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NON-HODGKIN'S LYMPHOMA IN NORTHERN SWEDEN

A retrospective analysis of morphologic diagnosis and stage in a material from the Swedish Cancer Registry

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Morphologic diagnosis and clinical stage were studied in a retrospective material of non-Hodgkin's lymphomas comprising 352 patients diagnosed 1978 until 1982 and reported to a regional cancer registry. Classification was made according to the original Kiel classification. Patients who could be classified as belonging to low- (46%) or high-grade (47%) malignancy groups (n = 337) were further studied. The median age was high, 65 years, which probably reflects the low degree of selection in a regional register material compared to most hospital register-based materials. The proportion of stage I cases was rather high, in low-grade lymphomas 24%, and in high-grade 39%, which can be attributed to incomplete staging procedures in old patients. The aim of the study was to illustrate the distribution according to morphologic subclasses and clinical features in a material with a low degree of patient selection.

Comparisons of clinical materials of patients with non-Hodgkin's lymphomas (NHL) are hampered by several factors, among which one is the difficulty in obtaining a uniform and generally accepted histopathological classification. The Rappaport classification system (1), based on morphological criteria, is since the beginning of the eighties replaced by newer systems. Today, several centres in Europe use the Kiel classification (2–4), whereas most centers in the USA use the classification by Lukes & Collins (5) or the so-called 'working formulation' (6). This circumvents retrospective studies without re-examinations of histopathologic material. It also makes comparisons of materials based on different classification systems difficult. Another factor is different levels of selection in the materials. The majority of patients with NHL are elderly persons, more than 60 years old. A low median age probably reflects a substantial degree of selection. The distribution according to different morphological subgroups and clinical stages at presentation may also vary considerably due to differences in patient selection. There are few published clinical materials with a low degree of selection. Therefore it was considered to be of interest to analyze a material of patients including all known cases with NHL within a geographical region, and to study their histopathological and clinical features.

The Swedish Cancer Registry was established in 1958. The national registration is decentralized into six regional registers, in Northern Sweden since 1978. It is obligatory on clinicians, pathologists and cytologists to report every patient with a malignant diagnosis to the regional register. Studies on completeness of the national register was made by Mattsson & Wallgren (7) who studied non-notified cancer cases recorded on death certificates in 1978. The total deficit was found to be 4.5%, <2% when the diagnosis was morphologically and 30% when it was only clinically confirmed, especially in elderly patients. In lymphoma the deficit was 3.7%, in myeloma 16% and in leukemia 18%. Martinsson et al. (8) reported a higher deficit, 6.7%, in malignant lymphoma. They also pointed out the difficulties in calculating the true incidence from

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death certificates, as many patients die from intercurrent diseases without lymphoma being reported as underlying cause of death. Nevertheless, these studies demonstrated that a register-based study material of NHL in Sweden probably has a deficit of $<10\%$.

Material and Methods

All cases from 1978 to 1982 in 3 counties (Norrbotten, Västerbotten and Västernorrland) reported to the Regional Cancer Registry for Northern Sweden were collected. In this area there were approximately 800 000 inhabitants, i.e. 9% of the population in Sweden. During the actual time period malignant diseases were registered according to ICD 8 (9). The age standardized incidence of NHL in Sweden, not including chronic lymphocytic leukemia (CLL), was in 1978–1982: males 11.7 and females 7.7 cases per 100 000 per year with the population in Sweden in 1970 used as standard (10). The corresponding figures for our material were: males 12.6 and females 7.5 cases per 100 000 per year. During the period 1978–1982, 411 patients with NHL (ICD 8 code 200,202) and 142 patients with chronic lymphocytic leukemia (CLL) (ICD 8 code 204,15) had been reported to the registry.

