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Original Article

Eleven-Year Experience of Low Grade Lymphoma in Korea (Based on REAL Classification)

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Low grade lymphomas are malignancies of predominantly small lymphocytes that typically have long median survival periods due to low proliferative rates. It is considered an indolent disease, but patients with low grade lymphoma can almost never be cured with conventional treatment. New low-grade lymphoma entities have been classified by the International Lymphoma Study Group (ILSG) and are also categorized into the Revised European American Lymphoma (REAL) classification. The REAL classification utilizes a multiparameter definition of clinico-pathologic and biologic entities. According to this classification, we investigated the incidence, various clinical characteristics, treatment outcome and prognostic factors of low grade lymphoma.

Many clinical characteristics of low grade lymphoma in Korea differed from those of Western countries, especially in the incidence, therapeutic outcome and prognostic factors. In Korea, although the general incidence of low grade lymphoma is relatively low, the relative number of mucosa-associated lymphoid tissue lymphoma (MALToma) is very high, and the overall survival rate is better than that reported of Western countries. Thus, further investigation on treatment outcome and prognosis of low grade lymphoma entities, other than mucosa-associated lymphoid tissue lymphoma, are warranted.

Key Words: Low grade lymphoma, REAL classification, survival

INTRODUCTION

Low grade non-Hodgkin's lymphoma comprise a heterogenous group of disorders both in terms of their cellular and histological composition as well as their clinical course. In general, low grade lymphomas are characterized by a low to moderate proliferative activity and a long clinical course with median survival times ranging from 4.3 years to 8.1 years.[1]

Previous morphologic classifications, like the Working Formulation, identified three morphologically distinct categories of low grade lymphoma: small lymphocytic lymphoma, follicular small cleaved cell lymphoma, follicular mixed, small cleaved and large cell lymphoma.[2] In addition, pathologists have described several other non-Hodgkin's lymphomas using immunohistochemical and genotypic analysis. Several indolent lymphomas include musoca-associated lymphoid tissue lymphoma, node-based monocytoid B-cell lymphoma, mantle cell lymphoma, lymphoplasmacytoid lymphoma and diffuse small cleaved-cell lymphoma. The most commonly applied classification systems - the Working Formulation, the Kiel classification, and the recently proposed Revised European American Lymphoma classification - nowadays try to discriminate between low, intermediate and high grade subtype.[3] Even though it is well known that the incidence of low grade lymphoma in Korea is very low in comparison with Western countries, there has been no report on the details of low grade lymphoma. Based on the REAL classification, we undertook this study to evaluate the pathological and clinical characteristics, therapeutic outcomes and prognostic factors of low grade lymphoma which followed up for eleven years.

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MATERIALS AND METHODS

Study patients

From January 1989 to March 2000, 178 consecutive patients with the initial histopathologic diagnosis of low grade lymphoma were retrospectively reviewed at the Division of Hematology Oncology, Department of Internal Medicine, Yonsei University College of Medicine in Seoul, Korea. There was no established criteria for eligibility except low grade lymphoma classification, but 23 patients were excluded due to insufficient data and loss of follow up information. The median follow up duration was 35 (5-118) months. The number of patients with lymphoma was 1,249 (non-Hodgkin's lymphoma vs Hodgkin's disease 1,125 vs 124). The incidence of low grade lymphoma was 14.3%(178/1,249) of all malignant lymphomas and 15.8%(178/1,125) of all non-Hodgkin's lymphomas.

Classification and staging

The indolent non-Hodgkin's lymphomas (low grade lymphoma) were histopahologically classified into nine according to the REAL classification[3]: mucosa-associated lymphoid tissue lymphoma (MALToma), monocytoid B-cell lymphoma (MBCL), splenic marginal-zone lymphoma (SMZL), mantle cell lymphoma (MCL), small lymphocytic lymphoma (SLL), lymphoplasmacytoid lymphoma (immunocytoma), follicular small cleaved lymphoma (FSCL), follicular mixed lymphoma (FM) and diffuse small cleaved cell lymphoma (DSCL). Immunohistochemical staining was added for 148 selected cases.

We used the Ann-Arbor staging system for this study. Staging procedures included whole body computerized tomographic scan (neck, chest and abdominopelvis), whole body bone scan and gallium scan, PET scan and bilateral bone marrow aspiration and biopsy. We measured lactate dehydrogenase (LDH), beta-2 microglobulin, erythrocyte sendimetation rate (ESR) and albumin level. Since the LDH cutoff value changes with the method of measurement according to time, we used the LDH index (patient's LDH level/upper LDH cutoff level) to distinguish normal versus increased values.

Treatment and prognosis

Radiation therapy with operation or chemotherapy was introduced in localized low grade lymphoma. In patients with stage III or IV lymphomas, cytotoxic combination chemotherapy was the mainstay of therapeutic modalities.

Localized mucosa-associated lymphoid tissue lymphomas of the eye were treated with radiation therapy, and the patients at advanced stages were treated with additional systemic chemotherapy.

