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Specialist Interest Articles

Clinicopathological Features and Prognostic Factors in Extranodal Non-Hodgkin Lymphomas

Francesco d'Amore, Bjarne E. Christensen, Hans Brincker, Niels T. Pedersen, Karen Thorling, Jørgen Hastrup, Mogens Pedersen, Mogens Krog Jensen, Preben Johansen, Erik Andersen, Bjarne Bach and Erling Sørensen on behalf of the Danish LYFO Study Group

In a Danish population-based non-Hodgkin lymphoma (NHL) registry, 1257 newly diagnosed NHL cases were registered over a 5-year period. Of these, 463 (37%) were extranodal. The gastrointestinal tract was the most common site of extranodal involvement (30% of the cases). Histologically, 44% of all extranodal NHL cases had high-grade, 17% intermediate and 27% low-grade features, while 12% were unclassified. The most common histological subtype (Kiel) was the centroblastic diffuse (23% of cases). 50% of all extranodal NHL were localised (stage I_E or II_E) and 27% had B symptoms. Site-specific features included a strong age-correlation for thyroid and testes lymphoma (>50 years) and a high prevalence of female cases in thyroid and salivary glands lymphomas (M/F 0.14 and 0.30, respectively). Overall 7-year survival for extranodal NHL was 46% (median 4.9 years). Poor prognosis patients could be identified by the presence of one or more of the following presentation characteristics: age >65 years, B symptoms, high-grade histology, disseminated disease, elevated s-IgA and hyperuricaemia. Relative risk values ranged from 2.1 for age and B symptoms to 1.7 for hyperuricaemia.
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INTRODUCTION

FROM AN epidemiological point of view extranodal non-Hodgkin lymphoma (NHL) is a poorly investigated heterogeneous group of neoplasms. In Western countries, studies from the last 2 decades have shown a considerable variation (15–48%) in the reported rates of patients presenting with extranodal NHL [1–4]. In developing countries the prevalance of extranodal presentation is probably higher [5].

The large majority of extranodal NHL (70–94%) will have a diffuse histological pattern, usually consisting of large cells [5–8]. Extranodal NHL may occur at any extranodal site. When regarded as an extranodal localisation, tonsils (or the whole Waldeyer's ring) are the commonest site of involvement followed by gastrointestinal tract, skin and bone [2, 3]. Rare primary localisations such as heart [9], skeletal muscle [10], adrenal gland [11] and extrahepatic bile-ducts [12] have also been reported.

Correspondence to F. d'Amore.
F. d'Amore, B.E. Christensen and H. Brincker are at the Department of Haematology and N.T. Pedersen is at the Department of Pathology, Odense University Hospital, 5000 Odense C; K. Thorling is at the Department of Oncology and Radiotherapy and J. Hastrup is at the Department of Pathology, Aarhus University Hospital, Aarhus; M. Pedersen is at the Department of Oncology and Radiotherapy, M.K. Jensen is at the Department of Haematology and P. Johansen is at the Department of Pathology, Aalborg Hospital, Aalborg; E. Andersen is at the Department of Internal Medicine, Viborg Hospital, Viborg; B. Bach is at the Department of Haematology, Aarhus County Hospital; and E. Sørensen is at the Department of Medical Physics, Aarhus University Hospital, Aarhus, Denmark.
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However, the majority of the existing studies focusing specifically on extranodal NHL are retrospective, based on archival material often collected over decades [2]. Moreover, problems with assessment of clinical stage and classification of histopathological findings have made comparison of results difficult. Thus, a more systematic knowledge of extranodal NHL is needed and should come from large, prospective and possibly population-based series, where bias due to patient selection or hospital referral policy can be avoided [13]. The aim of this study, to our knowledge the largest unselected series of extranodal NHL published to date, was to illustrate the clinicopathological features and prognostic factors of this particular group of lymphomas on the basis of a Danish population-based registry for NHL.

PATIENTS AND METHODS

A population-based registry of all new cases of NHL in western Denmark (Jutland and Funen, 2.7 million inhabitants) was started on 1 January 1983, and is still ongoing. All hospitals and pathological laboratories in the region participated through a study group consisting of 18 specialists from the three main regional referral centres. Excluded from the registry were cases of acute lymphoblastic leukaemia, chronic lymphocytic leukaemia and multiple myeloma. For the present study, the data from 1257 consecutive cases of NHL registered between January 1983 and 31 March 1988 were analysed.

