Practical Utility of the Revised European-American Classification of Lymphoid Neoplasms for Japanese Non-Hodgkin's Lymphomas

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A clinicopathological study of 515 non-Hodgkin's lymphoma (NHL) cases was performed using the revised European-American classification of lymphoid neoplasms (REAL classification) in an HTLV1-nonendemic area of Japan. The following characteristics were revealed: 1) frequency of extranodal lymphomas was high (59%) with 79% B-cell lymphomas in this series, while the overall ratio of B:T/NK lineage was 3.7:1; 2) the most common type was the diffuse large B-cell lymphoma (46%), follicle center lymphomas occurred at an incidence lower (15%) than that in European and American populations, and marginal zone B-cell lymphomas accounted for as much as 12%; 3) peripheral T-cell lymphomas were common (19%), with the unspecified type predominant (11%), while adult T-cell lymphomas were present at a level equivalent to that among European and American patients (1%). Clear segregation of survival curves was rated according to cell lineage and B-cell lymphomas had a better prognosis than T/NK-cell lymphomas. Furthermore, new subtypes in the REAL classification, such as marginal zone B-cell and mantle cell lymphomas, exhibited distinct curves. Taken altogether, the REAL classification demonstrated advantages for assessment of Japanese NHL cases.

Key words: Lymphoma — REAL classification — Non-Hodgkin's lymphoma

In 1994, the International Lymphoma Study Group (ILSG) published the Revised European-American Classification of Lymphoid Neoplasms (REAL classification).[1)] Derived from the Kiel classification[2)] widely used in West European countries, this is based on histologic, immunologic and genetic features, as well as major clinical variables. The REAL classification is now widely accepted as an updated list of lymphoid neoplasms, with recent clinicopathological studies published in Europe and America[3–7)] giving positive estimates of its utility.

In Japan the Lymphoma Study Group's (LSG) classification[8)] has been generally used for diagnosis of non-Hodgkin's lymphomas (NHLs). This classification, with a pleomorphic type for adult T-cell lymphoma, focuses on morphological characteristics, and gives excellent reproducibility as well as uniformity in making diagnoses. However, the REAL classification covers entities which are not sub-classified in LSG, among them mantle cell lymphoma (MCL)[9)] and marginal zone B-cell lymphoma (MZBL), corresponding to low grade B-cell lymphoma of mucosal associated lymphoid tissue (MALT) type,[10, 11)] which have differing clinical, morphological and genomic features.

It is well known that the distribution of subtypes of malignant lymphoma demonstrates wide variation among races and countries. In the present study, we therefore applied the REAL classification to our cases, to examine the practical utility of the REAL classification for diagnosis of NHL in Japan.

MATERIALS AND METHODS

Materials Malignant lymphomas diagnosed in Saitama Cancer Center Hospital, in an HTLV1-nonendemic area, during the period from January, 1984 to December, 1996 amounted to 544 cases. All of the cases were reviewed by one of the authors (IT), and for difficult cases another author (SM) examined them and made the final classification. Out of all the examined cases, twenty-nine of Hodgkin's disease were excluded, and the remaining 515 cases of NHL were analyzed (Table I). In all cases, tissue specimens were obtained before initial therapy. Part of each was fixed in 10% buffered formalin and embedded in paraffin; the remainder was snap-frozen and stored at −60°C without fixation. Lymphocytic leukemias and myelomas lacking tissue samples were not included in this study.

Methods Diagnoses were performed based on the REAL classification. Briefly, NHLs were classified into two major categories, B-cell and T-cell/putative NK-cell (T/NK-cell) neoplasms. Both categories were then further divided into two groups, precursor and peripheral. Peripheral B-cell neoplasms comprised ten subtypes, and peripheral T/NK-cell neoplasms eight, including definite and provisional entities (Tables II and III).

Table I. Primary Site and Cell Lineage of Non-Hodgkin's Lymphomas

Primary site	Number of cases (%)		
	B	T/NK	Total
Nodal	156 (74)	54 (26)	210 (100)
Extranodal	249 (82)	56 (18)	305 (100)
Oropharynx	90	11	101
Stomach	59	3	62
Nasal cavity and nasopharynx	21	20	41
Soft tissue	11	6	17
Skin	5	10	15
Oral cavity	8	1	9
Thyroid gland	7	0	7
Salivary gland	6	0	6
Testis	4	0	4
Thymus	1	2	3
Others[a]	37	3	40
Total	405 (79)	110 (21)	515 (100)

B, B-cell non-Hodgkin's lymphoma; T/NK, T/NK-cell non-Hodgkin's lymphoma.
a) Others (numbers observed): lung (3), colon (3), rectum (3), larynx (3), uterus (3), breast (3), ovary (2), brain (2), bone (2), endocrine organ (2), lip (1), intestine (1), gall bladder (1), urinary bladder (1) and undetectable extranodal sites (7).