Low grade gastric MALToma confined to mucosa were initially treated with antibiotics to eradicate *Helicobacter pylori*. We also introduced surgical treatment or radiation therapy alone for treatment of gastric MALToma. In five cases (2.8%), we attempted therapeutic modalities combining surgery, radiation therapy and systemic chemotherapy.

The most commonly used regimens of combination chemotherapy are CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), m-BACOD (methotrexate, bleomycin, adriamycin, cyclophosphamide, vincristine, prednisolone), BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisolone), CVP (cyclophosphamide, vincristine, prednisolone), CEOP (cyclophosphamide, epirubicin, vincristine, prednisolone), I-COPA (Interferon α-2a, cyclophosphamide, vincristine, prednisolone, adriamycin) and COA (chlorambucil, vincristine, cytosine arabinoside) in that order.

Information on prognostic factors (age at diagnosis, performance status, serum LDH level, Ann Arbor stage, serum beta-2 microglobulin and albumin level) that had been associated with outcome was complete for 178 patients to identify independent prognostic factors. To select potential prognostic factors, we performed a series of univariate analysis. Based on the univariate analysis, step down multivariate analysis of complete response, disease free survival and overall survival was performed.

Criteria for response

We defined therapeutic response by the WHO

criteria. Complete response (CR) to treatment was defined as the disappearance of all clinical evidence of disease and the normalization of all laboratory values and radiographic results that had been abnormal before treatment. Partial response (PR) was defined as a 50% or greater reduction of the 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

The disease-free survival of patients with complete response was measured as the interval between the end of treatment and relapse, death or the date of the last follow-up evaluation in patients who had no relapse. Overall survival was measured as the interval between the beginning of treatment and death or the date of the last follow-up evaluation.

The univariate associations between therapeutic response and individual clinical features were analyzed with Fisher's exact test for two-by-k tables. Disease-free survival among patients with complete response and overall survival among all patients were estimated with the method of Kaplan-Meier. The univariate associations between individual clinical features and overall/disease free survival were determined with the log-rank test.

Some data on several prognostic factors were missing. These were dealt with by carrying out "complete case" analysis, in which patients were excluded from particular analyses if their files did not contain data on the required variables.

Features independently associated with complete remission rate, disease-free survival and overall survival, were identified in multivariate analyses by Cox's proportional-hazards regression.

RESULT

Patient characteristics

The clinical characteristics of the 178 patients are given in Table 1. The age of the patients

Table 1. Patient Characteristics

Clinical parameters	
Age(year)	50.8 (13-78)
Sex(male:female)	1.07 : 1
Stage	* †
I	88 (49.4)
II	56 (31.5)
III	7 (3.9)
IV	27 (15.2)
Performance status	
0 or 1	155 (87.1)
≥ 2	23 (12.9)
IPI(International Prognostic Index)	
Low	123 (69.1)
Low intermediate	27 (15.2)
High intermediate	14 (7.9)
High	14 (7.9)
Immunophenotype	
B	147 (82.6)
T	1 (0.6)
Unclassified	30 (16.9)
B symptom	
Absent	144 (80.9)
Present	14 (7.9)
Unknown	20 (11.2)
Multiple lymphadenopathy	
Absent	146 (82.0)
Present	32 (18.0)
Extranodal involvement	
Absent	143 (80.3)
Present	35 (19.7)
LDH	
≤1 × normal	115 (64.6)
>1 × normal	63 (35.4)
Beta-2 MG	
≤ normal	114 (64.0)
> normal	64 (36.0)
ESR	
≤ normal	65 (36.5)
> normal	35 (19.7)
Unchecked	78 (43.8)
Albumin	
≤ 3.5	30 (16.9)
> 3.5	148 (83.1)

*denotes numbers of patient and †percentage.

ranged from 13 to 78 years. There was no gender predominance. The majority (87.1%) of patients were at zero or one of the ECOG scale. The median follow up duration was 47 months.

Classification and immunophenotype

Low grade lymphomas were divided into 9 groups of patients in our study. These subtypes are summarized in Table 2.

Among the 178 cases of low grade lymphoma, the most common histopathologic subtype by far was MALToma (69.1%) followed by FM (9.0%), FSCL (6.2%), SLL (5.6%) and MCL (3.9%) in that order.

Of the 148 patients that were confirmed by immunohistochemical staining, only one patient had T-cell markers instead of B-cell markers. Thirty cases could not be determined nor classified properly (Table 1).

Distribution

The distribution of extranodal low grade lymphoma is listed in Table 3, and the organ distribution of MALToma is listed in Table 4.

The percentage of nodal and extranodal sites of lymphomatous involvement were 21.9% and 78.1% respectively. Extranodal involvement of lymphoma was mostly comprised of MALToma. In most cases, the stage of MALToma was confined to stage I and II, and the rate of complete remission of MALToma (82.1%) was quite higher than any other subtype. The two most common extranodal involvement sites were the stomach and eye. Extranodal low grade lymphoma (43.2%) and MALToma (49.2%) were most common in the stomach, followed by the eyes (Table 3, 4).

