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Eight-Year Experience of Malignant Lymphoma

-Survival and Prognostic Factors-

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Several reports have suggested a geographic difference in the histopathologic characteristics and prognosis of malignant lymphoma around the world. We tried to evaluate the clinical and histopathologic characteristics, therapeutic outcomes, and prognostic features of malignant lymphoma, particularly in Korean patients. Three hundred and seventy-six adult patients with the initial histopathologic diagnosis of malignant lymphoma of Yonsei University College of Medicine over an 8-year period were analyzed, retrospectively, with the following results:

1) There were 47 cases of Hodgkin's disease (HD) (12.5%) and 329 of non-Hodgkin's lymphoma (NHL) (87.5%) with a 1 : 7 ratio. The most common histopathologic subtype of HD was mixed cellularity (44.7%), and that of NHL was intermediate grade (70.8%), especially diffuse large-cell type (44.1%), whereas follicular type was less common. In regard to the incidence of extranodal presentation, it is rare in HD (4.2%), but occurs in 49.8% of patients with NHL. 2) The complete remission (CR) rate was 91.5% in HD and 63.6% in NHL, and the 5-year and 7-year disease-free survival rates were 71.3% and 57.0% in HD; 67.0% and 49.6% in NHL. The 5-year and 8-year overall survival rates were 90.7% and 68.0% in HD; 65.2% and 60.2% in NHL. 3) By multivariate analysis, we found that age, performance status, histopathologic grade, stage, serum lactate dehydrogenase (LDH) and β_2-microglobulin were the useful prognostic factors in predicting survival in NHL, while no definite prognostic factors were found in HD. Also, in NHL patients less than 60 years old, stage, serum LDH, and histopathologic grade were closely associated with their therapeutic outcomes.

In conclusion, the characteristics of malignant lymphoma in our hospital differ from those in Western countries with respect to the clinical, histopathologic and immunophenotypic patterns, but the prognostic factors and overall therapeutic outcomes were quite comparable to those of other reports from Western countries.

Key Words: Malignant lymphoma, survival, prognostic factor

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The term malignant lymphoma refers to a heterogenous group of diseases having variable etiologies, distinct histopathologic appearances, cellular biologies, myriad clinical presentations, and therapeutic outcomes, ranging from early death to cure in humans. HD is a relatively uncommon disease of unknown and perhaps variable etiology, the incidence of which has been stable in recent years, while the incidence of NHL has increased markedly during the past two decades (Levin and Hoover,

1992; Muller, 1992). This trend should encourage vigorous further study of these diseases at the laboratory and clinical level. In the past 20 years, there has been a dramatic improvement in the prognosis of patients with HD and NHL, and it is now often considered curable in patients with these diseases (Armitage, 1993; DeVita and Hubbard, 1993). However, many patients still die of their disease and this dilemma has refocused our attention on the need to evaluate treatment outcomes and to identify patients with different long-term prognoses to individualize therapy.

Recently, the prevalence of these diseases has increased in Korea because there have been numerous advances in our understanding of the pathophysiology of these disorders and in their treatment (Kim *et al.* 1992b; Hahn *et al.* 1995). However, very few studies have described the long-term outcomes and prognostic factors for patients with malignant lymphoma in Korea.

This study was undertaken to evaluate the clinical and histopathologic findings, therapeutic outcomes, and prognostic features of malignant lymphoma after long-term follow-up. This will help to design more effective therapeutic starategies according to the patient's characteristics in Korea.

MATERIALS AND METHODS

Study patients

From January, 1988 to December, 1995, 395 consecutive patients with the initial histopathologic diagnosis of malignant lymphoma were evaluated retrospectively at the Department of Internal Medicine, Yonsei University College of Medicine. Patients were considered eligible if they were 15 years old; no upper age limit was established. Our analyses excluded 19 patients whose tissue specimens were inadequate for histopathologic study or who had not received any kind of therapies, leaving 376 patients. The median follow-up duration was 37(1~96) months.

Diagnosis and staging

A tissue biopsy was performed in all patients for diagnostic purposes. In 218 selected cases, immunohistochemical staining was added for accurate diagnostic purposes. Histopathologic classification was done according to the Rye classification of the HD and the NCI Working Formulation (WF) of the NHL (Lukes and Butler, 1966; National Cancer Institute, 1982). After all sites of diseases were measured and recorded, patients were staged according to the Ann Arbor staging system (Carbone *et al.* 1971). Each patient had a complete blood count, chemistry panel, bone marrow aspiration and biopsy, chest radiograph, neck, chest and abdominal computed tomographic scan, whole body bone scan, and gallium scan.

Treatment

Although radiotherapy or an operation was undertaken in some patients with localized HD or localized extranodal NHL, combination chemotherapy with or without radiotherapy was the mainstay of therapeutic modalities according to the patient's characteristics, histopathologic subtypes and Ann Arbor stages. In HD, the chemotherapy regimens included the following: C-MOPP (cyclophosphamide, vincristine, procarbazine, and prednisolone), ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), or various regimens combining C-MOPP and ABVD. The management of NHL was mostly based on adriamycin containing various combination chemotherapy regimens. These included CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone), BACOP (bleomycin, adriamycin, cyclophosphamide, vincristine, and prednisolone), m-BACOP (methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine, prednisolone), ProMACE-CytaBOM (prednisolone, adriamycin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, methotrexate), and MACOP-B (methotrexate, adriamycin, cyclophosphamide, vincristine, prednisolone, bleomycin). A number of patients who had subtypes of low-grade received an adriamycin-free regimen (CVP: cyclophosphamide, vincristine, prednisolone).

Criteria for response

We defined therapeutic responses by WHO criteria. Complete remission (CR) was defined as the complete disappearance of all clinical evidence of lymphoma by physical examination and restaging

work-up, and no histologic evidence of lymphoma if it had been found earlier on bone marrow or spinal fluid examination; Partial remission (PR) was defined as a greater than 50% reduction of the sum products of the greatest size and its perpendicular diameter of measurable tumor lesions for at least 4 weeks. No response (NR) was defined as stable or progressive disease.