All histologic and/or cytologic material was reviewed. Immunohistochemical methods had been used in a minority of the patients before 1982. The diagnosis was based on the original Kiel classification (2, 3). In each case a consensus diagnosis was reached after review by two of the authors (UD & GR). In 15 patients cytologic specimens only were available which, however, allowed adequate subclassification and these patients were included in the study. A separate review of patients reported to the registry as Hodgkin's disease had previously been performed in the same population (11). At this review, 11 of these patients had been re-evaluated as NHL and they were included in the present material. A prerequisite for inclusion in the present study was a diagnosis based on histologic and/or cytologic material. It is controversial whether CLL should be classified as lymphocytic (LC) NHL or as a special hematological disease. Most CLL diagnoses are based on a leukemic blood picture with more than $5 \times 10^9/l$ lymphocytes with or without typical bone marrow smears (12). We have chosen to exclude 127 CLL cases who were included in another study (unpublished study by Erlanson et al.). Of the patients with CLL diagnosis, 15 were fulfilling the criteria for inclusion in our study (histologic and/or cytologic material from other tissue than bone marrow available), and were thus included. On the other hand, non-bone marrow tissue specimen was lacking in 13 patients with a diagnosis of NHL with leukemic blood picture, and consequently these cases were considered as CLL and excluded from the present study. A further 55 patients were excluded due to results of the morphological review, namely: Waldenström's macroglobulinemia with diagnosis based upon clinical parameters (16 pts), other malignancies (17 pts), benign diagnosis as lymphadenitis, dermatitis (12 pts). Ten cases had technically insufficient histopathological material and were therefore excluded. After the histopathological review, 369 patients remained in the study.

All clinical records were reviewed. Seventeen patients were excluded: post mortem diagnosis after autopsy (11 pts), inadequate clinical records (3 pts), missing files (2 pts), lost to follow-up (1 pt). This left 352 evaluable patients for further study.

Of the evaluable patients 303/352 (86%) were referred to the department of oncology in Umeå, mostly for initial investigation and treatment. Many of them were later followed at the local hospitals. Forty-nine patients were treated in local hospitals.

Based on data from the reviews staging was performed according to the Ann Arbor classification (13). The underlying material for this staging was, however, not uniform. Chest radiogram was available in 93% of the patients. The abdominal lymph nodes were studied by lymphography (111 pts), sonography (27 pts) and/or by computer tomography (from 1981, 44 pts) in 165/352 (47%) of the patients. Diagnosis was obtained by laparatomy in 35 cases, generally because of bulky abdominal disease or gastrointestinal involvement. Gastric lymphoma was diagnosed after gastroscopy in 5 cases. Bone marrow investigation was made in 305/352 (87%) of the patients. The staging procedure was inadequate especially in elderly patients. Staging of retroperitoneal/abdominal lymphoma in patients younger and older than 70 years was made in 69% vs. 40% and bone marrow investigation in 91% vs. 81% respectively.

Results

The median age of the 352 patients was 65 years (range 1–98 years). The sex ratio (males/females) was 1.3:1. The age distribution is shown in Fig. 1. Two hundred and thirty patients (65%) were 60 years or older and 132 patients (37%) were older than 70 years.

Low-grade (LG) and high-grade (HG) lymphomas had similar age distribution with the exception that all patients with LG lymphomas were older than 30 years. In the LG follicular and small cell centrocytic lymphomas the median age was lower than in the diffuse LG lymphomas, 57–59 vs. 63–70 years (Table 1).

One hundred and sixty-two cases (46%) were classified as LG and 165 (47%) as HG lymphomas. Twenty-five patients were classified as belonging to subtypes with debatable relation to NHL malignancy grade (Table 2).

Among 337 patients classified as LG or HG, about one-third were in stage I and two-thirds in stages II–IV at presentation. In LG lymphomas, 33/53 (62%) of the patients with small cell diffuse lymphomas (LC and IC) were in stage IV while the stages were more equally distributed