Intestinal lymphomas not involving the stom-

Table 2. Classification and Frequency of Low Grade Lymphoma

Subtype	No (%)
Mucosa associated lymphoid tissue lymphoma (MALToma)	122 (68.5)
Follicular mixed small and large cell lymphoma (FM)	16 (9.0)
Follicular small cleaved cell lymphoma (FSCL)	11 (6.2)
Small lymphocytic lymphoma (SLL)	10 (5.6)
Mantle cell lymphoma (MCL)	7 (3.9)
Diffuse small cleaved cell lymphoma (DSCL)	5 (2.8)
Lymphoplasmacytoid lymphoma (LPL)	4 (2.2)
Splenic marginal zone lymphoma (SMZL)	2 (1.1)
Monocytoid B cell lymphoma (MBCL)	1 (0.6)
Total	178 (100.0)

Table 3. Extranodal Distribution

Location	No (%)
Stomach	60 (43.2)
Eye	52 (37.4)
Thyroid	8 (5.7)
Small bowel	4 (2.9)
Tongue	4 (2.9)
Larynx, pharynx	3 (2.2)
Breast	3 (2.2)
Vagina	2 (1.4)
Large bowel	2 (1.4)
Parotid gland	1 (0.7)
Subtotal	139 (78.1)
Total	178 (100.0)

Table 4. Organ Distribution of MALToma

Organ distribution	No (%)
Stomach	60 (49.2)
Eye	44 (36.1)
Thyroid	6 (4.9)
Small bowel	3 (2.5)
Breast	3 (2.5)
Large bowel	2 (1.6)
Vagina	2 (1.6)
Spleen	1 (0.8)
Parotid gland	1 (0.8)
Total	122 (100.0)

ach occupied 4.3% of all low grade lymphomas, and 4.1% of all MALTomas. Six out of eight lymphomas of thyroid were MALToma. Lymphomas in the upper respiratory tract, including tonsil, larynx, and nasopharynx, also accounted for up to 5.1% of all low grade lymphomas (Table 3, 4).

Therapeutic outcomes

After various therapeutic modalites shown in Table 5 and Table 6, the overall response rate in this study was 95%, with CR 75.3% and PR 19.7%.

Table 5. Therapeutic Modalities

Treatment	No (%)
Chemotherpy alone	57 (32.0)
Radiation therapy alone	38 (21.3)
Radiation therapy +surgery	29 (16.3)
Surgery alone	24 (13.5)
Chemotherapy + surgery	11 (6.2)
Chemotherapy + radiation therapy	10 (5.7)
Chemotherapy + surgery + radiation therapy	5 (2.8)
Chemotherapy + PBSCT	2 (1.1)
No treatment	2 (1.1)
Total	178 (100.0)

PBSCT, peripheral blood stem cell transplantation.

Table 6. Initial Regimen of Chemotherapy

Regimen	No (%)
Eradication with antibiotics	48 (56.5)
CHOP	10 (11.8)
m-BACOD	10 (11.8)
BACOP	6 (7.0)
CVP	3 (3.5)
CEOP	3 (3.5)
I-COPA	3 (3.5)
COA	2 (2.4)
Total	85 (100.0)

The relapse rate was 16.9% (Table 7). The 5-year overall survival rate was 76.7%, 10-year 63.9%, and the 5-year disease free survival rate among patients who showed complete response was 69.5% (Table 7, Fig. 1).

The overall survival and disease free survival rates according to stages are also shown in Fig. 1. The 5-year overall survival rates were 96% (stage I), 81% (stage II), 70% (stage III) and 36% (stage IV). The 5-year disease-free survival rates were 78% (stage I), 75% (stage II), 56% (stage III) and 19% (stage IV).

The 5-year overall survival rates of each subtype are depicted in Table 8 and Fig. 2, which show that the mantle cell lymphoma had poor prognosis (5-year survival rate 28.5%) whereas DSCL, MBCL, SLL, LPL, FSCL, FM and MALToma had good prognosis. The five-year survival rates were 100% DSCL and MBCL, 75% LPL, 71.6% MALToma, 68.5% SLL, 59.2% FM and 50.5% FSCL in order.

Fig. 3 illustrates the survival curve of low grade lymphoma according to the international prognostic index. The five-year survival rates according to the index were 93% in the low group, 57% in the low-intermediate group, 48% in the high-intermediate group and 24% in the high group.

Fig. 4 shows that extra-nodal lymphomas survive longer than nodal lymphomas (84% vs 63% five-year survival rates).

Fig. 5 reveals that MALToma in orbit has a higher survival rate than stomach MALToma. The five-year survival rates for MALToma were 98% in the eye, 87% in the stomach and 84% in the thyroid (p=0.04).