Sites of disease

Cases were defined as extranodal NHL when they presented with disease at one or more extranodal sites and after routine

staging procedures (see *Clinical and histological assessment*), either did not have nodal involvement or a "minor" nodal component could be detected along with a clinically "dominant" extranodal one. A minor nodal or a dominant extranodal component were respectively defined as <25% or >75% of the total tumour volume, as estimated by routine clinical staging. It is debated whether tonsils and Waldeyer's ring should be considered as a nodal or an extranodal site [16]. In accordance with other studies [17, 18], the LYFO registry classified primary lymphomas of the tonsils and Waldeyer's ring as nodal. Bone marrow involvement was assessed by morphological and immunophenotypical analysis. However, cases with bone marrow involvement were only included on condition that they fulfilled the definition criteria for extranodal NHL.

Extension of disease

For clinical staging the Ann Arbor Classification [14] was used with some modifications [15]. Cases were defined as localised when a single extranodal site was involved without any further sign of dissemination (stage I_E) or when confluent locoregional lymph-nodes were involved (stage II_E). Cases showing any sign of further involvement at presentation were classified as disseminated or stage IV. Thus, in our study, stage II_E corresponded to Musshoff's stage II_{1E} and stage IV corresponded to Musshoff's stage II_{2E} [15], i.e. one extranodal localisation with involvement of regional lymph nodes distant from the primary extranodal site, and Ann Arbor's stage III_E and IV.

Clinical and histological assessment

Name, date of birth, sex, histology, clinical stage, information about constitutional symptoms, sites of involvement and a number of serological parameters were registered for each patient before treatment. Routine clinical staging included a thorough history and physical examination with particular attention to all lymphoid regions, biopsy from involved tissue, bone marrow aspirate and biopsy (Islam needle), ear, nose and throat examination, chest X-ray, abdominal computed tomography (CT) and/or lymphangiogram supplemented by a liver and spleen scan. Laparotomy was not used routinely.

The following laboratory parameters were considered: serum (s) values of lactate dehydrogenase (LDH) (normal range 150–500 U/l), Ca^{2+} (normal range 1.19–1.29 mmol/l), urate (normal range 0.15–0.45 mmol/l), IgA (normal range 0.40–2.80 g/l), IgG (normal range 6.2–13.3 g/l) and IgM (normal range 0.18–1.30 g/l).

The histological diagnosis and classification was in every new case reached by consensus among a panel of 3 haemopathologists. This allowed a uniform classification not hampered by interobserver variation. In the large majority of cases, frozen sections were available for further immunohistochemical analysis. The Kiel classification [19] was used. Moreover, cases were graded as low, intermediate or high grade according to the National Cancer Institute Working Formulation for Clinical Usage [20]. NHL of diffuse centroblastic type was considered as high grade [21].

Primary treatment regimens

All cases of NHL were treated according to their clinical stage and histology. Two randomised trials were performed in the period 1 January 1983–31 March 1988. The first, aimed at disseminated low-grade NHL, compared continuous chlorambucil treatment (10 mg per day for 6 weeks followed by a maintenance dose of 2 mg per day) given for a period of 9 months with CHOP (cyclophosphamide 750 mg/m^2 intravenously on day 1, hydroxydaunomycin 50 mg/m^2 intravenously on day 1, vincristine 1.4 mg/m^2 intravenously on day 1 and prednisone 100 mg orally on days 1–5) given every 4 weeks for nine courses. 20 out of 70 cases with disseminated low-grade extranodal NHL entered this randomisation (10 received chlorambucil and 10 CHOP). The other trial included intermediate and high-grade NHL (stage I–IV). It compared CHOP administered every 4 weeks for a total of nine courses with CVBP (cisplatin 50 mg/m^2 intravenously on day 1, bleomycin 30 mg intravenously on day 1, etoposide 100 mg/m^2 intravenously on day 1 and 100 mg/m^2 orally on days 2–4, and prednisone 100 mg orally on days 1–4) also given every 4 weeks for a total of nine courses. 63 out of 322 patients (20% of the joint intermediate and high-grade group) entered this randomisation (31 received CHOP and 32 CVBP). Localised cases of intermediate or high-grade histology were additionally treated with involved-field radiotherapy prior to chemotherapy. Radiotherapy consisted of 30 Gy in 15 fractions given by linear accelerators (4–15 MeV) as daily fractions Monday–Friday over 21 days.

The large majority of non-randomised patients were treated following common general guidelines resulting in a rather homogeneous therapeutic background. After a diagnostic excision biopsy, cases with localised disease (stage I_E and II_E) of low-grade histology received involved-field radiotherapy as 30 Gy in 15 fractions given daily over 21 days. Patients with localised disease of intermediate or high-grade histology received a combination of radiotherapy and chemotherapy, where the above mentioned involved-field radiotherapy schedule was followed by a course of CHOP every 4 weeks for a total of nine courses. Patients with disseminated low-grade NHL were treated either with single-agent chemotherapy (chlorambucil or cyclophosphamide) or CVP (cyclophosphamide) 400 mg/m^2 intravenously on days 1–5, vincristine 1.4 mg/m^2 intravenously on day 1 and prednisone 100 mg orally on days 1–5) administered once monthly for 6–9 courses. Cases of disseminated intermediate or high-grade NHL were treated with CHOP every 4 weeks for nine courses.