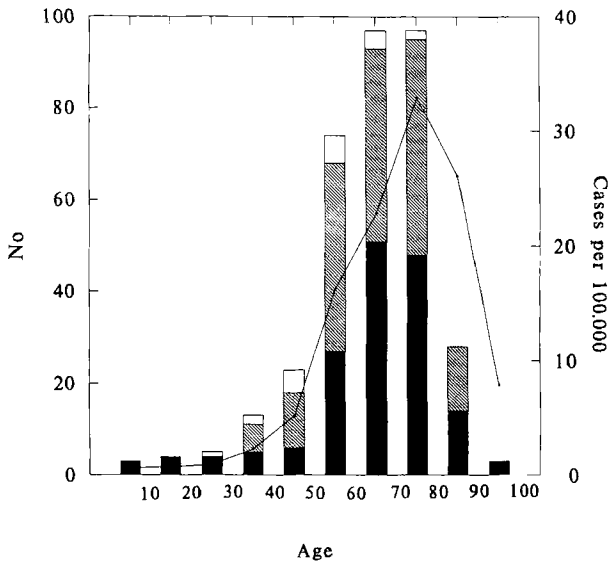

Fig. 1. Age distribution in 352 patients with non-Hodgkin's lymphoma. Low grade: ▨, High grade: ■, Other lymphomas: □. The continuous line represents the age-specific incidence rates per 100 000 based on the same patients.

Table 1

Distribution of morphologic subclasses

Kiel classification	n	%	Median age years (range)	M/F
Low grade (LG)				
LC	26	7	70 (54–78)	2.9:1
IC	27	8	67 (44–75)	2.4:1
CC				
Small cell (sc)	5	2	59 (40–70)	5:1
Large cell (lc)	8	2	62 (37–84)	1:1
CB/CC				
Foll	50	14	58 (32–86)	1:1
Foll + diff	8	2	57 (53–73)	1:1
Diff	30	9	70 (38–82)	1.3:1
Mycosis fungoides	5	1	65 (61–83)	0.7:1
Unclass. low grade NHL	3	1	75 (52–78)	
Total low grade NHL	162	46	65 (32–88)	1.6:1
High grade (HG)				
CB	73	21	67 (26–89)	1.5:1
IB	54	15	65 (19–93)	1.1:1
LB	9	3	10 (1–64)	1.3:1
Unclass. high grade NHL	29	8	67 (19–98)	1.4:1
Total high grade NHL	165	47	67 (1–98)	1.3:1
Other lymphomas				
True histiocytic lymphoma	5	1	57 (39–71)	0.3:1
AILD	10	3	61 (41–86)	0.7:1
Lennert's lymphoma	3	1	62 (49–94)	2:1
Unclassifiable lymphoma	7	2		
Total other lymphomas	25	7	61	0.8:1
All patients	352		65	1.3:1

Abbreviations: LC = Lymphocytic; IC = Immunocytic; CC = Centrocytic; CB = Centroblastic; CB/CC = Centrocytic/centroblastic; IB = Immunoblastic; LB = Lymphoblastic; Foll = Follicular = Nodular; Diff = Diffuse; AILD = Angioimmunoblastic lymphadenopathy

in the lymphomas with follicular histology. In HG lymphomas stage I was the most common; 65/165 pts (39%). Table 2 summarizes the clinical stages according to malignancy grade.

Ninety-four of the 352 patients presented with systemic (B) symptoms: 33/162 (20%) of LG, 47/165 (28%) of HG and 14/25 (56%) of the other lymphomas. B symptoms were more frequent in patients with generalized stages (II–IV) than in those with localized disease (stage I), as demonstrated in Table 2.

Bone marrow investigation was performed in 305 of 352 (87%) patients; by histologic examination in 278 cases and by smear in the other cases. Bone marrow involvement was seen in 52/146 (36%) of LG, in 15/136 (12%) of HG and in 4/23 (17%) of the other lymphomas. Table 3 shows the bone marrow involvement in different lymphoma subgroups.

Clinical extranodal involvement at presentation was diagnosed in 306 sites in 185 (51%) of the 352 patients (Figs 2 and 3). Among LG lymphomas in stage I 16/38 (37%) were extranodal compared to 37/65 (57%) of stage I HG patients (Table 2). Extranodal involvement was seen in many different organs, in LG lymphomas predominantly in bone marrow and spleen, and in HG lymphomas in many different organs as shown in Table 4.