The associations between each presenting characteristics and complete response rate, disease-free survival rate, overall survival rate are listed in

Table 7. Treatment Response

Complete response (%)	134 (75.3)
Partial response (%)	35 (19.7)
No response (%)	9 (5.1)
Relapse rate (%)	30 (16.9)
5-yr DFS (%)	69.5
5-yr OS (%)	76.7 (63.9 at 10 years)

Table 8. Clinical Features and Therapeutic Outcomes According to Histopathologic Subtypes

Subtype (No)	Age (range)	M:F	International prognostic index			Stage					CR (%)	PR (%)	Relap (%)	5-yr OS	5-yr DFS
			L(%)	LI(%)	HI(%)	H(%)	I(%)	II(%)	III(%)	IV(%)					
MALToma (123)	50 (13-78)	0.89:1	101 (82.1)	17 (13.8)	2 (1.6)	3 (2.4)	76 (61.8)	40 (32.5)	-	7 (5.7)	101 (82.1)	25 (20.3)	22 (17.9)	71.6	87.5
FM (16)	52 (20-75)	3:01	8 (50)	4 (25)	3 (18.8)	1 (6.3)	4 (25)	8 (50)	1 (6.3)	3 (18.8)	9 (56.3)	6 (37.5)	1 (6.3)	59.2	68.7
FSCL (11)	51 (35-68)	1.75:1	1 (9.1)	3 (27.3)	5 (45.5)	2 (18.2)	-	2 (18.2)	3 (27.3)	6 (54.5)	8 (72.7)	3 (27.3)	3 (27.3)	50.5	59.2
SLL (10)	55 (45-68)	1:01	3 (30)	1 (10)	3 (30)	3 (30)	3 (30)	1 (10)	-	6 (60)	5 (50)	2 (20)	3 (30)	68.5	60
MCL (7)	51 (29-64)	2.5:1	2 (28.6)	1 (14.3)	-	4 (57.1)	-	1 (14.3)	2 (28.6)	4 (57.1)	2 (28.6)	2 (28.6)	2 (28.6)	28.5	-
DSCL (5)	43 (13-71)	0.67:1	4 (80)	-	1 (20)	-	4 (80)	-	1 (20)	-	4 (80)	1 (20)	1 (20)	100	-
LPL (4)	60 (54-72)	1:01	3 (75)	-	1 (25)	-	1 (25)	2 (50)	-	1 (25)	3 (75)	1 (25)	0 0	75	-
SMZL (2)	49, 62	1:01	1 (50)	1 (50)	-	-	-	-	-	-	2 (100)	0 0	1 (50)	0	-
MBCL (1)	43	1:00	-	1 (100)	-	-	-	-	1 (100)	-	1 (100)	0 0	1 (100)	100	-

MALToma, Mucosa associated lymphoid tissue lymphoma; FM, Follicular mixed small and large cell lymphoma; FSCL, Follicular small cleaved cell lymphoma; SLL, Small lymphocytic lymphoma; MCL, Mantle cell lymphoma; LPL, Lymphoplasmacytoid lymphoma; DSCL, Diffuse small cleaved cell lymphoma; SMZL, Splenic marginal zone lymphoma; MBCL, Monocytoid B cell lymphoma; CR, complete response; PR, partial response; NR, no response; Relap, relapse; DFS, disease free survival; OS, overall survival.

