvement of PE-NHL of the Waldeyer's ring and all other sites of the head and neck

	Waldeyer's ring PE-NHL	PE-NHL of all other sites of the head and neck	p
M:F	22:9	12:9	NS
Median age, years	54	56	NS
Stage at presentation, n (%)			
Stage I	12 (38.7)	17 (81)	<0.05
Stage II	19 (61.3)	4 (19)	<0.05
Histology, n (%)			
Low grade	3 (9.8)	3 (14.5)	NS
Intermediate grade	18 (58)	12 (57.1)	NS
High grade	10 (32.2)	6 (28.6)	NS
Response to treatment (CR)	29 (93.5)	20 (95.2)	NS
Actuarial 5-year disease-free period, %	39.2	88.2	<0.05
Actuarial 5-year overall survival, %	51.4	83.6	<0.05
Involvement of GI tract at first relapse	6/12	0/3	NS

NS = Non-significant.

Discussion

In the present series of 387 cases of NHL, the PE-NHL of the head and neck constitute 13.4% of the cases. The median age at diagnosis was 55 years, the M:F ratio 1.9:1 and the most frequent primary site was Waldeyer's ring where the tonsils were mainly involved. More than half of the patients were in stage I, the remainder being in stage II. The majority of the patients had tumors which belonged to the aggressive histological varieties, particularly diffuse large cell and immunoblastic lymphomas. These results are in accordance with those reported by other [3, 6, 9–13]. A few comments, however, are warranted. First, in the present series strict criteria were employed to distinguish extranodal from nodal lymphomas. As a result cases with advanced disease were practically excluded from analysis. We feel that the extranodal origin of lymphomas in such an advanced stage is at least uncertain. Second, the incidence of lymphomas with follicular pattern (13.6%) in the present series is comparable with the incidence reported in the West [9–10, 12] and higher than that reported in the Middle East [4].

The initial response rate to treatment was very high, with 94.2% CR rate, regardless of the way of management (chemotherapy, radiotherapy or both). More than 30% of the patients who achieved CR subsequently relapsed mostly in the distant nodal or extranodal sites. It is of interest that 9 of the 12 patients with distant relapses had been treated with chemotherapy (± radiotherapy). Sex and age did not affect prognosis. Histology found by others to be an important prognostic factor [3, 6, 10, 12] did not attain statistical significance in our series. The single most important prognostic factor was the stage of the disease. Patients in stage I had a better outcome than patients in stage II disease. The importance of stage has been stressed repeatedly in the literature [3, 9, 13] but differences in survival between stages I and II was not statistically significant in all the reported series [6].

The survival analysis of the present study suggests that patients with PE-NHL of the Waldeyer's ring have a poorer prognosis than patients with PE-NHL of all other sites of the head and neck evaluated as a group. This difference cannot be explained by differences in age, sex and histology. It can partially be explained by the relatively higher incidence of stage II disease in the primary WR lymphomas. Stage distribution, however, is not the only factor adversely affecting survival in the WR lymphomas. A difference in survival between the two groups (WR and non-WR) in favor of the non-WR group of patients was demonstrated when only stage I disease was analyzed.

A feature which may be related to the poor survival of the PE-WR lymphomas was the high incidence of distant extranodal relapses in this group of patients. The association of WR lymphoma with lymphomas of other extranodal sites, particularly the GI tract, at presentation or in relapse has been emphasized by many authors [9, 14, 15]. No case of GI involvement was detected when our patients were first evaluated at presentation, though upper GI tract endoscopy was performed routinely. In contrast, 6 of 12 patients subsequently developed clinical GI tract involvement and 2 more patients lung involvement. This behavior may be an expression of the homing phenomenon [16], but the exact mechanism remains unclear.

The above data suggest that the primary WR lymphomas constitute a rather distinctive group of lymphomas differing in biologic behavior from the other primary extranodal sites of the head and neck.

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