Statistical analysis

Comparisons between patient groups (i.e., HD vs NHL) were based on the chi-square test for categorical data and the Wilcoxon rank-sum test for continuous data. Disease-free survival was calculated from the date of CR to the date with evidence of tumor relapse. Overall survival was measured from the date of initial diagnosis to the date of death or last follow-up. Survival curves were estimated by the Kaplan and Meier method, and comparisons between curves were based on the log-rank test. Multivariate analyses using logistic regression and Cox's proportional hazards model were performed to adjust the simultaneous effects of different prognostic factors on CR rate and survival. All tests were two-tailed.

RESULTS

Patient characteristics

The clinical characteristics of the 376 patients were given in Table 1. There were 47 cases of HD (12.5%) and 329 of NHL (87.5%) with a 1 : 7 ratio. Men were affected more often than women (1.5 : 1 for HD and 2.1 : 1 for NHL). The peak incidence of HD was in the third and fourth decade, while the incidence of NHL increased steadily with age and showed a peak in the sixth decade (Table 1, Fig. 1) ($p<0.01$). As indicated in Table 1, the evaluation of pretreatment clinical variables between HD and NHL groups was not different with respect to sex ratio, stage, hemogram, albumin, β_2-microglobulin (MG), and lactate dehydrogenase (LDH).

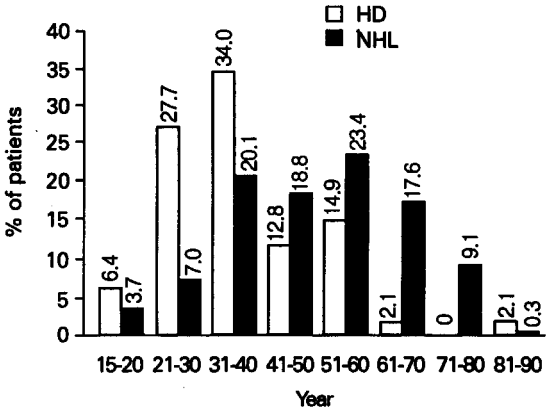

Fig. 1. Age distribution of malignant lymphoma.

Histopathologic and immunophenotypic findings

Among 47 cases of HD, the most common histopathologic subtype of HD was mixed cellularity (MC) (44.7%), followed by nodular sclerosis (NS)(27.6%), lymphocyte depletion (LD)(14.9%), and lymphocyte predominance (LP)(12.8%). In patients with NHL, the most common was intermediate grade (70.8%), followed by high grade and then low grade. Especially, the diffuse large-cell type was the most common histopathologic subtype (44.1%), whereas the follicular variety was less common.

Two hundred and eighteen patients were confirmed by immunohistochemical staining. Of these patients, 78(35.8%) patients had T-cell markers and 130(59.6%) had B-cell markers. Ten cases (4.6%) could not be determined and classified properly.

The prevalence of each histopathologic subtype and the results of immunophenotyping are shown in Table 1.

Clinical features and distribution of primary sites

At the time of presentation, peripheral lymphadenopathy was the most common presenting symptom, especially in HD (83.0% for HD vs 48.3% for NHL, $p<0.01$). Unlike HD, it was more common for patients with NHL to present with abdominal discomfort and pain (2.1% for HD vs 20.7% for NHL, $p<0.01$). Also, various symptoms due to

Table 1. Patient characteristics

	HD	NHL	Total
Number(%)	47(12.5)	329(87.5)	376
Clinical parameters			
Age(year)	36(16~81)*	49(15~80)	47(15~81)
Sex(male : female)	1.5 : 1	2.1 : 1	2.0 : 1
Performance status†			
0 or 1	44(93.6)	304(92.4)	348(92.6)
≥2	3(6.4)	25(7.6)	28(7.4)
Histopathologic grade			
Lymphocyte predominence(LP)	6(12.8)		
Nodular sclerosis(NS)	13(27.6)		
Mixed cellularity(MC)	21(44.7)		
Lymphocyte depletion(LD)	7(14.9)		
Low grade		*37(11.2)*	
Small lymphocytic lymphoma(SLL)		23(7.0)	
Follicular, small cleaved cell lymphoma(FSCL)		9(2.7)	
Follicular, mixed, small and large cell lymphoma(FML)		5(1.5)	
Intermediate grade		*233(70.8)*	
Follicular, large cell lymphoma(FLCL)		10(3.0)	
Diffuse, small cleaved cell lymphoma(DSCL)		19(5.8)	
Diffuse, mixed, small and large cell lymphoma(DML)		59(17.9)	
Diffuse, large cell lymphoma(DLCL)		145(44.1)	
High grade		*47(14.3)*	
Immunoblastic lymphoma(IBL)		36(11.0)	
Lymphoblastic lymphoma(LL)		5(1.5)	
Small noncleaved cell lymphoma(SNCL)		6(1.8)	
Others		*12(3.7)*	
Immunophenotyping			
T-cell		78(35.8)	
B-cell		130(59.6)	
Unclassified		10(4.6)	
Stage I	8(17.0)	85(25.8)	93(24.7)
II	22(46.8)	109(33.1)	131(34.9)
III	9(19.2)	46(14.0)	55(14.6)
IV	8(17.0)	89(27.1)	97(25.8)
Laboratory parameters			
Hemogram			
Hb(g/dL)	12.2(6.8~16.0)	12.6(6.0~16.6)	12.5(6.0~16.6)
WBC(×1,000/μL)	8.6(2.8~19.3)	8.0(0.4~106.6)	8.1(0.4~106.6)
Lymphocyte(%)	22(0~57)	24(0~90)	24(0~90)
Eosinophil(%)	2(0~11)	2(0~25)	2(0~25)
Platelet(×1,000/μL)	291(124~662)	263(25~616)	268(25~662)
Albumin(g/dL)	4.1(1.7~5.1)	4.0(1.8~5.5)	4.0(1.7~5.5)
β_2-microglobulin(mg/L)	2.3(1.1~6.7)	2.8(0.5~23.0)	2.7(0.5~23.0)
LDH(IU/L)	130(56~517)	217(48~3310)	205(48~3310)

HD: Hodgkin's disease, NHL: non-Hodgkin's lymphoma
*: $p<0.01$(vs non-Hodgkin's lymphoma)
†: Performance status was assessed according to the Eastern Cooperative Oncology Group scale.
Values are denoted as mean(range).

