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Primary Extranodal and Nodal Non-Hodgkin's Lymphoma

A Survey of a Population-based Registry

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Abstract—*In a population-based registry, there were 580 patients with non-Hodgkin's lymphoma (NHL); 236 had primary extranodal lymphoma (41%). The initial localization of the primary extranodal lymphomas varied markedly, although 36% were primary gastrointestinal lymphomas. Histological classification was performed by a regional panel of pathologists according to the Kiel Classification and the International Working Formulation. Twelve per cent of the patients with nodal NHL had a localized disease in contrast to 40% with primary extranodal NHL. Low grade lymphomas were encountered in 30 and 10% of the patients with primary nodal and extranodal NHL, respectively. Recurrence-free survival rate for patients with localized low-grade malignancy and disseminated intermediate grade NHL is significantly better for extranodal lymphoma than for nodal NHL. Patients with disseminated high-grade extranodal NHL had the worst prognosis of all. We conclude that primary nodal and primary extranodal lymphomas should be considered as distinctive and separate entities.*

INTRODUCTION

As A RULE malignant lymphomas are defined as neoplasms of lymph nodes and other lymphoid tissues, such as the tonsils, Waldeyer's ring, thymus and spleen. Nevertheless, a substantial percentage of non-Hodgkin's lymphomas originate at other sites such as the gastrointestinal tract, skin, lung, orbit and testis, and are therefore referred to as primary extranodal tumours.

The relative frequency of primary extranodal non-Hodgkin's lymphomas (P-EN NHL) among patients with non-Hodgkin's lymphoma suggests that there is a difference in incidence between countries: Israel 36% [1], Finland 28% [2], Italy 48% [3] and U.S.A. 24% [2].

Despite the relative predominance of P-EN NHL, information on the subject is rather sparse in the literature. These tumours are distributed throughout in the body and it is difficult to assemble a series representative of a single site. Moreover, a comparison of various series reported in the literature is very difficult due to a lack of uniform criteria for both the definition and the registration of extranodal lymphomas as well as the use of different systems for clinical staging and histological classification.

However, until now it has not been clear whether lymphomas of nodal and extranodal origin differ in natural history as well as biological behaviour.

This series represents data on nodal and extranodal NHL lymphomas collected prospectively from a population-based registry. The aim of regis-

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tration was to evaluate clinical and histological presentation, course and survival of all new cases of NHL retrospectively.

PATIENTS AND METHODS

A population-based registry of all new cases of NHL within the region (1.58 million inhabitants) of the Comprehensive Cancer Centre West (CCCW) in The Netherlands was started on 1 June 1981. The registry was set up by an NHL Study Group consisting of 45 specialists from the 15 hospitals in the region while data collection and quality controls were carried out by registrars of the CCCW. Patients with mycosis fungoides, acute lymphoblastic leukaemia, classic chronic lymphocytic leukaemia and multiple myeloma as well as those diagnosed post mortem were excluded from the study.

Sites of NHL involvement were considered primary extranodal when the patient's symptoms were caused mainly by extranodal NHL at initial clinical examination. When organ involvement was diagnosed during staging procedures or in the course of disease, the site was not considered a *primary* extranodal localization. Patients who did not have primary extranodal NHL were presumed to have nodal NHL. Primary mesenterial lymph node localizations were considered nodal lymphomas.

There is still controversy about whether tonsils and Waldeyer's ring should be considered primary extranodal or nodal involvement. The pathologist's point of view [4] is to consider these sites as nodal while the clinician classifies them as extranodal [5, 6]. For purposes of analysis, *primary* localizations in the tonsil, and Waldeyer's ring, were considered sites of extranodal NHL in this study.

To fulfill the requirement of a uniform system of classification, a panel of four pathologists reviewed newly diagnosed cases weekly. Tumours were classified only when frozen sections were available for additional immunological and enzyme histochemical studies [7]. NHL was classified according to the Kiel Classification System [8] with some modifications, i.e. intermediate lymphocytic lymphoma, defined according to Weissenburger *et al.* [9], and true histiocytic lymphoma, according to Van der Valk *et al.* [10], were considered separate entities. In addition, according to the International Working Formulation [11], each lymphoma was graded as a low, intermediate or high-grade malignancy.