NHL of lymphoblastic type was treated as acute lymphoblastic leukaemia with induction (including L-asparaginase), consolidation (alternating CHOP and high-dose methotrexate), maintenance therapy (oral methotrexate and 6-mercaptopurine) and CNS prophylaxis with intrathecal methotrexate.

In patients aged 70 years or more or patients with a left ventricular ejection fraction of 50% or less, where CHOP would have been the treatment of choice, anthracyclines were either completely avoided or doxorubicin was substituted by less cardiotoxic anthracyclines such as epirubicin or mitoxantrone.

Additional radiotherapy was given for bulky tumours (>5 cm of maximum diameter) or persistent lesions after chemotherapy.

Follow-up

At the time of analysis, the median follow-up for all extranodal NHL was 3.7 years (maximum possible follow-up: 7 years). Patients were followed with 2-monthly post-treatment controls within the first 6 months, 3-monthly controls up to 2 years and 6-monthly controls from 2 to 5 years after treatment was discontinued; thereafter once yearly up to a planned total post-treatment observation period of 10 years. Each control consisted routinely of a physical examination and a blood analysis (haematology, electrolytes, liver enzymes). At every second control a routine chest X-ray was taken.

Table 1. Patient population: nodal vs. extranodal NHL

Characteristic	No. of patients (%) Nodal (n = 794)	Extranodal (n = 463)	
Age (yr)			$P = 0.04$
Mean	60.4	63.5	
Range	2–94	5–94	
Median	64	67	
Sex			
Male	421 (53)	220 (48)	
Female	373 (47)	243 (52)	
B symptoms			$P = 0.01$
No	500 (63)	320 (70)	
Yes	278 (35)	125 (27)	
Unknown	16 (2)	18 (3)	
Clinical stage			$P = 0.001$
Localised	508 (34)	233 (50)	
Disseminated	270 (64)	212 (46)	
Unknown	16 (2)	18 (4)	
Histology			$P = 0.03$
Low	288 (36)	123 (27)	
Intermediate	129 (16)	81 (17)	
High	304 (39)	203 (44)	
Unclassified	73 (9)	56 (12)	

Statistical analysis

Statistical differences between cross-tabulated values in frequency tables were evaluated by the Pearson χ^2 test.

Time at risk began at the date of conclusive histological diagnosis and ended at the date of last known status or at the date of death. Survival curves were plotted using the method of Kaplan and Meier. Statistical differences in the univariate analysis were evaluated by the Taron–Ware test [22]. Prognostic factors for survival were identified by Cox regression analysis [23]. Variables reaching statistical significance ($P < 0.05$) at univariate level were included in the multivariate analysis. Only cases without missing variables were included in the regression analysis. The BMDP statistical programme package (Statistical Software, Los Angeles) was used. Programmes 1D, 2D and 4F were used for data description and frequency tables, programmes 1L and 2L for univariate and multivariate analysis.

RESULTS

In the period 1 January–31 March 1988, the LYFO study registered 1257 newly diagnosed cases of NHL; of these, 463 (37%) were classified as extranodal NHL. The average annual incidence rate for NHL in western Denmark was $9.3/10^5$ per year, and for extranodal NHL $3.4/10^5$ per year. The general characteristics of the patient populations with either nodal or extranodal NHL are compared in Table 1. Extranodal cases were more frequently localised (50% vs. 34%, $P = 0.001$) and less cases had B symptoms (27% vs. 35%, $P = 0.01$). On the other hand, nodal cases had a lower median age (64 vs. 67 years, $P = 0.04$) and were more frequently of low-grade histology (36% vs. 27%, $P = 0.03$). In 295 cases of extranodal NHL (24% of all NHL or 64% of all extranodal NHL) no sign of nodal involvement could be detected after routine clinical staging. In 168 cases of extranodal NHL (13% of all NHL or 36% of all extranodal), a minor nodal involvement was present along with a clinically dominant extranodal component.

Clinicopathological features

The clinico pathological data for the patient population with extranodal NHL are summarised in Table 2.

Age. A young (<50 years) and an older (≥50 years) age group were compared. Testes lymphoma was only present in the older age group, which also included almost the entire group (96%) of thyroid lymphomas. The younger age group had a significantly higher occurrence of hepatic and intestinal lymphomas.

Sex. The overall M/F for extranodal NHL was 0.9. Apart from testes lymphoma, a significantly higher amount of intestinal and pulmonary lymphomas was found in male cases, whereas salivary gland lymphomas clearly prevailed in female cases (M/F = 0.30) as did thyroid lymphomas (M/F = 0.14). Hypercalcaemia was more common in male patients.