Table 2. Clinical presentations

	HD(%) (n=47)	NHL(%) (n=329)	Total(%) (n=376)
Chief complaint			
Lymphadenopathy	39(83.0)*	159(48.3)	198(52.7)
Abdominal discomfort	1(2.1)*	68(20.7)	69(18.4)
Sore throat	–	40(12.2)	40(10.6)
Nasal obstruction	1(2.1)	19(5.8)	20(5.3)
Fever	4(8.5)	11(3.3)	15(4.0)
Headache	–	13(4.0)	13(3.5)
Ocular swelling	–	13(3.9)	13(3.5)
Generalized weakness	2(4.3)	4(1.2)	6(1.5)
Hoarseness	–	2(0.6)	2(0.5)
B symptoms	17(36.2)	126(38.3)	143(38.0)
Fever	15(31.9)*	55(16.7)	70(18.6)
Night sweats	11(23.4)	49(14.9)	60(16.0)
Weight loss	8(17.0)	87(26.4)	95(25.3)

HD: Hodgkin's disease, NHL: non-Hodgkin's lymphoma
*: $p<0.01$(vs non-Hodgkin's lymphoma)

Table 3. Incidence of primary nodal distribution and extranodal involvement

	HD(%) (n=47)	NHL(%) (n=329)	Total(%) (n=376)
Primary nodal distribution			
Cervical	39(83.0)*	171(52.0)	210(55.9)
Axillary	8(17.0)	43(13.1)	51(13.6)
Inguinal	5(10.6)	52(15.8)	57(15.2)
Hilar	6(12.8)	19(5.8)	25(6.6)
Mediastinal	16(34.0)	42(12.8)	58(15.4)
Celiac	1(2.1)	23(7.0)	24(6.4)
Para-aortic	10(21.3)	66(20.1)	76(20.2)
Splenic	4(8.5)	16(4.9)	20(5.3)
Mesentric	3(6.4)	45(13.7)	48(12.8)
Extranodal involvement			
Bone marrow	3(6.4)	23(7.0)	26(6.9)
Meninges	–	4(1.2)	4(1.1)
Bone	2(4.3)	19(5.8)	21(5.6)
Skin	1(2.1)	6(1.8)	7(1.9)
Liver	3(6.4)	14(4.3)	17(4.5)
Spleen	4(8.5)	14(4.3)	18(4.8)
Others	2(4.3)	30(9.1)	32(8.5)

HD: Hodgkin's disease, NHL: non-Hodgkin's lymphoma
*:$p<0.01$(vs non-Hodgkin's lymphoma)

extranodal involvement were more common in NHL than in HD. Constitutional B symptoms related to their disease were noted in one-third of total patients; the most common was fever in HD (31.9%) and weight loss in NHL (26.4%)(Table 2). Among total patients, the most common site of nodal presentation was the cervical area, and the next two most common areas of involvement were the para-aortic and mediastinal areas. In contrast to NHL, the incidence of nodal presentation on cervical and

Table 4. Primary extranodal distribution

Site	HD(%) (n=47)	NHL(%) (n=329)	Total(%) (n=376)
Alimentary tract	–	59(17.9)	59(15.7)
Stomach	–	40(12.1)	40(10.6)
Small bowel	–	13(4.0)	13(3.5)
Large bowel	–	6(1.8)	6(1.6)
Upper respiratory tract	1(2.1)	57(17.3)	58(15.4)
Waldeyer's ring	1(2.1)	25(7.6)	26(6.9)
Nasopharynx	–	18(5.5)	18(4.8)
Para-nasal sinus	–	7(2.1)	7(1.8)
Oropharynx	–	4(1.2)	4(1.1)
Larynx	–	3(0.9)	3(0.8)
Thyroid	–	3(0.9)	3(0.8)
CNS	–	13(4.0)	13(3.5)
Bone	–	6(1.8)	6(1.6)
Skin	–	5(1.5)	5(1.3)
Eye	–	12(3.7)	12(3.2)
Lung	–	1(0.3)	1(0.3)
Testis/Ovary	1(2.1)	1(0.3)	2(0.5)
Breast	–	3(0.9)	3(0.8)
Others	–	4(1.2)	4(1.1)
Total	2(4.2)*	164(49.8)	166(44.2)

HD: Hodgkin's disease, NHL: non-Hodgkin's lymphoma
*: $p<0.01$(vs non-Hodgkin's lymphoma)

Table 5. Therapeutic modalities

	HD(%) (n=47)	NHL(%) (n=329)	Total(%) (n=376)
Operation alone	–	3(0.9)	3(0.8)
Radiotherapy alone	10(21.2)	23(7.0)	33(8.8)
Chemotherapy alone	15(31.9)	158(48.0)	173(46.0)
Operation + Radiotherapy	2(4.3)	16(4.9)	18(4.8)
Operation + Chemotherapy	2(4.3)	36(10.9)	38(10.1)
Radiotherapy + Chemotherapy	16(34.0)	81(24.6)	97(25.8)
Operation + Radiotherapy + Chemotherapy	2(4.3)	12(3.6)	14(3.7)

HD: Hodgkin's disease, NHL: non-Hodgkin's lymphoma

mediastinal areas was higher in patients with HD ($p<0.01$) (Table 3). Also, there were some differences in the two groups with regard to the incidence of extranodal presentation, which was rare in HD (4.2%), but occurred in 49.8% of patients with NHL ($p<0.01$). The most common site was the gastrointestinal tract, and followed by the upper respiratory tract including Waldeyer's ring, nasopharynx, paranasal sinus, oropharynx and larynx (Table 4).