Patients were staged according to the Ann Arbor Classification system [12], based on physical examination (Waldeyer's ring included), surgical and/or endoscopy reports and additional examinations such as a bone marrow biopsy, chest X-ray (minimal requirement), CT scan of the abdomen or lymphangiography and isotopic scans of the liver and spleen. The minimal requirements for *adequate* clinical staging can be summarized as sufficient data on all lymph node localizations (including the tonsils) as well as the state of the liver, spleen, lung and bone marrow. When one or more examinations had not been performed, patients were considered not to be staged adequately. Cases of II_E gastrointestinal and mesenterial NHL were subdivided, according to Musshoff [13], into stage II_{1E}, involvement of confluent regional lymph nodes (mesenteric and paragastric), and stage II_{2E}, involvement of regional but non-confluent lymph nodes (para-aortic, parailiacal and inguinal). Other extranodal stage II tumours were not subdivided.

Treatment, as agreed upon by the Study Group, depended on the stage and histological classification of the lymphoma. Patients with localized lymphomas (stage I_E–II_E) received radiotherapy (35–50 Gy to involved fields). When chemotherapy was administered the regimen consisted of CVP [cyclophosphamide (300 mg/m^2 orally on days 1–5), vincristine (1.4 mg/m^2 intravenously on day 1), prednisone (60 mg orally on days 1–5)] for low-grade NHL stages III and IV or CHOP [cyclophosphamide (750 mg/m^2 intravenously on day 1), Adriamycin® (50 mg/m^2 intravenously on day 1), vincristine (1.4 mg/m^2 intravenously on day 1), prednisone (60 mg orally on days 1–5)] for stages II, III and IV intermediate and high-grade NHL. Radiotherapy was given for bulky tumours (>5 cm diameter) or persistent lesions after chemotherapy. Lymphoblastic NHL was treated as acute lymphoblastic leukaemia with induction, consolidation and maintenance therapy and intrathecal methotrexate.

Response to treatment was assessed according to standard criteria, restaging procedures were required.

Survival time and recurrence-free survival (RFS) time were calculated from the date of diagnosis of the disease. Death due to the tumour was considered the end-point for survival, while relapse of NHL was also taken into consideration for RFS. Survival curves were compared using the log-rank test.

RESULTS

General

From 1 June 1981 until 1 September 1986, 640 new cases of NHL were diagnosed and registered: 580 were evaluable; 30 were lost to follow-up and 30 had incomplete registration forms.

Of the 580 evaluable patients, 236 had primary extranodal (P-EN) NHL (41%) and 344 nodal NHL (59%). Twenty-six cases of extranodal NHL originated in the tonsil and 11 in Waldeyer's ring. Neither primary thymus nor primary spleen lymphoma was encountered (Table 1). The most frequent P-EN NHL site was the stomach (23%).

Table 1. *Localization of site specific primary extranodal lymphoma* (n = 236)

	Total		Total
ENT localization	49	*Others*	101
Tongue	5	Gallbladder	1
Parotis	3	Lung	9
Floor of mouth	1	Pleura	2
Buccal mucosa	1	Bone marrow only	33
Tonsil	25	Bone	6
Waldeyer's ring	11	Connective tissue	5
Nose, sinus	3	Skin (other than mycosis fungoides)	4
		Breast	5
*Gastrointestinal localizations**	86	Ovary	1
Stomach	54	Prostate	1
Small intestine	13	Testis	4
Colon	14	Kidney	2
Rectum	2	Orbit	5
Multiple GI sites	3	Lacrimal gland	1
		Conjunctiva	1
		Brain, spinal cord, etc.	15
		Thyroid gland	4
		Multiple organs	2

*Ten mesenterial lymph nodes excluded.

Primary gastrointestinal NHL accounted for 36% of all P-EN NHL.

The distributions by age and sex of nodal and extranodal NHL were nearly similar (Table 2).

Stage

The distribution according to clinical stage is summarized in Table 3; 40% of patients with P-EN NHL had a localized (stage I_E or II_{1E}) disease, compared with 12% of patients with nodal NHL ($P < 0.01$).

In the case of stage IV P-EN NHL the patients usually exhibited symptoms of the involvement of one organ but during staging procedures it appeared that an adjacent organ or the bone marrow was involved. Evaluation of the required examinations for adequate clinical staging reveals that all these procedures were performed in 67–68% of all NHL cases, with no significant difference between the nodal and P-EN NHL (Table 2). In the other cases (32–33%) some examinations were not done (for example no bone marrow biopsy in case of stage III or IV disease because of other NHL manifestations).