Clinical stage. NHL of the stomach, salivary glands and thryoid were more frequently localised, whereas NHL of the lungs, liver and bones were mostly widespread. Disseminated disease was significantly associated with low-grade histology, s-LDH elevation, hypercalcaemia, hyperuricaemia and paraproteinaemia.

B symptoms. B symptoms were common in disseminated cases, particularly those with hepatic, pulmonary, intestinal or myeloid involvement. Conversely, B symptoms rarely occurred in NHL of salivary glands, CNS and skin. The presence of B symptoms correlated with high-grade histology, elevated s-LDH, hypercalcaemia and paraproteinaemia.

Sites of involvement. Table 3 shows the number of cases at specific extranodal sites and their pattern of extranodal involvement (with or without nodal component). The frequency data in Table 2 indicate that low-grade histology was the most frequent in cases involving salivary glands or bone marrow. Intermediate-grade histology, particularly the centrocytic type, was common in gastric and intestinal lymphomas and high-grade histology was predominant in NHL of CNS, testes, bones, thyroid, liver, lungs and stomach. s-LDH elevation was present in about 2/3 of the cases of pulmonary and hepatic lymphoma and was frequent also when bones, bone marrow or CNS were involved. Hypercalcaemia was most common in primary bone lymphomas. Myeloid involvement was significantly associated with the presence of abnormal biochemical parameters in general.

Histology. Table 4 shows the distribution of histological subgroups among extranodal NHL. Centroblastic diffuse (CB) was the most common histological subtype. Diffuse centroblastic-centrocytic (CB/CC) and centrocytic (CC) lymphomas accounted together for almost the entire intermediate-grade group. Lymphoplasmacytic/-cytoid, non-polymorphic (IC) and follicular CB/CC lymphomas were the main histological subtypes in the low-grade group.

Site-specific data on histological subgroups are shown in Table 2. Diffuse CB was the most common histology in NHL of stomach, intestine, CNS, thyroid, lungs and testes and IC in NHL of salivary glands, nasal cavity and paranasal sinuses. Over half of the bone marrow-infiltrating cases were either of IC or CC type. IC was also often associated with paraproteinaemia, mostly of IgM type (66% of all cases of paraproteinaemia). Biochemically, high-grade histology had a significantly higher

Table 2. Extranodal NHL: clinicopathological features (summary of frequency tables)

	Age		Sex		Stage‡		B symptoms‡		No. of extranodal sites			Most common sites of involvement											Histology§		
	<50 (82)†	≥50 (381)	M (220)	F (243)	L (233)	D (212)	Absent (320)	Present (125)	1 (376)	2 (67)	>2 (20)	ST (87)	IN (52)	SK (56)	SG (17)	TH (25)	LU (24)	LI (27)	TE (15)	CNS (33)	BO (41)	BM (89)	L (123)	I (81)	H (203)
Sex																									
M	41†	179																							
F	41	202																							
Stage																									
L	41	192	108	125																					
D	41	171	104	108																					
B symptoms																									
Absent	55	265	152	168	204*	116*																			
Present	27	98	60	65	29*	96*																			
Extranodal sites																									
1	66	310	178	198	228*	134*	281*	81*																	
2	13	54	32	35	5*	60*	34*	31*																	
>2	3	17	10	10	0*	18*	5*	13*																	
Most common sites of involvement																									
ST	15	72	45	42	60*	22*	64	18	70	14	3														
IN	17*	35*	36*	16*	27	22	25*	24*	34*	11*	7*														
SK	11	45	25	31	29	23	45*	7*	45*	5*	6*														
SG	4	13	4*	13*	12*	5*	17*	0*	15	2	0														
TH	1*	24*	3*	22*	17*	6*	18	5	23	0	2														
LU	5	19	17*	7*	1*	22*	10*	13*	7*	6*	11*														
LI	9*	18*	13	14	2*	25*	8*	19*	9*	11*	7*														
TE	0*	15*	15*	0*	10*	4*	11	3	11	2	2														
CNS	4	29	11	22	19	12	27*	4*	25	6	2														
BO	8	33	15	26	12*	29*	25	16	17*	17*	7*														
BM	16	73	42	47	0*	89*	43*	46*	50*	33*	6*														
Histology																									
L	22	101	54	69	57*	64*	94*	27*	104	15	4	18*	13	14	12*	4*	8*	6*	4*	6*	6*	43*			
I	10	71	43	38	50*	27*	57*	20*	66	13	2	27*	12	6	3*	5*	2*	0*	1*	3*	4*	11*			
H	36	167	95	108	103*	91*	135*	59*	161	31	11	40*	22	15	1*	15*	12*	14*	10*	23*	27*	23*			
Elevated laboratory parameters																									
LDH	21	93	50	64	34*	80*	61*	53*	72*	28*	14*	11*	11	12	3	5	16*	17*	3	11*	18*	31*	17	10	75*
CA	7	18	18*	7*	7*	18*	13*	12*	16*	8*	1*	2	2	3	0	0	1	2	0	1	8*	10*	4	4	12*
UR	7	46	23	30	18*	33*	32	19	32*	16*	5*	6	4	8	3	3	4	6	2	1	5	18*	13	8	23*
IgA	2	32	16	18	18	15	20	13	27	7	0	6	4	4	1	2	2	3	1	2	4	6*	5	6	23
IgG	5	37	19	23	17	23	27	13	32	8	2	5	5	7	3	2	5	2	1	0	3	11*	20*	4	18
IgM	9	44	24	29	18	34	35	17	41	10	2	7	10	5	1	2	5	4	1	3	4	20*	28*	9	16
PP	4	31	19	16	8*	27*	19*	16*	25*	6*	4*	4	5	0	0	1	5	2	1	2	2	22*	22*	5	8