Therapeutic outcomes

Therapeutic modalities for all patients are shown in Table 5. The overall response rate in this study was 83.2%, with CR in 67.0% and PR in 16.2%. The complete remission (CR) rate was 91.5% in HD and 63.6% in NHL, while 20.9% of HD and 22.0% of NHL relapsed. The 5-year and 7-year disease-free survival rates were 71.3% and 57.0% in HD; 67.0%

Table 6. Treatment responses

	HD(%) (n=47)	NHL(%) (n=329)	Total(%) (n=376)
Complete response(%)	43(91.5)*	209(63.6)	252(67.0)
Partial response(%)	1(2.1)	60(18.2)	61(16.2)
No response(%)	3(6.4)	60(18.2)	63(16.8)
Relapse rate(%)	9(20.9)	46(22.0)	55(21.8)
5-yr DFS	71.3%(57.0% at 7 years)	67.0%(49.6% at 7 years)	67.8%(51.2% at 7 years)
5-yr Overall survival	90.7%(68.0% at 8 years)*	65.2%(60.2% at 8 years)	68.9%(60.8% at 8 years)

HD: Hodgkin's disease, NHL: non-Hodgkin's lymphoma, DFS: disease-free survival
*: $p<0.01$(vs non-Hodgkin's lymphoma)

Table 7. Chemotherapeutic regimens

Regimen	No. of cases(%)	Complete remission(%)	5-yr DFS	5-yr Overall survival
HD	35			
MOPP	12(34.3)	10(83.3)	65.6%	91.7% (61.1% at 96 M)
MOPP/ABVD	13(37.1)	12(92.3)	37.5%	92.3% (92.3% at 84 M)
ABVD	10(28.6)	10(100.0)	85.7%	88.9%† (88.9% at 45 M)
NHL	287			
CHOP	78(27.2)	54(69.2)	60.6%	65.8% (65.8% at 96 M)
BACOP	123(42.9)	71(57.7)	66.2%	70.0% (70.0% at 96 M)
MACOP-B	9(3.1)	6(66.7)	66.7%	87.5% (87.5% at 96 M)
ProMACE/CytaBOM	16(5.6)	9(56.3)	88.9%	54.7% (54.7% at 71 M)
m-BACOP	43(15.0)	24(55.8)	95.6%†	47.4%†
CVP	15(5.2)	10(66.7)	72.9%†	62.3%
Stanford	3(1.0)	1(33.3)	—	66.7%§ (33.3% at 20 M)

HD: Hodgkin's disease, NHL: non-Hodgkin's lymphoma
DFS: disease-free survival, M: months
†: disease-free survival rate at 2 years
†: overall survival rate at 3 years, §: overall survival rate at 1 year

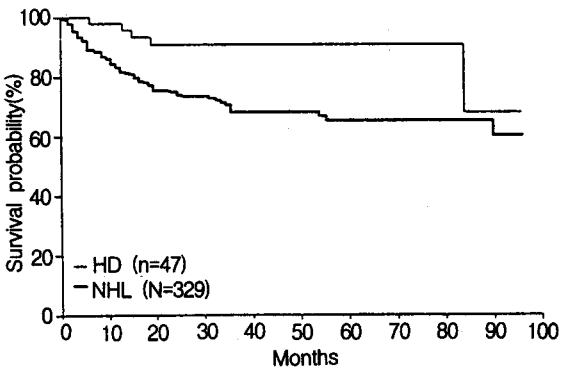

Fig. 2. Survival curves of patients with malignant lymphoma: HD vs NHL.

and 49.6% in NHL. The 5-year and 8-year overall survival rates were 90.7% and 68.0% in HD; 65.2% and 60.2% in NHL (Table 6, Fig. 2). The influence of chemotherapeutic regimens on survival of HD and NHL was not observed (Table 7). The clinical characteristics and therapeutic outcomes according to the histopathologic subtypes are indicated as Table 8 & Fig. 3.

Prognostic factors

There were many pretreatment features of patients with HD and NHL that correlated with prognosis. Many pretreatment clinical variables, including patient demographics, number and site of disease in-

Table 8. Clinical features and therapeutic outcomes according to histopathologic subtypes