Histology

Table 4 shows the histological subtypes according to the Kiel Classification System and the grade of malignancy of the Working Formulation. It should be noted that 34% of P-EN NHL and 14% of nodal NHL could not be classified because of the lack of frozen sections. Only 15% of the classified P-EN NHL were low-grade malignancies compared to 34% of nodal NHL ($P < 0.01$). In the P-EN NHL group, the immunoblastic, Burkitt's and lymphoblastic lymphomas were diagnosed relatively more often than in the group with nodal NHL. Of the patients with P-EN NHL, 25% presented initially with stage $I_E + II_{1E}$ intermediate or high-grade

Table 2. *Characteristics of patients with extranodal and nodal lymphoma*

Characteristics		Extranodal NHL $n = 236$	Nodal NHL $n = 344$	
Sex	M/F	106/130	174/170	
Age:	median in years	65	64	
	range	4–94	0–91	
Evaluation				
(1)	adequate clinical staging	158 (67%)	234 (68%)	
(2)	adequate pathological investigation	135 (57%)	289 (84%)	$P = 0.0001$
(3)	both (1 + 2)	100 (42%)	196 (57%)	$P = 0.0007$

Table 3. Stage by grades of malignancy for patients with extranodal and nodal lymphomas

	Working formulation									
	Extranodal NHL					Nodal NHL				
Stage	Low	Int*	High	Rest†	Total	Low	Int	High	Rest	Total
I	6	37	12	25	80	18	10	5	6	39
II	2	20	2	6	30	7	34	7	8	56
II_1	2	5	4	3	14	2	—	—	—	2
II_2	2	7	4	4	17	—	—	2	2	4
III	1	5	—	4	10	31	28	10	7	76
IV	10	19	10	46	85	44	73	18	32	167
Total	23	93	32	88	236	102	145	42	55	344

*Int: intermediate grade malignancy.
†Rest: some were classified (for example Lennerts' lymphoma) but not according to the Working Formulation; most of the cases were not classifiable.

Table 4. Histological classification (according to a modified Kiel Classification System as well as the Working Formulation) of extranodal and nodal NHL

	Extranodal	Nodal
Classified	155 (100%)	297 (100%)
Low grade	23 (15%)	102 (34%)
Lymphocytic	—	10
Lymphoplasmocytoid immunocytoma	14	15
Follicular centroblastic/centrocytic	9	77
Intermediate grade	93 (60%)	145 (49%)
Diffuse centroblastic/centrocytic	12	25
Centrocytic	4	3
Intermediate lymphocytic	2	15
Follicular centroblastic	5	9
Diffuse centroblastic	60	78
Immunocytoma pleomorphic	10	15
High grade	32 (21%)	42 (14%)
Immunoblastic	16	18
Lymphoblastic	31	3
Burkitt	7	2
True histiocytic	6	9
Others	7 (4%)	8 (3%)
Not classified	81	47
Total	236	344

malignancy while this combination was encountered in only 4% of the cases of nodal lymphoma (Table 3).

Treatment

Although patients were treated according to regional guidelines, it is worthwhile to evaluate the proposed protocols. This was done for patients with a disseminated (stage II, II_2, III, IV) intermediate and high-grade NHL. Fifty-four per cent of the patients with nodal NHL and 50% with P-EN NHL were treated initially as proposed by the NHL Study Group; in both NHL groups the percentage of complete remission was 40. Considering all patients ($n = 580$) complete remission was achieved in 48 and 44% of all P-EN ($n = 236$) and all nodal ($n = 344$) NHL patients, respectively.

Survival

There was no significant difference in the 4-year survival rate between patients with nodal and P-EN NHL (48% and 52%, respectively; $P = 0.2$). The recurrence-free survival times for the two groups were similar; 4-year recurrence-free survival rate was 20% for patients with nodal NHL (18 patients at risk) and 27% for those with P-EN NHL (14 patients at risk). Analyses of survival according to stage showed that patients with stage I had a similar survival compared to patients with stage II_1 NHL; survival of patients with stage II, II_2, III and IV did not differ according to stage. For this reason we grouped stages I and II_1 as localized and stages II, II_2, III and IV as disseminated NHL. Patients with localized nodal NHL had a better survival than those with localized P-EN NHL (Fig. 1; $P = 0.01$). No difference in survival time and recurrence-free survival time was found between the groups with disseminated NHL. The 4-year survival rate for patients with localized P-EN NHL and nodal tumours was significantly better than that for patients with disseminated NHL ($P = 0.0002$ and 0.03 respectively). Adequate clinical staging procedures according to the protocol adopted by the Study Group led to significantly longer survival; this applied to patients with nodal ($P = 0.01$) as well as P-EN NHL ($P = 0.02$).