In a retrospective study of clinical records it is difficult to get a more exact assessment of the tumor volume. Large tumors were often compared to different objects (e.g. a man's fist, a child's head, a grapefruit or a tennis ball). From the files it was, however, possible to roughly approximate the size of the tumor if larger than 10 cm in diameter. Bulky lymphoma was diagnosed in 61/332 (19%) of all cases, in 26/157 (17%) of the LG and in 35/165 (21%) of the HG patients. In nodal disease, 48/66 (73%) of the cases presented with bulky lymphoma in the mesenteric and/or retroperitoneal region (30 patients with palpable mass or radiologic diagnosis and 19 with diagnosis at laparatomy). Among the 50 follicular CB/CC lymphomas all bulky lymphomas (8 pts) were located in the retroperitoneum

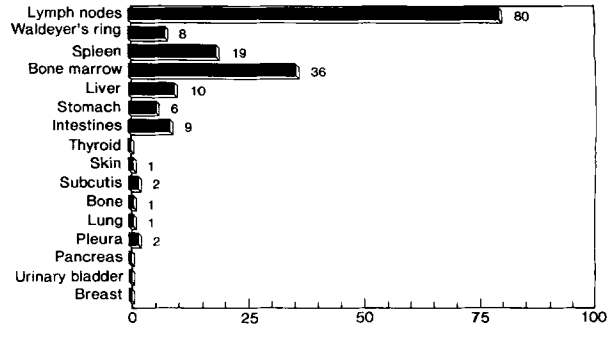

Fig. 2. Initial organ involvement. Low-grade lymphoma stages I–IV. (n = 157)

Table 2

Clinical stages and systemic (B) symptoms according to morphological diagnosis (number of patients with extranodal lymphoma stage I–II in parenthesis)

	Total	Stage			
		I (E) n (n)	II (E) n (n)	III n	IV n
Unclass LG	3	2 (2)			1
LC	26	5 (2)	2	2	17
IC	27	6 (4)	3 (1)	2	16
CC					
sc	5				5
lc	8	2 (1)	2	2	2
Cb/cc					
Foll	50	14	11 (1)	12	13
Foll + Diff	8	1	2 (1)	4	1
Diff	30	8 (5)	8 (3)	3	11
Myc. fungoides	5	2 (2)			3
Low grade	162	40 = 25%	28 = 17%	25 = 15%	69 = 42%
B-symptoms	33 = 20%	0	3 = 11%	6 = 24%	24 = 35%
Unclass hG	29	16 (8)	3	4	6
CB	73	29 (16)	13 (6)	12	19
IB	54	19 (13)	8	10	17
LB	9	1	2	2	4
High grade	165	65 = 39%	26 = 16%	28 = 17%	46 = 28%
B-symptoms	47 = 28%	3 = 5%	11 = 42%	11 = 39%	22 = 48%

Abbreviations: LC = Lymphocytic; IC = Immunocytic; CC = Centrocytic; CB = Centroblastic; CB/CC = Centrocytic/centroblastic; IB = Immunoblastic; LB = Lymphoblastic; Foll = Follicular = Nodular; Diff = Diffuse; AILD = Angioimmunoblastic lymphadenopathy

Table 3

Bone marrow infiltration

	Number with bone marrow infiltration/ number examined	Number not examined
LC	15/24	2
IC	12/24	3
CC		
small cell	4/5	
large cell	1/7	1
CB/CC		
Follicular	9/47	3
Foll. + Diff.	1/8	
Diffuse	9/27	3
Myc. fungoides	0/2	3
Unclass. LG	1/2	1
CB	7/60	13
IB	4/46	8
LB	2/9	
Unclass. HG	2/21	8
Other lymphomas	4/23	2
Total	71/305	47

and/or mesenterium. Eleven patients presented with bulky intestinal lymphoma, and in 6 of them it was located in the ileocoecal region (Table 4).

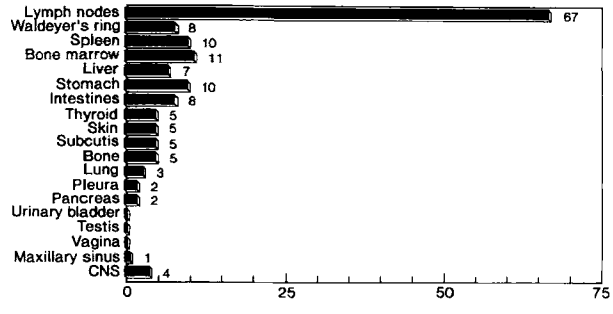

Fig. 3. Initial organ involvement. High-grade lymphoma stages I–IV. (n = 165)

Discussion

This report describes a material of lymphoma patients from a defined geographic area, including all patients with a histopathologically verified diagnosis. The median age in our material was 65 years, which is somewhat higher than in most European studies (14–21) and significantly higher than in American materials, where the median age is often around 55 years (6, 22–24), which probably reflects a higher grade of selection. The age distribution corresponds well with most cancers, with about 50% of all cases occurring in ages above 65 years (25).