	Age(yr)*	M : F	Stage (%) I	II	III	IV	BM involve(%)	CR(%)	5-yr Disease-free survival (% at maximum follow-up)	5-yr Overall survival (% at maximum follow-up)
HD										
LP (n=6)	41(20~81)	4 : 2	1(1.7)	4(66.7)	1(1.7)	0	0	6(100)	62.5%(62.5% at 81 M)	83.3%(83.3% at 83 M)
NS (n=13)	30(16~58)	6 : 7	2(15.4)	5(38.5)	3(23.1)	3(23.1)	1(7.7)	12(92.3)	50.8%(50.8% at 76 M)	91.7%(91.7% at 96 M)
MC (n=21)	36(19~63)	13 : 8	4(19.0)	10(47.6)	3(14.3)	4(19.0)	1(4.8)	19(90.5)	92.9%(46.4% at 84 M)	95.2%(47.6% at 96 M)
LD (n=7)	41(26~52)	5 : 2	1(14.3)	3(42.6)	2(28.6)	1(14.3)	1(14.3)	6(85.7)	75.0%(75.0% at 76 M)	85.7%(85.7% at 84 M)
NHL										
Low (n=37)	51(33~71)	23 : 14	18(48.6)	8(21.6)	2(5.4)	9(24.3)	7(18.9)	36(97.3)	41.4%(41.4% at 71 M)	89.1%(89.1% at 77 M)
SLL (n=23)	51(33~71)	13 : 10	16(69.6)	3(13.0)	0	4(17.4)	3(13.0)	23(100)	93.8%(93.8% at 68 M)	100 %(100 % at 72 M)
FSCL (n=9)	50(33~67)	6 : 3	2(22.2)	1(11.1)	2(22.2)	4(44.4)	4(44.4)	8(88.9)	25.0%(25.0% at 71 M)	71.1%(71.1% at 77 M)
FML (n=5)	49(36~68)	4 : 1	0	4(80.0)	0	1(20.0)	0	5(100)	50.0%†	100 %†
Intermediate (n=233)	49(15~80)	160 : 73	55(23.6)	83(35.6)	34(14.6)	61(26.2)	11(4.7)	142(60.9)	72.0%(48.7% at 84 M)	67.9%(60.4% at 96 M)
FLCL (n=10)	40(26~78)	10 : 0	2(20.0)	4(40.0)	2(20.0)	2(20.0)	2(20.0)	7(70.0)	100 %(100 % at 81 M)	80.0%(80.0% at 88 M)
DSCL (n=19)	55(18~80)	13 : 6	4(21.1)	7(36.8)	2(10.5)	6(31.6)	3(15.6)	12(63.2)	57.1%(57.1% at 70 M)	62.9%(62.9% at 73 M)
DML (n=59)	50(21~78)	43 : 16	10(16.9)	28(47.5)	3(5.1)	18(30.5)	2(3.4)	34(57.6)	74.2%(55.7% at 84 M)	76.2%(60.9% at 96 M)
DLCL (n=145)	49(15~78)	94 : 51	39(26.9)	44(30.3)	27(18.6)	35(24.1)	4(2.8)	89(61.4)	72.4%(41.3% at 84 M)	65.7%(65.7% at 96 M)
High (n=47)	45(15~76)	35 : 12	8(17.0)	15(31.9)	9(19.1)	15(31.9)	4(8.5)	23(48.9)	66.5%(66.5% at 88 M)	44.3%(44.3% at 96 M)
IBL (n=36)	48(15~69)	29 : 7	7(19.4)	13(36.1)	8(22.2)	8(22.2)	1(2.8)	20(55.6)	73.2%(73.2% at 88 M)	51.4%(51.4% at 96 M)
LL (n=5)	23(17~28)	3 : 2	0	2(40.0)	1(20.0)	2(40.0)	2(40.0)	2(40.0)	0%†	80.0%†(40.0% at 20 M)
SNCL (n=6)	49(15~76)	3 : 3	1(16.7)	0	0	5(83.3)	1(16.7)	1(16.7)	100 %†	41.7%†(20.8% at 21 M)
Others (n=12)	48(27~69)	5 : 7	4(33.3)	3(25.0)	1(8.3)	4(33.3)	1(8.3)	8(66.7)	75.0%†	30.3%

HD: Hodgkin's disease, NHL: non-Hodgkin's lymphoma, BM: bone marrow, CR: complete remission, M: months
†: survival rate at 3 years, †: survival rate at 1 year
***: Values are denoted as mean(range).**

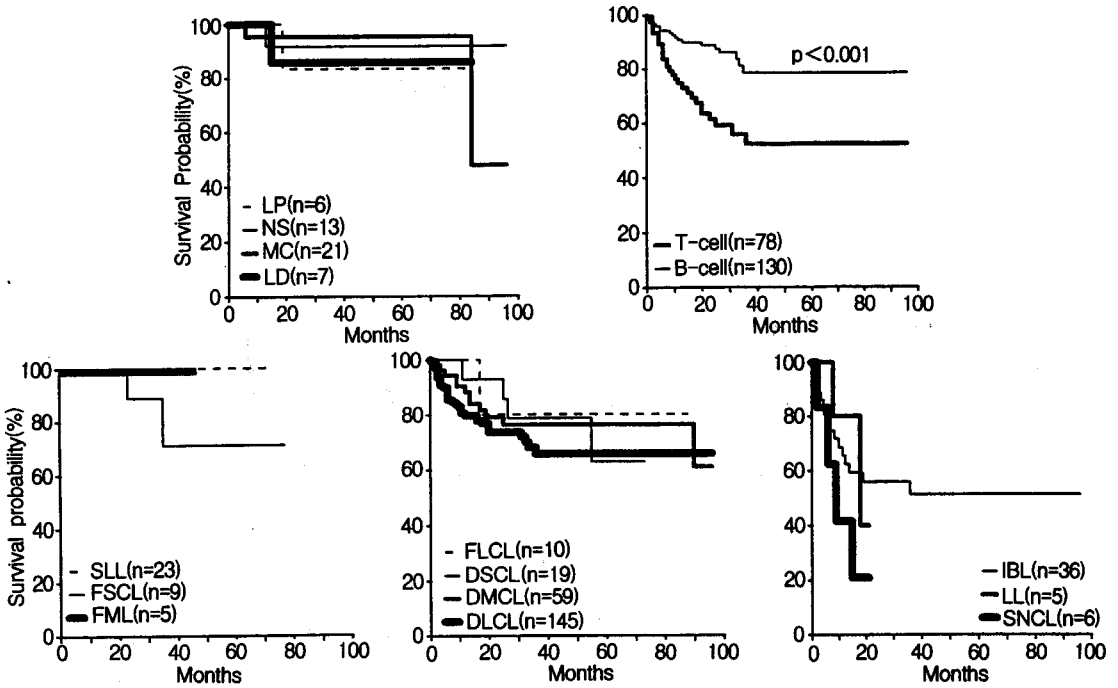

Fig. 3. Survival curves of patients with malignant lymphoma according to histopathologic and immunophenotypic subtypes.

volvement, presence of B symptoms, stage, histopathologic subtypes, and tumor burden were evaluated for statistical analyses. Laboratory determinations, including peripheral blood counts and serum enzymes, which were routinely tabulated as part of the pretreatment staging process, were also analyzed.

To identify potential prognostic factors, a series of univariate analyses were performed. There were no significant factors in HD. On the other hand, we observed that several features were correlated with therapeutic outcomes in NHL.

Of these variables, age, performance status, presence of B symptoms, histopathologic grade, immunophenotype, stage, number of extranodal sites, levels of Hb, albumin, LDH, and β_2-MG were influenced on the achievement of CR (Table 9). By multivariate analysis using logistic regression, age ($p=0.049$), histopathologic grade ($p=0.006$), and stage ($p<0.001$) were independent predictive factors influencing CR. Among the patients who were 60 years old or younger, the independently influencing factors on CR were histopathologic grade ($p=0.035$), immunophenotype ($p=0.038$), and stage ($p<0.001$) (Table 10).