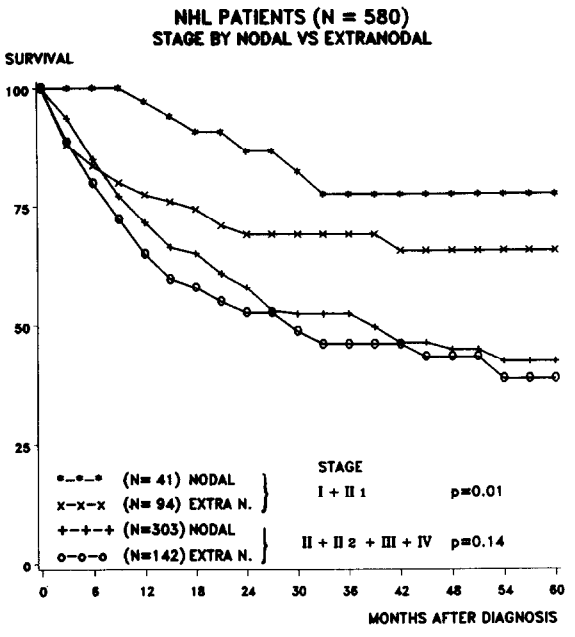

Fig. 1. Survival for patients with primary extranodal and primary nodal NHL with localized (stage I + II_1) and more disseminated disease (stage II, II_2, III + IV).

Remarkable was the discrimination in survival—and recurrence-free survival—obtained with the Working Formulation for patients with various grades of P-EN NHL (Fig. 2). This was not as pronounced for patients with nodal NHL since the survival times for intermediate and high-grade malignancies were identical (Fig. 2) and the recurrence-free survival times were similar for all three grades of malignancy.

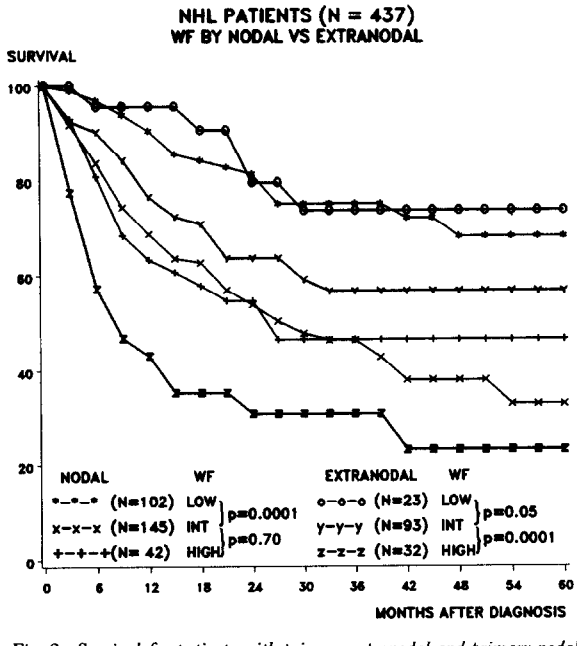

Fig. 2. Survival for patients with primary extranodal and primary nodal NHL by grade of malignancy according to the Working Formulation.

Since the distribution of stages differed for each of the three grades of malignancy for both nodal and extranodal NHL, six groups were formed by combining localized and disseminated stages with low-, intermediate- and high-grade malignancies. Survival times for nodal and P-EN NHL per subgroup are shown in Figs. 3A, B and C. Stage gave a better indication of survival times for patients with intermediate-grade malignancy nodal NHL and low- or high-grade extranodal NHL. Where stage was discriminatory with respect to survival for some grades of malignancy of nodal NHL it was not for extranodal lymphoma and vice-versa.

The survival time for patients with localized nodal NHL did not differ from that of patients with extranodal lymphoma by grade of malignancy; but it differed significantly in patients with disseminated high-grade nodal lymphoma compared with disseminated high-grade extranodal NHL ($P = 0.002$) in favour of the nodal NHL (Figs. 3A, B and C).