*$P < 0.05$ (Pearson χ^2). †No. of patients. ‡18 patients not reported. §56 patients unclassified.

L = localised, D = disseminated, ST = stomach, IN = intestine, SK = skin, SG = salivary glands, TH = thyroid, LU = lungs, LI = liver, TE = testes, CNS = central nervous system, BO = bones, BM = bone marrow, L = low grade, I = intermediate grade, H = high grade, LDH = elevated s-LDH (n = 114), CA = hypercalcaemia (n = 25), UR = hyperuricaemia (n = 53), IgA = elevated s-IgA (n = 34), IgG = elevated s-IgG (n = 42), IgM = elevated s IgM (n = 53), PP = paraprotein (n = 35).

Table 3. Extranodal NHL: sites and patterns of involvement

Site	Nodal component		
	Without*	With†	Total‡
Stomach	64§	23	87
Fundus	—	—	17
Corpus + antrum	—	—	70
Skin	41§	15	56¶
Intestine	27	25	52
Jejunum	—	—	15
Ileum	—	—	18
Ileocoecal region	—	—	8
Colon	—	—	10
Rectum	—	—	1
Bone	28	13	41
Central nervous system	30§	3	33
Liver	7	20	27
Thyroid	14	11	25
Lungs	10	14	24
Salivary glands	14§	3	17
Testes	11§	4	15
Connective tissue	8	4	12
Paranasal sinuses	8	2	10
Nasal cavity	6	1	7
Uterus	4	2	6
Breast	3	3	6
Orbita/intraocular	4	—	4
Pancreas	2	2	4
Oral cavity	3	—	3
Other localisations	17	8	25
Bone marrow	37	52	89

*No detectable nodal involvement.
†Minor nodal involvement.
‡In excess of 463; >1 site can be involved in the same case.
§ > 70% of cases without sign of nodal involvment.
¶Including 19 cases of *mycosis fungoides*.

Table 4. Extranodal NHL: Histological subgroups

Histology	No. of cases (%)
Low grade	123 (27%)
Lymphocytic	5
Lymphoplasmacytic/-cytoid, non-polymorphic	63
Follicular centroblastic/centrocytic	37
Unclassifiable low-grade	18
Intermediate grade	81 (17%)
Diffuse centroblastic/centrocytic	47
Centrocytic (follicular and diffuse)	33
Follicular centroblastic	2
High grade	203 (44%)
Diffuse centroblastic	105
Immunoblastic	30
Lymphoblastic (Burkitt type)	6
Lymphoblastic (convoluted type)	2
Lymphoblastic (non-specified)	16
Unclassifiable high-grade	43
Unclassified	56 (12%)
Total	463 (100%)

occurrence of elevated s-LDH, hypercalcaemia and hyperuricaemia than the other malignancy grades. Elevated serum levels of IgG or IgM were significantly associated with low-grade histology.

Serum levels. Elevated s-LDH and hyperuricaemia were simultaneously present in 26 cases. Hence, almost half of all cases with hyperuricaemia (n = 53) also had elevated s-LDH. Similarly, more than half of the cases of hypercalcaemia (13/25) also had elevated s-LDH. Two thirds of all paraproteinaemias (23/35 cases) were of IgM type.

Treatment and mortality data

Overall results from the low-grade randomisation group showed no significant difference in survival or remission rates between patients treated with CHOP and those treated with chlorambucil. However, the time to progression was significantly different in the two groups, with median values of 45 and 34 months, respectively (P = 0.03). These results also applied to randomised low-grade extranodal NHL (n = 20).