Also, several variables were associated with survival. Of these, age is one of the most important variables associated with outcome, and the presence of B symptoms and poor performance status were additional clinical characteristics that were associated with poor outcome. Several features which were associated with disease distribution and tumor burden, including advanced stage and number of extranodal sites, were found to correlate with poor prognosis on survival, respectively. In pretreatment laboratory variables, decreased levels of hemoglobin and serum albumin, and elevated levels of LDH and β_2-MG were found to correlate with survival. Also, when patients were grouped according to histopathologic and some immunohistochemical patterns, higher grades and T-cell lineages were significantly associated with poor outcome, respectively. On the other hand, some parameters such as sex, dimension of largest diameter (≥ 10 cm), and use of colony-stimulating factor were not associated with thera-

Table 9. Univariate analysis of predictive variables for complete remission, disease-free survival, and overall survival

Factors	Complete remission	Disease-free survival	Overall survival
Clinical determinants			
Age(≤60 vs >60 year)	0.028	0.048	0.009
Sex(male vs female)	0.060	0.958	0.266
Performance status(0 or 1 vs ≥2)	<0.001	0.705	<0.001
B symptoms	<0.001	0.036	<0.001
Dimension of largest diameter(<10 vs ≥10 cm)	0.061	0.444	0.898
Histopathologic grade	<0.001	0.951	<0.001
Cell lineage(B- vs T-cell)	0.002	0.247	<0.001
Stage	<0.001	<0.001	<0.001
Number of extranodal sites(<2 vs ≥2)	0.001	<0.001	<0.001
Bone marrow involvement	0.469	0.022	0.098
Use of colony-stimulating factor	0.073	0.160	0.330
Laboratory determinants			
Hb(>12.0 vs ≤12.0 g/dL)	0.012	0.187	0.003
Albumin(>3.0 vs ≤3.0 g/dL)	0.013	0.011	<0.001
LDH(normal vs >normal)	<0.001	0.159	<0.001
β_2-microglobulin(normal vs >normal)	0.005	0.001	<0.001

Table 10. Multivariate analysis of predictive variables for complete remission, disease-free survival, and overall survival

Factors	Complete remission	Disease-free survival	Overall survival
All ages			
Age(≤60 vs >60 year)	0.049	0.001	0.001
Performance status(0 or 1 vs ≥2)	0.526	0.382	0.006
B symptoms	0.097	0.023	0.567
Histopathologic grade	0.006	0.749	0.015
Cell lineage(B- vs T-cell)	0.150	0.626	0.202
Stage	<0.001	<0.001	<0.001
Number of extranodal sites(<2 vs ≥2)	0.497	0.935	0.575
Hb(>12.0 vs ≤12.0g/dL)	0.393	0.648	0.222
Albumin(>3.0 vs ≤3.0 g/dL)	0.789	0.355	0.374
LDH(normal vs >normal)	0.076	0.790	<0.001
β_2-microglobulin(normal vs >normal)	0.535	0.066	0.001
Age-adjusted(≤60 year)			
Performance status(0 or 1 vs ≥2)	0.393	0.638	0.417
B symptoms	0.585	0.013	0.410
Histopathologic grade	0.035	0.873	0.049
Cell lineage(B- vs T-cell)	0.038	0.898	0.244
Stage	<0.001	0.026	<0.001
Number of extranodal sites(<2 vs ≥2)	0.535	0.845	0.630
Hb(>12.0 vs ≤12.0 g/dL)	0.309	0.153	0.901
Albumin(>3.0 vs ≤3.0 g/dL)	0.483	0.088	0.752
LDH(normal vs >normal)	0.106	0.940	0.009
β_2-microglobulin(normal vs >normal)	0.661	0.692	0.074

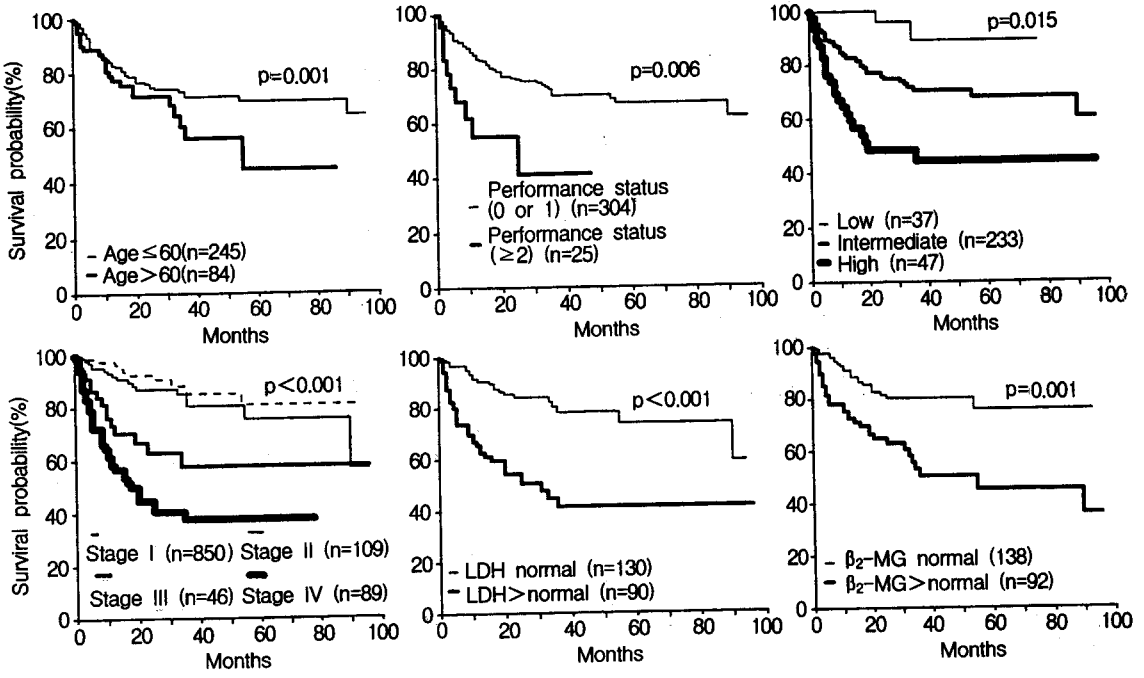

Fig. 4. Survival curves of patients with NHL according to prognostic factors.

peutic outcomes (Table 9).