There was a significant difference in the recurrence-free survival rate between localized and disseminated low-grade lymphoma for nodal and extranodal NHL ($P = 0.02$ and 0.0001, respectively). The RFS of intermediate-grade disseminated nodal and extranodal NHL differed significantly ($P = 0.01$) in favour of the P-EN NHL. However, the recurrence-free survival rate for disseminated high-grade lymphoma was significantly better for patients with a nodal NHL than for those with an extranodal lymphoma ($P < 0.007$).

When primary tonsilar and Waldeyer's NHL were considered as a separate group and excluded from P-EN NHL, their clinical stage and histological classification exhibited a closer resemblance to those of P-EN NHL. The survival time and recurrence-free survival time, listed according to stage and histology, for nodal NHL and primary tonsilar and Waldeyer's ring NHL were, however, equal.

DISCUSSION

An advantage of a population-based registry vs. a hospital registry is that data in the former are not biased by referal policy. A major disadvantage, however, could be a lack of common treatment protocols. This disadvantage was partially eliminated in this analysis because the NHL Study Group of the CCCW reached consensus on treatment before the registry was started.

At first presentation P-EN and nodal NHL differ in clinical stage and histological classification. P-EN NHLs are more localized diseases (40% in stage I_E or II_{1E}). Nevertheless primary extranodal lymphomas do not necessarily remain localized throughout the course of the disease; moreover, in at least some of the disseminated cases included in