Overall results from the high-grade randomisation group have already been reported [24]. In both nodal and extranodal NHL, CHOP was superior to CVBP for inducing complete response (CR 70% vs. 25%, respectively; P = 0.0001) and overall response (96% vs. 68%, respectively; P = 0.0004). No significant difference in median response duration (1.1 vs. 0.76 years, respectively; P = 0.16) and median survival (3.4 vs 2.6 years, respectively; P = 0.74) was found.

In the present series (463 cases), 239 deaths were reported after a 7-year observation period. Autopsy was done in 48% of the cases. In 63% of the deceased patients, disseminated lymphoma was the reported cause of death. In 4% of the cases, death was due to treatment complications and in 23% to causes not related to NHL. The cause of death was unknown in 10% of the cases.

Survival and prognostic factors

After a 7-year observation period the overall survival for extranodal NHL was 46% (median 4.9 years) vs. 49% (median 5.9 years) for nodal cases (P = 0.05). Table 5 shows the variables included in the univariate analysis of prognostic factors for

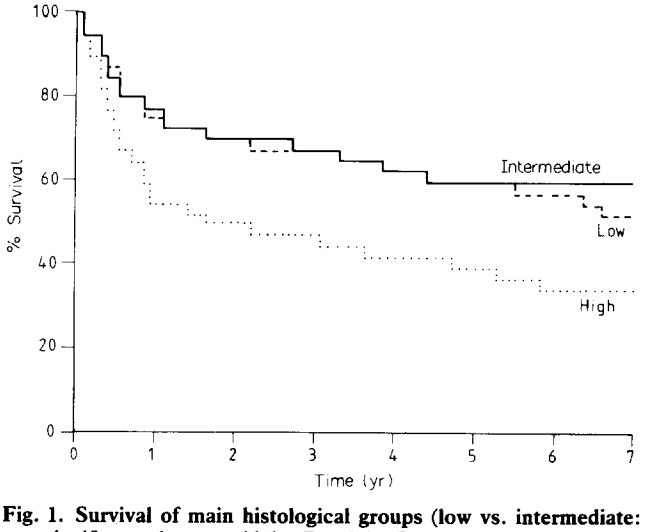

Fig. 1. Survival of main histological groups (low vs. intermediate: not significant; low vs. high: $P < 0.0005$; intermediate vs. high: $P < 0.0005$).

Table 5. Extranodal NHL: univariate analysis of prognostic factors

Prognostic factor	χ^2	df	*P*
B symptoms	61.8	1	<0.0005
Hypercalcaemia	33.6	1	<0.0005
Hyperuricaemia	28.9	1	<0.0005
Elevated s-LDH	27.9	1	<0.0005
Age > 65 years	26.4	1	<0.0005
High-grade histology	22.1	3	<0.0005
Disseminated disease	16.5	1	<0.0005
>2 extranodal sites	15.0	2	0.001
Elevated s-IgA	13.2	1	0.001
Liver involvement	12.1	1	0.001
Additional nodal component	6.2	1	0.013
Testes involvement	5.9	1	0.015
Bone marrow involvement	4.6	1	0.031
Gastric involvement	3.7	1	NS
Lung involvement	3.5	1	NS
CNS involvement	3.3	1	NS
Thyroid involvement	2.9	1	NS
Intestinal involvement	0.8	1	NS
Elevated s-IgM	0.4	1	NS
Elevated s-IgG	0.3	1	NS
Sex	0.1	1	NS
Skin involvement	0.0	1	NS
Bone involvement	0.0	1	NS
Randomisation	5.1	3	NS

NS = Not significant at 0.05 level.

survival. Those reaching significance level ($P < 0.05$) were subsequently included in the multivariate analysis. However, testes involvement was not included because of the limited size of this group ($n = 15$). Survival values for low and intermediate grade extranodal NHL did not differ significantly, whereas they were significantly ($P < 0.0005$) lower for high-grade cases (Fig. 1).

The Cox regression analysis was first performed for clinical variables (age, histology, stage, B symptoms, number of extranodal localisations, presence of additional nodal component, liver-

Table 6. Extranodal NHL: multivariate analysis of prognostic factors

	First analysis ($n = 392$)		Second analysis ($n = 303$)	
Factor	*P*	RR	*P*	RR
Age >65	0.0000	2.4	0.0001	2.1
Presence of B symptoms	0.0000	2.3	0.0002	2.1
High-grade histology	0.0002	1.7	0.0004	1.9
Disseminated disease	0.0045	1.6	0.0010	1.8
Elevated s-IgA	ND	—	0.0146	1.9
Hyperuricaemia	ND	—	0.0125	1.7
Hypercalcaemia	ND		NS	
Liver involvement	NS		NS	
Nodal component	NS		NS	
Elevated s-LDH	ND		NS	
Bone marrow invovlement	NS		NS	
>2 Extranodal sites	NS		NS	

RR= relative risk, ND= not done, NS= not significant ($P > 0.05$).