Table II. Incidences of B-cell Lymphomas and Case Characteristics

B-cell lymphomas	Number of cases		Age range (Median)	Number of cases
	n	M/F		LN/Extra
I. Precursor B-cell lymphoma				
B-lymphoblastic	0	0/0	—	0/0
II. Peripheral B-cell lymphomas				
Small lymphocytic	1	0/1	77	1/0
Lymphoplasmacytoid	2	1/1	77 (77)	0/2
Mantle cell	9	9/0	51–82 (59)	6/3
Follicle center	75	35/40	11–79 (53)	57/18
Grade 1	25	12/13	16–77 (51)	20/5
Grade 2	29	14/15	11–76 (54)	24/5
Grade 3	21	9/12	11–79 (53)	13/8
Marginal zone B-cell	61	28/33	19–81 (60)	1/60
Splenic marginal zone	0	0/0	—	0/0
Plasmacytoma	9	5/4	48–75 (60)	1/8
Diffuse large B-cell	238	135/103	10–92 (63)	87/151
Burkitt	7	4/3	4–61 (37)	1/6
High-grade B-cell, Burkitt-like	3	2/1	51–92 (57)	2/1
Total	405	219/186	4–92 (60)	156/249

n, number of cases; M, male; F, female; LN, lymph node; Extra, extranodal site.

For the REAL classification, the following were employed: clinical information, hematoxylin and eosin (HE)-stained sections and immunostaining of panmarkers for cell lineages (B-cell, T/NK-cell, Null-cell) on paraffin-embedded tissue sections in all cases. In addition, immunophenotyping by flow-cytometry, detailed immunohistochemical analysis of unfixed-frozen sections, karyotyping and Southern blot analysis of immunoglobulin and T-cell receptor genes were conducted on a case by case basis.

Table III.   Incidences of T/NK-cell Lymphomas and Case Characteristics

T/NK-cell lymphomas	Number of cases		Age range (Median)	Number of cases
	n	M/F		LN/Extra
I. Precursor T-cell lymphomas				
T-lymphoblastic	7	2/5	17−55 (22)	3/4
II. Peripheral T/NK-cell lymphomas				
Mycosis fungoides	2	1/1	77−78 (78)	0/2
Peripheral T-cell, unspecified	58	39/19	18−87 (59)	25/33
Angioimmunoblastic	14	9/5	23−81 (60)	14/0
Angiocentric	18	14/4	16−76 (59)	4/14
Intestinal T-cell	1	0/1	62	0/1
Adult T-cell	7	6/1	36−72 (50)	5/2
Anaplastic large-cell	3	1/2	18−68 (46)	3/0
Anaplastic large-cell, Hodgkin's-like	0	0/0	—	0/0
Total	110	72/38	16−87 (59)	54/56

Table IV.   Primary Antibodies

Antibodies	Clone	Source	Pretreatment	Dilution
CD20	L26	DAKO	−	1:50
CD45RA	MB-1	Bio-Science	−	1:10
CD79a	JCB117	DAKO	+	1:25
CDw75	LN-1	Nichirei	+	1:1
CD74	LN-2	Nichirei	+	1:1
CD3	(polyclonal)	DAKO	+	1:50
CD45RO	UCHL-1	DAKO	−	1:1
CD43	MT-1	Seikagaku Co.	−	1:50
CD5	4C7	Novocastra	+	1:25
CD10	56C6	Novocastra	+	1:40
CD15	C3D-1	DAKO	−	1:50
CD21	1F8	DAKO	+	1:10
CD30	BerH2	DAKO	+	1:20
CD45	LCA	DAKO	−	1:1
CD56	1B6	Novocastra	+	1:50
CyclinD1/bcl-1	P2D11F11	Novocastra	+	1:25
bcl-2	124	DAKO	+	1:40
c-myc		Oncogene Science	−	1:10
ALK/p80	(polyclonal)	Nichirei	+	1:10
p53	DO-7	DAKO	+	1:50
CD68	KP1	DAKO	+	1:50
TdT	(polyclonal)	DAKO	+	1:10

   Clinical information for each case was abstracted from medical records and pathological reports, which included patient ID, age, sex, biopsy site, Ann-Arbor staging[12] (I to IV), history of viral infection (HTLV-1), treatment data and overall survival. As to the primary site of lymphoma, we used the following definition[13]: a lymphoma was considered to be extranodal when the main bulk of disease was found to be present at an extranodal site by examination using various clinicopathological procedures.