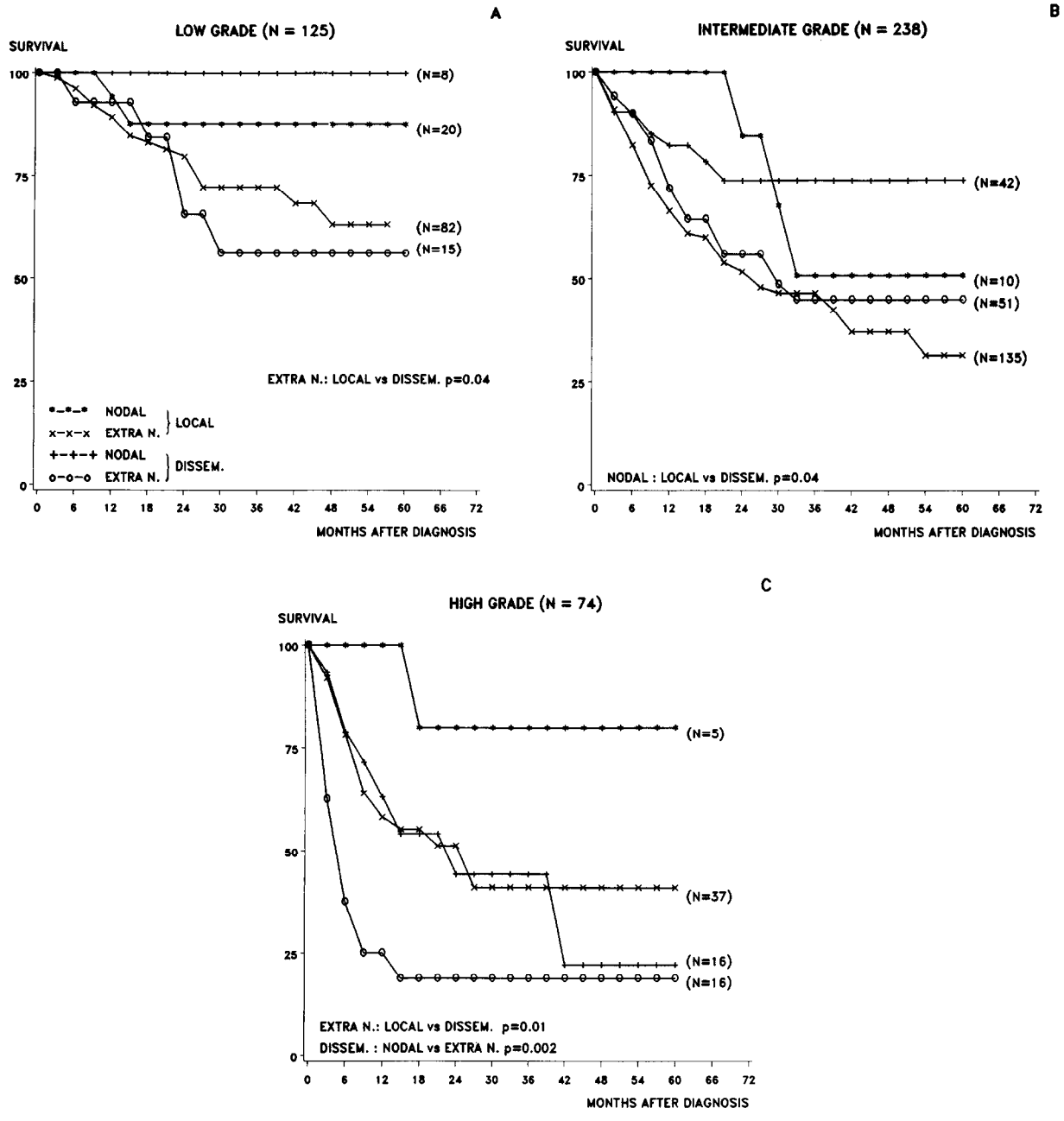

Fig. 3. Survival for patients with nodal and extranodal NHL by stage (localized and disseminated) and grade of malignancy (A = low, B = intermediate and C = high). Only the P *values* < 0.05 *between the different groups are indicated.*

the nodal group, the disease may well have begun at an extranodal site. P-EN NHL was diagnosed as a low-grade malignancy less often than nodal NHL (15% vs. 34%, respectively) and also could be classified less often (34% vs. 14%), which might be explained by the fact that a malignant lymphoma in a primary extranodal localization is generally an unexpected diagnosis and the patient is frequently examined first by a general surgeon instead of a haematologist or oncologist. Although 41% of NHLs are extranodal, these tumours are so widely distributed throughout the body that they still represent a small percentage of the tumours occurring at a particular site.

Comparable data are scarce at the moment. This is partly because most hospital registries and many other population-based cancer registries are based on older International Classifications of Disease (ICD) systems [14–16] for coding of the diseases, and these systems do not differentiate between primary nodal NHL and P-EN NHL (because of the lack of specific codes). A special coding tool for cancer registries, published in 1976 by the World Health Organization, is called the *International Classification of Diseases for Oncology (ICD-O)* [17]. Although *ICD-O* makes the registration of both nodal and extranodal NHL possible, variations in national and international definitions of primary

extranodal lymphoma still hamper the comparison of data.

Special attention should be paid to staging procedures for classification of P-EN NHL. Musshoff [13] proposed splitting stage II_E P-EN NHL into II_{1E} and II_{2E} disease depending upon whether regional lymph nodes near the organ (II_{1E}) or farther distant (II_{2E}) were involved. The relevance of stage II_{1E} and II_{2E} to survival for gastrointestinal NHL has been confirmed many times [18–20]. Our analysis of primary gastrointestinal NHL supports these findings and we concluded that stage II_{2E} gastrointestinal NHL should be considered a systemic rather than a local disease (to be published). Except for gastrointestinal NHL the stages of P-EN NHL were not further subdivided but it would be worthwhile to do so for patients with stage II_E P-EN NHL in order to analyse the difference in survival between stage II_{1E} and II_{2E}. If the difference found for gastrointestinal NHLs also applies for the remaining P-EN NHLs, stage II_{2E} P-EN NHL should be considered a systemic lymphoma instead of a localized one. A multidisciplinary approach would be needed to implement such staging procedures widely. As far as nodal NHL is concerned, only stage I should be considered a local disease, because stage II has as poor a prognosis as stage III and IV lymphomas.

A striking difference in survival and RFS between nodal and extranodal lymphomas was found when the patients were grouped according to grade of malignancy. This might be explained by a difference in distribution according to clinical stage or by the fact that P-EN NHL does not behave similarly to nodal NHL, even when the grade of malignancy is the same. When subgroups of localized and disseminated low-, intermediate- and high-grade NHL were formed, patients with disseminated high-grade P-EN NHL had the worst prognosis of all. The recurrence-free survival rate was better, however, for patients with localized low-grade and disseminated intermediate-grade extranodal lymphomas compared to nodal NHL. For these reasons a difference in distribution of stages cannot be fully responsible for the discriminatory effect of the grades of malignancy according to the Working Formulation.

Although primary tonsilar and Waldeyer's ring NHL are mostly considered as extranodal NHL, the survival and RFS are equal to that of nodal lymphoma.

The differences in presentation (clinical stage and histological classification: Tables 2–4), survival (even with equal histology: Fig. 3) and relapse-free survival form a strong indication that primary nodal and extranodal NHL are distinctive and separate entities. Primary tonsilar and Waldeyer's ring NHL should be considered as nodal lymphomas as proposed by others [21, 22].

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