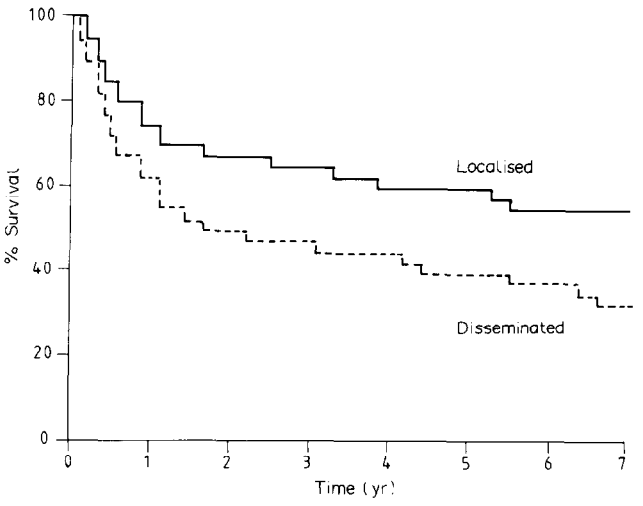

Fig. 2. Survival of localised ($n = 233$) vs. disseminated ($n = 212$) cases ($P < 0.0005$).

and bone marrow involvement) in 392 patients. Excluded were patients with missing variables ($n = 18$) and patients with incompletely defined histology ($n = 53$), mostly belonging to the unclassified group. The variables identified by the model were in order of relative risk (RR) magnitude: age >65 years, presence of B symptoms, high-grade histology and disseminated disease (stage III_E and IV). The analysis was then repeated with the addition of biochemical variables, i.e. s-LHD, s-Ca, s-urate and s-IgA on 303 patients where information about all variables, both clinical and biochemical, was available. Results of the second analysis were consistent with those of the first, i.e. the same clinical variables in the same order of inclusion were identified. Additionally, the second analysis also identified elevated s-IgA and hyperuricaemia as factors with independent predictive value for survival. Results of the multivariate analysis are summarised in Table 6.

Parameters such as elevated s-LDH, presence of >2 extranodal sites or of a nodal component, presence of bone marrow involvement and hypercalcaemia lost statistical significance in the multivariate analysis. Bone marrow and liver involvement, number of extranodal sites and presence of a nodal component were related to B symptoms and clinical stage. Elevated s-LDH correlated strongly with high-grade histology and, more weakly, also with clinical stage and hyperuricaemia. Factors such as elevated serum levels of IgG and IgM did not reach statistical significance at univariate level.

DISCUSSION

The ongoing LYFO registry collected 1257 new cases of NHL over a 5-year period. The registry is population-based, i.e. all new cases of NHL from a well-defined geographical area are included.

The occurrence of extranodal NHL in the present material was high, i.e. 37% of all NHL cases. However, the value is reduced to 23% if one looks only at the apparently pure extranodal cases, i.e. those without any evidence of coexisting nodal involvement at presentation. 103 cases (8% of the whole material) were localised to the tonsils/Waldeyer's ring. They were mostly localised (65% of the cases) and of high-grade histology (mainly diffuse CB). Their 7-year survival was 46% (median 3.5 years), which did not differ significantly from that of extranodal NHL cases considered as a group.

In 1972 a large retrospective study from the National Cancer Institute, based on information from regional cancer registries from the 1950s and 1960s, found 24% extranodal NHL among more than 8000 reviewed cases of lymphoma [2]. 10% of all extranodal NHL in that study were localised to the tonsils. Recently, data from a Dutch population-based NHL registry [25] reported a high occurrence of extranodal cases (41% on a total of 580 NHL). This study also recorded NHL of tonsils and Waldeyer's ring as extranodal (15% of all extranodal cases). Furthermore, of a total of 33402 malignant lymphomas registered in the Kiel Lymph Node Registry between 1972 and 1987, 13453 cases (40%) were listed as extranodal [26].

The comparison of incidences for extranodal NHL reported in different studies is hampered by variation of study design, by the heterogeneous definition of primary extranodal disease and by differences in staging procedures. In spite of these difficulties there seems to be a certain degree of concordance between this and other studies suggesting that between a quarter and a third of all cases of NHL present with an extranodal localisation as the sole or the clinically dominant site of involvement. In our study we could not discern an overall correlation between prognosis and specific extranodal presentations. The results of the Cox regression analysis for prognostic factors suggested that in extranodal NHL prognosis is probably more a consequence of the cell type and tumour bulk than of the extranodal localisation of the tumour *per se*. However, one has to be cautious with general conclusions, particularly for those sites which were counted in only a small number of patients, i.e. salivary glands ($n = 17$) and testes ($n = 15$). The presence of liver and/or bone marrow involvement had inverse impact on survival at univariate level, but lost significance in the multivariate analysis due to correlation with B symptoms and clinical stage. Testes involvement did also reach statistical significance at univariate level ($P = 0.015$) but was not included in the regression analysis because of the limited size of the group ($n = 15$). However, frequency data (Table 2) showed an association of testes involvement with both older age and high grade histology, i.e. two of the major prognostic factors eventually identified by the Cox model. The difference seen at univariate level between the P values of disseminated disease ($P < 0.0005$) and presence of additional nodal component ($P > 0.013$) can be explained by the fact that "additional nodal component" also contains localised cases (stage II_{1E}), who contribute to improvement of prognosis in this group.