In order to further refine prognostic information, we performed multivariate analysis using Cox's proportional hazards model. In NHL patients of all ages, age (p=0.001), presence of B symptoms (p=0.023), and stage ($p<0.001$) were closely associated with disease-free survival (Table 10). As well, six features were independently associated with overall survival, including age (p=0.001), performance status (p=0.006), stage ($p<0.001$), histopathologic grade (p=0.015), serum LDH ($p<0.001$) and β_2-MG (p=0.001) (Table 10, Fig. 4). Among the patients who were 60 or younger, the presence of B symptoms (p=0.013) and stage (p=0.026) were closely correlated with disease-free survival, and remained independently significant prognostic factors on overall survival were stage ($p<0.001$), serum LDH (p=0.009), and histopathologic grade (p=0.049)(Table 10).

According to the number of International Prognostic Index (age, performance status, number of extranodal sites, Ann Arbor stage, and serum LDH) (Shipp and Harrington, 1993), we also defined the low risk (0~1 risk factor), low-intermediate risk (2 risk factors), high-intermediate risk (3 risk factors), and high risk groups (≥4 risk factors). After categorizing patients according to the above criteria, we found that the number of risk factors based on the International Prognostic Index had an influence on survival, as shown in Fig. 5 ($p<0.001$).

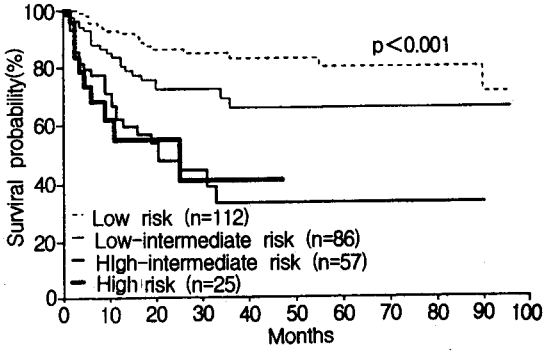

Fig. 5. Survival curves of patients with aggressive NHL according to the International Prognostic Index.

DISCUSSION

There have been several reports which indicate considerable differences in malignant lymphoma around the world (Kadin *et al.* 1983; Shih and Liang, 1991; Kim *et al.* 1992b; Muller, 1992; Hahn *et al.* 1995). As well, much new information has become available in the last 10 years concerning lymphoma, resulting in the recognition of new entities and refinement of previously recognized disease categories.

When compared with other reports of Western countries, our results revealed several differences with respect to the incidence of HD, the histopathologic subtypes and the incidence of primary extranodal presentation. First, the incidence of HD were less common than in Western countries (35~50%) but similar to that in Japan (12%) and other reports from Korea (8.6~11.4%) (Kim *et al.* 1982; Talvalka *et al.* 1982; Kadin *et al.* 1983; Muller, 1992; Kim *et al.* 1992b; Hahn *et al.* 1995). This disparity may be due to either the socioeconomic status of the population itself or the characteristic role of some etiologic factors. Indeed, HD has a low incidence rate in many countries, especially in developing countries. On the other hand, in certain endemic areas of Japan, HD is strikingly uncommon but the incidence of T-cell NHL is markedly high, which is probably associated with type-C retrovirus (Kadin *et al.* 1983).

Second, the MC subtype was the most common form in HD (44.7%) and this was in accordance with the incidence in Korean and Japanese studies (Kadin *et al.* 1983; Kim *et al.* 1992b; Hahn *et al.* 1995). On the other hand, the most common form in Western countries was the NS subtype, in which the proportion has been approxiamtely 40~75% (Kim *et al.* 1982; Talvalkar *et al.* 1982; Muller, 1992).

Third, among cases of NHL, the incidence of intermediate grade lymphoma, especially the diffuse large-cell subtype, was definitely more common in Korea than in Western countries (Kim *et al.* 1982; Newell *et al.* 1987; Muller, 1992). However, the incidence of low grade lymphoma was strikingly less common in this study, in which the proportion of NHL was 11.2%. This result was similar to that in recent Korean, Japanese and Taiwanese studies (Kadin *et al.* 1983; Su *et al.* 1985; Shih and Liang, 1991; Kim *et al.* 1992a; Kim *et al.* 1992b; Hahn *et al.* 1995). This discrepancy was presumably due to the fact that follicular lymphomas which are more common in Western countries rarely occur in Asian countries. Recent data from the U.S. showed that the frequencies of low and intermediate grade lymphoma were 38.1% and 33.1%, respectively, and the most common subtype was follicular small-cleaved-cell type (22.5%), followed by diffuse large-cell type (Kim *et al.* 1982; Newell *et al.* 1987; Muller, 1992).

Fourth, among 218 patients who were confirmed by immunohistochemical staining, the proportion of T-cell lymphoma was 35.8%. In the review of 312 cases of NHL (Kim *et al.* 1992a), the incidence of T-cell lymphoma in Korea was 35.2%. This showed a quite comparable incidence to that of other reports from Japan (Suchi and Tajima, 1979) and China (Su *et al.* 1985), but it was much higher than in Western countries (18.7%) (Lukes *et al.* 1978).

Another feature was that the frequency of primary extranodal presentation was 44.2%, and most extranodal lesions were found in patients with NHL. This was similar to that of other reports from Korea, Japan and Europe (43~53%) but much higher than that in the U.S. (20%) (Freeman *et al.* 1972; Kadin *et al.* 1983; Shih and Liang, 1991; Kim *et al.* 1992a; Kim *et al.* 1992b; Muller, 1992; Hahn *et al.* 1995). This fact, that extranodal lymphoma is more common in Korea, may contribute to a higher rate of intermediate grade and in particular the diffuse large-cell subtype, because the incidence of the follicular subtype, which is also known as a favorable type, has been known to be rare in extranodal sites and early diagnosis is more difficult than primary nodal lymphoma. In this study, extranodal lymphomas occurred most frequently in the stomach and Waldeyer's ring. Kadin *et al.* suggested that many primary gastric and tonsillar lymphomas may have arisen in pre-existing lymphoid hyperplasias (Kadin *et al.* 1983). On the basis of these observations, differences in race, geography and the prevalence of some etiologic factors such as *Helicobacter pylori* may be responsible for the relatively high incidence of primary extranodal lymphoma in Korea.