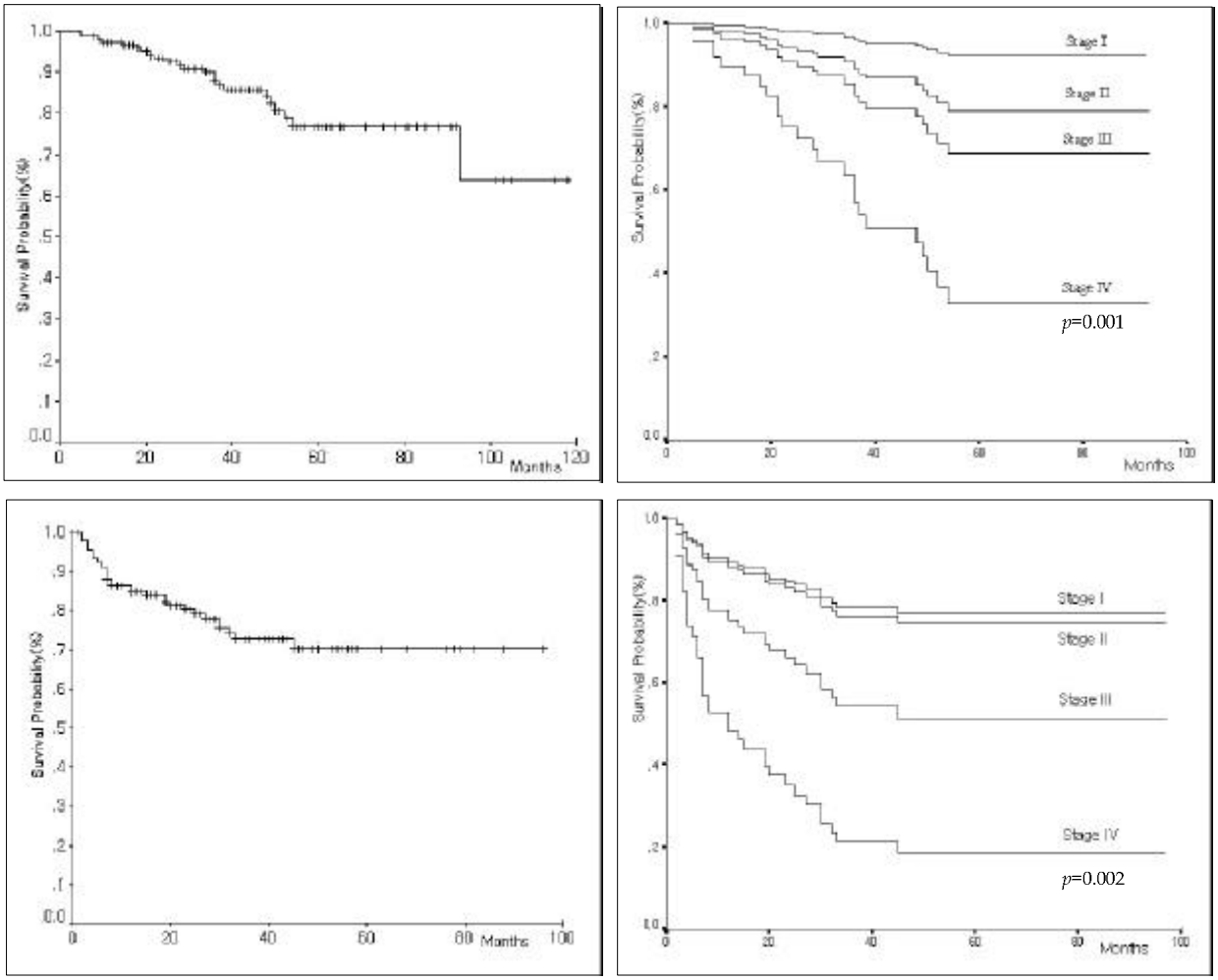

Fig. 1. Overall survival (upper column) and disease free survival (lower column) of patients with low-grade lymphoma according to stage.

Table 9. The clinical parameter such as old age, Ann Arbor stage III, IV, high ECOG scale, high and high intermediate international prognostic index, presence of B symptom, multiple lymphadenopathy, extranodal involvement, bone marrow involvement, high serum level of LDH, beta-2 microglobulin and low albumin level were significant factors associated with the overall survival rate. The sex and high serum level of ESR were insignificant factors.

In multivariate analysis, age, stage, performance status, serum LDH, albumin were statistically significant in all patient, but only performance status and albumin level below 60 years of age. The beta-2 microglobulin and international prognostic index were not important prognostic factors associated with overall survival (Table 10).

The causes of death are given in Table 11. The total number of deaths was 25 (14.0%) and the main cause of death was disease progression.

DISCUSSION

In the last two decades, increased understanding of the immune system and the genetic abnormalities associated with non-Hodgkin's lymphoma have led to the identification of several previously unrecognized types of lymphomas. These include MCL, MBCL, MALToma, SMZL, primary mediastinal large B-cell lymphoma, and a variety of T-cell lymphomas (anaplastic large cell). Therefore, measures to modify existing classifications and a new proposal by the Interna-

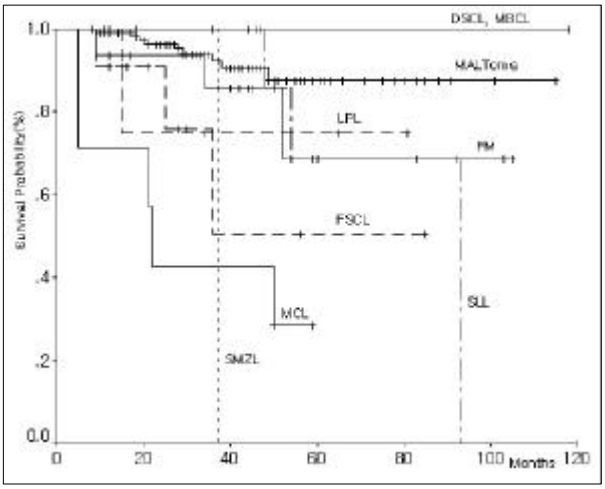

Fig. 2. Overall survival curves of patients with low grade lymphoma according to the histopathologic subtypes. DSCL, Diffuse small cleaved cell lymphoma; MBCL, Monocytoid B cell lymphoma; SLL, Small lymphocytic lymphoma; LPL, Lymphoplasmacytoid lymphoma; FSCL, Follicular small cleaved cell lymphoma; FM, Follicular mixed small and large cell lymphoma; MALToma, Mucosa associated lymphoid tissue lymphoma; SMZL, Splenic marginal zone lymphoma; MCL, Mantle cell lymphoma.

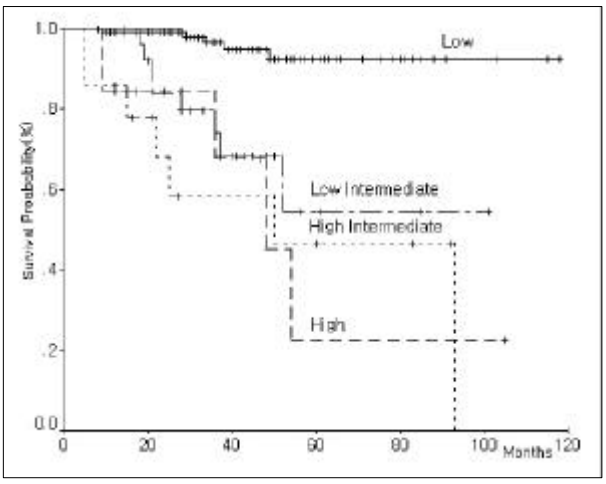

Fig. 3. Overall survival curves of patients with low grade lymphoma according to the international prognostic index(p=0.03).

tional Lymphoma Group to incorporate some aspects of the Kiel classification and Working Formulation have been put forward.[4]

The indolent non-Hodgkin's lymphomas are malignancies of predominatly small mature B lymphocytes. The low proliferation rates of low grade lymphomas logically explains the typical long median survival periods of these patients.