Elevation of s-IgA was one of the biochemical parameters identified by the regression analysis as having independent additional prognostic value. The biological background of this apparent difference between IgA on one side and IgG and IgM on the other as related to clinical course and prognosis is not clear and certainly deserves further study.

Clinical staging in extranodal NHL deserves particular attention. The Ann Arbor classification [14] is still the most widely accepted staging system for NHL. However, the prognostic information provided by the system is less satisfactory for NHL than for Hodgkin's disease [27, 28]. In fact, this may partly be due to the far more frequent extranodal involvement in NHL than in Hodgkin's disease. In the present study of extranodal NHL no additional prognostic information could be obtained by distingushing between stage I_E and stage II_{1E} ($P = 0.05$). A good discriminator for extranodal NHL seemed to be the distinction between localised (stage I_E and II_{1E}) and disseminated (stage II_{2E}, III_E and IV) cases (Fig. 2). The importance of differentiating between stage II_{1E} and II_{2E} has already been pointed out for gastrointestinal lymphomas [29, 30]. A simplified staging system for extranodal NHL (e.g. localised versus disseminated) could be attractive and it should be evaluated prospectively. However, it would probably be worthless unless it can rely on a rigorous staging approach based on standardised and comparable staging procedures.

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Effect of Chemotherapy with or without Buserelin on Serum Hormone Levels in Premenopausal Women with Breast Cancer

Carla I. Falkson, Hendré C. Falkson and Geoffrey Falkson

Serial determinations of serum oestradiol (E2), follicle-stimulating hormone (FSH) and luteinising hormone (LH) were done to assess the effect of chemotherapy, with or without a gonadotropin-releasing hormone analogue, buserelin, on ovarian function in 147 premenopausal women treated for breast cancer. Cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) plus buserelin was given to 81 women with metastatic disease, and 66 women were randomised to adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with buserelin or CMF alone. Baseline mean E2 of patients treated with cytostatics plus buserelin fell from premenopausal levels and remained low while patients were on study. E2 levels remained at premenopausal values in patients treated with CMF alone. Downregulation of FSH and LH occurred with cytostatics plus depot buserelin, but fluctuated with the nasal administration; on CMF alone, FSH and LH levels increased. Buserelin plus cytostatics more effectively caused ovarian ablation than cytostatic treatment alone. Depot buserelin was more effective than nasal buserelin.
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INTRODUCTION

OVARIAN ABLATION remains an important therapeutic manoeuvre in the management of premenopausal women with breast cancer. Oophorectomy is associated with morbidity and some psychological problems; the availability of a medical castration is therefore a useful addition to the oncologist's armamentarium. It has been demonstrated that intranasal administration of buserelin (D Ser[Bu] LHRH ethylamide) throughout the menstrual cycle will cause anovulation [1] and activity has been demonstrated with buserelin in premenopausal women with breast cancer [2]. Buserelin is well tolerated when given concomitantly with combination chemotherapy and therapeutic results are not adversely affected when buserelin is given with chemotherapy in premenopausal women with metastatic breast cancer [3].

This study was undertaken in order to assess the effect of chemotherapy with or without buserelin on ovarian function of premenopausal women with breast cancer.

PATIENTS AND METHODS

Serial determinations of serum oestradiol (E2), follicle-stimulating hormone (FSH) and luteinising hormone (LH) were done in 147 premenopausal women who received chemotherapy with or without buserelin. Hormone values were obtained by radioimmunoassays. All patients had histologically confirmed breast cancer. The median age of the patients was 43 (range 28–57) years. Of the 147 patients studied, 108 were still menstruating regularly, and 39 had had a hysterectomy with ovaries intact. All 147 were premenopausal as determined by pretreatment serum hormone levels. The normal range for a woman to be considered premenopausal was 50–1376 pmol/l for E2,

Correspondence to C.I. Falkson, Department of Medical Oncology, Private Bag X 169, Pretoria 0001, South Africa.
The authors are at the Department of Medical Oncology, University of Pretoria, Pretoria, South Africa.
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