These diverse clinical, histopathologic and immunophenotypic characteristics highly suggest the possible role of genetic or environmental factors on the etiopathogenesis of malignant lymphoma. Thus, further international comparative studies are needed in terms of racial, sociocultural and economic factors.

In this study, the CR rate of patients with HD was 91.5%, and the 5-year and 8-year overall survival rates were 90.6% and 68.0%, respectively. When compared with other reports, our results were equivalent and excellent. In other reports (Longo *et al.* 1991; DeVita *et al.* 1993; DeVita and Hubbard, 1993), the CR rate varies from 73-to-92%, and the overall survival rate usually averaged between 80-to-89% at 5 years. Since our study population of HD was small and one patient died due to late relapse and disease progress at 8 years and who had also previously been diagnosed as mixed cellularity subtype, our data showed a relatively long-term plateau followed by a sharp drop in the survival curve after 8 years of observation. Although most events took place in the first 2 years of follow-up, our data indicates that HD could not be assessed for cure only after 5 years of observation. According to the data after more than 20 years of follow-up (Longo *et al.* 1986), 84% of patients attained CR, and the 10-year overall survival rate of total patients was 48%. Therefore, to establish the clinical course and final outcome of HD in Korea, long-term follow-up in a large population will be needed.

According to the accumulated experience in Western countries, the CR rate varies from 50-to-80%, and the overall survival rate was 50~75% at 5 years in patients with NHL (Yi *et al.* 1990; Vose *et al.* 1991; Armitage, 1993; Shipp and Harrington, 1993; Shivdasani *et al.* 1993). This result was similar to our therapeutic outcomes. In this study, the CR rate was 63.6%, and the overall survival rates at 5 and 8 years were 65.2% and 60.2%, respectively, in patients with NHL. It is difficult to explain the reason why our therapeutic outcomes are comparable to those in Western countries, although the prevalence of aggressive histopathologic subtypes, such as diffuse large-cell subtype, were more common in our hospital. The one possibility was that the percentage of patients who were under 60 years of age (74.5% vs. 59.0%) or had good performance status (92.4% vs. 76.3%) tend to be higher in our hospital than in other reports (Shipp and Harrington, 1993; Shivdasani *et al.* 1993). Since the projected dose intensity of chemotherapeutic drugs can be easily administered in patients who are younger or have good performance status, we may postulate that these favorable factors influenced the outcome in this study.

In previous analyses of patients with malignant lymphoma, a variety of pretreatment clinical characteristics were consistently associated with survival. These clinical variables reflected three basic features: (1) the tumor's growth and invasive potential (LDH, stage, mass size, number of extranodal sites of disease); (2) the patient's response to the tumor (performance status, B symptoms); and (3) the patient's ability to tolerate intensive therapy (performance status, age) (Coiffier *et al.* 1993; Shipp, 1994). In our study, several features were associated with therapeutic outcomes, including age, performance status, presence of B symptoms, histopathologic grade, cell lineage, stage, number of extranodal sites, serum Hb, albumin, LDH and β_2-MG in NHL. Although the dimension of largest diameter and the use of colony-stimulating factor were not significant factors for predicting survival, they showed a tendency to influence the achievement of CR in which p-values were 0.061, 0.073, respectively. Since mass size and the use of colony-stimulating factor are associated with tumor burden and dose intensity of the treatment, we considered that these factors can, in part, also be important variables in predicting therapeutic outcomes and further cumulative analyses including these factors will be required. By multivariate analysis, we found that of all the abovementioned factors, age, performance status, histopathologic grade, stage, serum LDH and β_2-MG were the useful independent prognostic factors predicting survival. Also, in NHL patients under 60 years of age, stage, serum LDH, and grade were closely associated with their therapeutic outcomes. On the other hand, there were no significant prognostic factors predicting therapeutic outcomes in HD. However, the number of patients with HD was relatively small in our study and further clinical studies with larger numbers of patients should be required to identify potential prognostic factors.

In an attempt to standardize the reporting of results and allow improved comparisons between clin-

ical trials, Shipp and Harrington proposed an International Prognostic Index including age, number of extranodal disease sites, serum LDH, performance status, and Ann Arbor stage in patients with aggressive NHL (Shipp and Harrington, 1993). This index has been widely established by classifying patients according to the number of risk factors present at the time of diagnosis using this list of five variables. We also attempted to classify patients according to the International Prognostic Index risk category. After categorizing patients, therapeutic outcomes based on survival were correctly predicted in patients with aggressive NHL. Therefore, clinical prognostic factors incorporated in the International Prognostic Index can be used to identify specific risk groups and to compare different therapeutic approaches.

We also analyzed the significance of immunophenotype in predicting outcome in 208 patients. As shown in Fig. 3, our results showed a more favorable outcome in patients with B-cell phenotype than T-cell phenotype. Recently, Hutchison *et al.* reported that the B-cell lineage was associated with favorable survival when stratified for stage among patients with large-cell lymphoma (Hutchison *et al.* 1995). To clarify the significance of immunophenotype on survival, further exploration of the association between treatment response and immunophenotype is warranted.

In conclusion, the characteristics of malignant lymphoma in our hospital differed from those in Western countries with respect to the clinical and histopathologic patterns, but the prognostic factors and overall therapeutic outcomes were quite comparable to other reports from Western countries. The identification of specific risk groups would have important therapeutic implications because substantial numbers of patients still die of the disease. The clinical application of the above-mentioned prognostic parameters will aid in the design of future therapeutic trials and in the selection of appropriate therapeutic approaches for individual patients.

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