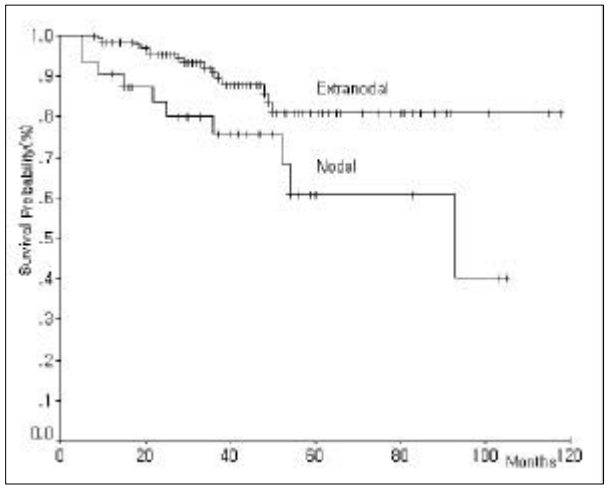

Fig. 4. Overall survival curves of patients with low grade lymphoma according to nodal vs extranodal distribution (p=0.002).

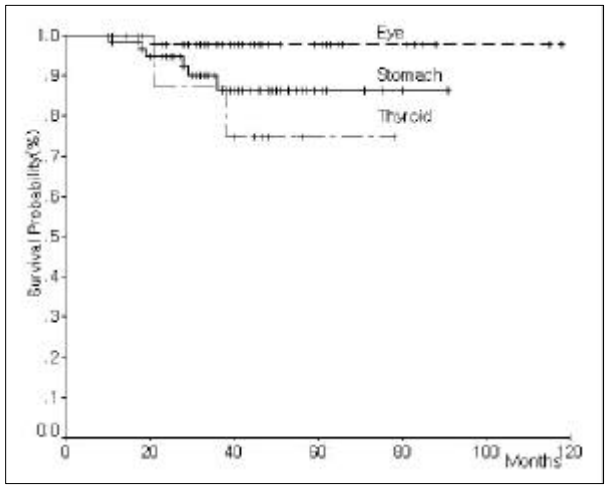

Fig. 5. Overall survival curves of patients with MALToma according to the location (p=0.04, eye vs thyroid).

Within this broadly defined group of lymphomas, there is considerable heterogeneity with regard to histology, biology and clinical features.[1,5-22] The clinical relevance of low grade lymphoma under the REAL classification needs to be evaluated especially in new entities.[23]

Three new indolent B-cell entities were added to the REAL classification: marginal zone cell lymphoma (MZCL), MCL and immunocytoma. The MZCL consists of MALToma, node based MBCL, and SMZL. These three lymphomas have very close morphologic and immunophenotypic similarities. In a review of 376 advanced-stage

Table 9. Univariate Analysis of Patients Charactersistrics

Characteristics	Complete response		DFS (disease free survival)		OS (overall survival)	
	rate(%)	*p* value	5-yr rate(%)	*p* value	5-yr rate(%)	*p* value
All patients	75.3		69.5		76.7	
Age		0.310		0.083		< 0.001
≤ 60	75.4		79.4		77.8	
> 60	24.6		20.6		22.2	
Sex		0.034		0.098		0.573
M	46.3		50		51.6	
F	53.7		50		48.4	
Ann Arbor Stage		< 0.001		0		< 0.001
Stage I, II	88.1		94.1		86.9	
Stage III, IV	11.9		5.9		13.1	
ECOG		< 0.001		0.165		< 0.001
0 or 1	95.5		95.6		96.1	
2 - 4	4.5		4.4		3.9	
IPI		< 0.001		0.001		< 0.001
Low	76.1		84.3		77.1	
Low intermediate	14.2		9.8		12.4	
High intermediate	6.7		3.9		5.9	
High	3		2		4.6	
B symptom		0.002		0.003		0.005
Absent	85.1		88.2		83.7	
Present	3.7		1		5.2	
Uncertain	11.2		10.8		11.1	
Multiple lymphadenopathy		< 0.001		0.020		< 0.001
Absent	86.6		90.2		86.9	
Present	13.4		9.8		13.7	
Extranodal involvement		< 0.001		0.001		< 0.001
Absent	83.7		93.1		86.3	
Present	12.7		6.9		13.7	
BM involvement		0.002		0.004		0.005
Absent	83.2		87.3		85.1	
Present	16.8		12.7		14.9	
ESR		0.519		0.451		0.071
≤ normal	67.5		69.5		68.2	
> normal	32.5		30.5		31.8	
Serum LDH		0.002		0.007		< 0.001
≤ 1 × normal	70.9		77.5		71.2	
> 1 × normal	29.1		22.5		28.8	
Beta-2 microglobulin		0.007		0.004		< 0.001
≤ 1 × normal	69.4		76.5		71.2	
> 1 × normal	30.6		23.5		28.8	
Albumin		0.001		0.135		< 0.001
≤ 1 × normal	11.2		8.8		12.4	
> 1 × normal	88.8		91.2		87.6	