Table 4

Sites of extranodal lymphoma (bulky lymphoma in parenthesis)

	Low grade n	High grade n	Total n
Bone	2	9	11
Bone marrow	52	15	67
Brain		6	6
Breast	1		1
Intestines	14 (4)	14 (7)	28 (11)
Liver	16 (1)	11	27 (1)
Lung	1	4 (1)	5 (1)
Maxillary sinus		2	2
Pancreas	1	6 (4)	7 (4)
Pleura	3	6	9
Skin	8	9	17
Spleen	30 (4)	17 (3)	47 (7)
Stomach	10	17	27
Subcutis	3	9 (2)	12 (2)
Testis		1	1
Thyroid	1	8 (2)	9 (2)
Urinary bladder	1	1	2
Vagina		1	1
Waldeyer's ring	13	14	27
Total	156 (9)	150 (19)	306 (28)

The number of LG and HG lymphomas were about equal in our material. In this respect, it is difficult to compare our results with other materials as some authors have included CLL as proposed in the Kiel classification (14, 20) while the principle as regards inclusion of CLL or not is unclear in many reports (16, 18, 19). The staging of CLL is often different from malignant lymphoma which also may mirror reported differences in the clinical behavior (26).

In most materials from departments of oncology in Sweden, LC lymphomas represent only 4–8% of the NHL patients (15–17). CLL is in Sweden usually treated at hematological centers which explains why these patients were not included in the studies. Martinson et al. (8), including CLL in the LC lymphoma group, reported that LC represented 23% of their total NHL material from a defined geographical region. The indistinct borders between lymphomas and leukemias were also underlined by Shaerer et al. (27) who found different proportions of these entities in register materials from France and Switzerland.

The frequency of CC lymphomas varies greatly between different materials (4–15%) (6, 14, 19, 20, 28, 29). In Scandinavian materials this diagnosis is infrequent (1–4%) as was the case also in our study (8, 16, 17, 29). In 28% of our patients, a CB/CC lymphoma was diagnosed which is fairly comparable with most other materials. We included diffuse CB/CC lymphomas among the LG lymphomas as in the original Kiel classification.

The high proportion of unclassified HG lymphomas is compatible with the well-known difficulties of classifying the tumors with purely morphological methods. The proportion of CB (1–18%), IB (5–24%), and LB (5–18%) varies in different studies (6, 8, 13–20). However, if these subgroups are grouped together the variation is not particularly large which probably reflects differences in the morphological judgement.

As in another Swedish material (16) we observed a high proportion of cases in stage I. These figures are higher than in most other reported materials (6, 14, 18, 19, 22–24). It may reflect incomplete staging of many old patients in our material as well as differences in the selection of patients.

The proportion of patients with bone marrow involvement corresponds well to findings in other materials. Concerning involvement of different organs we could not find any consistent difference between our material and other reported materials although the staging procedure was incomplete, especially in the older patients (16, 18, 24, 30, 31). Among patients in stage I about one-third of the LG lymphomas and approximately 50% of the HG lymphomas were extranodal. Gastrointestinal involvement was the most common extranodal manifestation. The proportion of patients with systemic symptoms was high in our material which probably also reflects the low degree of selection that implied that many old and debilitated patients were included. In such patients it is often difficult to assess whether the systemic symptoms are due to lymphoma or to other causes.

In conclusion, the present study describes a material which encompassed all patients with NHL reported to a population-based cancer register. It demonstrates that NHL is a disease that mainly affects old patients. Review of the literature reveals varying proportions of patients in different subclasses of NHL. Although our study included many elderly patients the clinical features seem to be essentially comparable to other more selected materials. Different classification systems and indistinct borders between leukemia and lymphoma can largely explain differences in distribution of the subgroups. Consensus regarding the criteria for reporting NHL to cancer registries is demanded and could make data from different registries more comparable.

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