Table 10. Multivariate Analysis of Prognostic Factors

Factors	CR (complete response)	DFS (disease free survival)	OS (overall survival)
	p-value	*p*-value	*p*-value
All patients (N=178)			
Age (≤ 60, > 60)	0.336	0.132	0.015
Stage (I or II vs III or IV)	0.050	0.003	< 0.001
Performance status (0 or 1 vs 2-4)	0.163	0.399	0.008
IPI (L, LI, HI, H)	0.260	0.215	0.303
Serum LDH	0.250	0.277	0.007
$\leq 1 \times$ normal vs $> 1 \times$ normal			
Beta-2 microglobulin	0.097	0.016	0.480
$\leq 1 \times$ normal vs $> 1 \times$ normal			
Albumin	0.333	0.345	0.002
$\leq 1 \times$ normal vs $> 1 \times$ normal			
Age-adjusted (Age ≤ 60)			
Stage (I or II vs III or IV)	0.118	< 0.001	0.142
Performance status (0 or 1 vs 2-4)	0.015	0.759	< 0.001
IPI (L, LI, HI, H)	0.418	0.263	0.277
Serum LDH	0.245	0.565	0.328
$\leq 1 \times$ normal vs $> 1 \times$ normal			
Beta-2 microglobulin	0.351	0.232	0.691
$\leq 1 \times$ normal vs $> 1 \times$ normal			
Albumin	0.483	0.434	0.050
$\leq 1 \times$ normal vs $> 1 \times$ normal			

Table 11. Cause of Death

Cause of death	No (%)
Disease progression	12 (48)
Infection	7 (28)
Hemorrhage	3 (12)
Organ failure	2 (8)
Unknown	1 (4)
Total	25 (100)

indolent lymphomas, MZCL accounted for 11.4% (MALToma; 5.1%, MBCL; 5.6%, SMZL < 1.0%), a significant incidence among patients with indolent lymphomas, while 9.6% were of MCL.[24]

Our results revealed several differences with respect to incidence of histopathologic subtypes compared with the reports of Western countries. Our study showed a higher frequency of MALToma (68.5%) than in Western countries (5.1%).[24] This result might be related to the high prevalence of *Helicobacter pylori* infection in Korea,[25] and MALToma of the stomach is considered to be closely related to *Helicobacter pylori* infection.

Ko, et al. argued that the increased rate of gastric lymphoma, accounting for more than 70% of marginal zone lymphoma, compared to a pre-

vious study in 1991 is attributable to the enhanced ability of pathologists to differentiate marginal zone B-cell lymphomas from chronic active gastritis and gastric pseudolymphomas. As in the stomach, a similar increase was found in lymphoma of the orbit. More than 50% of orbital non-Hodgkin's lymphomas were marginal zone B-cell lymphomas, most of which were previously diagnosed as pseudolymphoma.[26] Furthermore, we found that the frequency of mantle cell lymphomas was lower than that reported of Western countries[24,26] in addition to rare occurrences of splenic marginal zone and monocytoid B-cell lymphomas, showing similarity with Ko's Korean report.[26]

The low frequency of advanced stage MALToma relative to other subtypes in our study and relative to Western reports (5.7% vs 30%)[16] was peculiar.

Low grade lymphomas are very responsive to primary therapy, either irradiation or chemotherapy. Despite high overall response rates, no therapy has been associated with sustained remission or cure in a significant proportion of patients. Intensive chemotherapy seems not to be translated to improved disease-free survival or overall survival and therefore cannot be recommended for first-line treatment. After successful initial cytoreductive therapy, long term application of interferon-α may enable prolonged disease-free survival or even overall survival.[27,28] We administered cytotoxic chemotherapy followed by consolidation treatment with alpha interferon in three patients. Two patients with no treatment died two months and four months after initial diagnosis.

New prospective treatment have emerged from the introduction of cytostatic agents such as purine analogues and 2-chlorodeoxyadenosine with combination chemotherapy.[29-31] Anti-CD20 monoclonal antibody therapy was introduced in patients with relapsed low grade lymphoma and specifically depleted bone marrow reserve, and effective in approximately 50% of response in follicular type.[32-34] Currently, the most promising treatment is the application of myeloablative radio-chemotherapy followed by autologous or allogenic bone marrow transplantation or peripheral blood stem cell transplantation, which may provide a curative outcome even for advanced stages of disease.[35-37] In this study, we experienced autologous peripheral stem cell transplantation for low grade lymphoma in two patients.

On low grade MALToma of the stomach, there was a report that radiotherapy should be considered in patients who do not respond to antibiotic therapy, due to the significant benefits in gastric preservation and low morbidity.[38]

Saul A et al noticed that the survival of patients with low-grade lymphomas is significantly better than other type patients for the first ten years (60% vs 35%). However, after ten years, a continuous relapse along with high death rates was reported for patients with the low-grade subtype, and patients with high grade non-Hodgkin's lymphoma showed higher survival rates than low grade subtype after 15 years (33% vs 26%).[1,15,16] Similarly, a previous analysis of patients with malignant lymphoma according to the NCI Working Formulation Classification in Korea reported that survival was better in low grade lymphoma compared to intermediate and high grade lymphomas. The 5-year overall survival rate of low, intermediate and high grade lymphoma were 89.1%, 67.9% and 44.3% respectively.[39]

According to the accumulated experience on low-grade lymphoma in Western countries, the CR rate is about 80%. Thirty-five percent remains in remission at 10 years and 26% at 15 years. The overall survival rate of low-grade lymphoma in Western countries was approximately 60% at 5 years, 45% at 10 years and 29% at 20 years.[1,15,16] These Western results were slightly lower than our therapeutic outcome. In this study, disease free survival at 5 years was 69.5%, and overall survival at 5 years and 10 years were 76.7% and 63.9%, respectively. Almost above 80% of the patients with low grade lymphoma survived for long periods, except SMZL and MCL.[3] This finding resulted from a high proportion of favorable subtypes, such as MALToma. However, in most studies, MCL had poor prognosis and our results compared to Western reports, were similar. In particular, the blastic and diffuse variants demonstrated a more aggressive clinical course, calling for further innovative therapy.[15,16,24,34,40] Therefore, its provisional inclusion into low grade lymphomas because its small B-cell proliferation

should be reconsidered.

In our study, we encountered 7 MALToma patients (4 stomach, 3 eye) with dissemination that could influence survival. Fischer, et al. suggested that MALToma, after dissemination, is not a favorable sub-category of low grade disease, showing only a median failure-free survival period of 2.3 years in advanced stages when treated with combination chemotherapy.[24] By the Non-Hodgkin's Lymphoma Classification Project, using overall survival, the various lymphoma types were divided into four broad groups for prognostic purposes. Those with 5-year overall survival rates greater than 70% included follicular lymphoma, marginal zone B-cell lymphoma of the MALToma type. Lymphomas within 50% to 70% included the small lymphocytoid, lymphoplasmacytoid, and nodal marginal zone B-cell lymphoma. Lymphomas with less than 30% 5-year overall survival included MCL.[2]

At least one quarter of non-Hodgkin's lymphomas arise from tissue other than lymph nodes and even from sites that normally contain no lymphoid tissue. In Western countries, reports have shown considerable variation - from 24% to 48% - in the prevalence of extranodal lymphoma.[41] In our study, primary extranodal distribution accounted for up to 78% of all low grade lymphomas. We obtained this finding from the high incidence of MALT lymphomas of the stomach and eye in Korea, and gastrointestinal localization was identified as the most common form of extranodal lymphoma in a previous study.[42] Moreover the overall survival of extranodal lymphomas was better than that of nodal lymphomas in our study. However, other reports argue that this difference was due to histologic type and stage rather than the primary extranodal or nodal localization per se.[43]

Many prognostic studies of malignant lymphomas have been performed. In most studies, including ours, older age, poor performance status, advanced stage, presence of B symptoms, bulky disease, bone marrow involvement, the number of extranodal involvement, increased serum LDH, and high serum beta-2 microglobulin levels are consistent with survival related parameters.[6-14,39] Other studies also suggested ESR and serum albumin as candidates for prognostic factors.[12,13] Furthermore, the subtype was one of the most important prognostic factors that could determine therapeutic modality.

In our study, several features associated with prognosis included age, stage, performance status, international prognostic index, presence of B symptom, multiple lymphadenopathy, extranodal involvemnt, bone marrow involvement, elevated serum ESR, LDH, beta-2 microglobulin, and decreased serum albumin. By multivariate analysis, age, stage, performance status, serum LDH and albumin level were useful independent prognostic factors in predicting survival, whereas the international prognostic index, beta-2 microglobulin and ESR levels had no statistical significance. Performance status and serum albumin were also closely associated with their therapeutic outcomes in patients under 60 years of age.

The international prognostic index was not an independent factor in our study. Some authors have claimed the international index was useless in classifying low grade lymphoma, whereas serum determination of lactate dehydrogenase (LDH) and beta-2 microglobulin, were considered the most important prognostic factors of low grade lymphoma.[14] However, in contrast to all age groups, serum beta-2 microglobulin and LDH (age < 60) had no impact on the CR rate, DFS and overall survival in multivariate analysis of our study.

More accumulated data on low grade lymphomas, excluding MALToma, is necessary for clarifying clinical significance, such as survival depending on therapeutic strategies by the prognostic index based on REAL classification.

In Korea, the proportion of low grade lymphomas was relatively low. However, among them, the incidence of MALToma was very high. Since the treatment outcome of MALToma was quite fair, the overall treatment outcome seemed to be better than other reports. Moreover, various treatment modalities should be investigated according to other subtypes in REAL classification and nodal/extranodal distribution. Aggressive therapies might be evaluated in high-risk patients with the use of prognostic models such as the international index of prognostic factors and risk models.

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