   For HE staining and immunostaining, 4 μm sections were used. Immunohistochemical reactions were performed by the streptavidin-biotin immunoperoxidase method[14] using the antibodies listed in Table IV, with or without antigen unmasking pretreatment. Immunophenotypes were assessed with fresh tissue by flow cytometry[15] using antibodies against CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD19, CD20, CD21, CD33, CD45, CD56, CD57, HLA-DR, IgG, IgA, IgM, IgD, surface

Table V. Risk Groups with the REAL Classification[a]

\<B-cell lymphomas\>	\<T/NK-cell lymphomas\>
I. Indolent (low risk)	I. Indolent (low risk)
Small lymphocytic lymphoma	Mycosis fungoides/Sezary syndrome
Lymphoplasmacytic lymphoma	
Marginal zone B-cell lymphoma	II. Aggressive (intermediate risk)
Follicle center lymphoma, grade I–II	Peripheral T-cell lymphoma, unspecified
II. Aggressive (intermediate risk)	Angioimmunoblastic lymphoma
Plasmacytoma	Angiocentric lymphoma
Mantle cell lymphoma	Intestinal T-cell lymphoma
Follicle center lymphoma, grade III	Anaplastic large-cell lymphoma
Diffuse large B-cell lymphoma	
High-grade B-cell lymphoma, Burkitt-like	III. Very aggressive (high risk)
III. Very aggressive (high risk)	Precursor T-lymphoblastic lymphoma
Precursor B-lymphoblastic lymphoma	Adult T-cell lymphoma
Burkitt's lymphoma	

a) From references 18 and 19.

immunoglobulin κ and λ chains, in 253 cases. Cell suspensions were analyzed using a FACS scan flow cytometer (Becton Dickinson, Mountain View, CA). Karyotyping was performed for 306 cases as previously reported.[16] Southern blot analysis of immunoglobulin and T-cell receptor genes[17] was conducted to determine whether lesions were monoclonal in 56 cases.

Overall survival time was defined as the period from pathological diagnosis to the time of death from any cause, or the time of last contact with a surviving patient. The final follow-up date was December 28, 1998. Survival distributions were estimated using the Kaplan-Meier method, and differences in survival between subtypes were analyzed using the log-rank test.

On the basis of clinical course without treatment, REAL subtypes were divided into three risk groups: low, intermediate and high (Table V).[18, 19] The low risk group exhibited an indolent course, with survival measured in years; the intermediate group, an aggressive course with survival measured in months; and the high risk group, a very aggressive course with survival measured in weeks.[20] The practical utility of this grouping was also analyzed.

RESULTS

Primary sites and cell lineage Data for primary sites and cell lineages for 515 cases of NHL are presented in Table I. Two hundred and ten cases (41%) had a nodal manifestation, and 305 cases (59%) were extranodal. As for the cell-lineage, B-cell lymphomas accounted for 79% and T/NK-cell lymphomas for 21% (B:T/NK=3.7:1) (only three cases of NK-cell lymphoma). The ratio differed markedly with the site of manifestation: B-cell lymphomas were three times more numerous than T/NK-cell lymphomas in

the lymph nodes, but five times more in extranodal sites, this difference being statistically significant ($P<0.05$, χ^2 test). In extranodal sites, the B-cell type was dominant in many organs, including the stomach, oral cavity, thyroid gland, salivary gland and testis. On the other hand, the T/NK-cell type was relatively frequent in the skin, thymus, nasal cavity and nasopharynx.

Distribution of subtypes by clinicopathological parameters Data for the distribution of subtypes of B-cell NHL by clinicopathological parameters are presented in Table II. Diffuse large B-cell lymphomas (DLBL) (238 cases) constituted almost half of all NHL. This type had the widest range of age, and occurred predominantly in extranodal sites. DLBL comprised a heterogeneous population in many respects, such as morphology, phenotype, karyotype, genetic abnormality and clinical course. The follicle center lymphoma (FCL) was the second most common subtype (75 cases), occurring predominantly in lymph nodes. Divided into grades (1, 2 and 3) based on morphology of neoplastic cells, the numbers in each grade were evenly distributed. The MZBL, one of the newly recognized subtypes in the REAL classification, accounted for 61 cases, almost all in extranodal sites. Though the number of MCL cases was small, this subtype had a striking male predominance (89%). The age at diagnosis was younger in Burkitt's lymphomas (Burkitt L) (median 37 y, ranging from 4 y to 61 y) than in the other types of B-cell lymphoma (median 61 y).

Clinicopathological characteristics of patients with T/NK-cell subtypes are presented in Table III. Peripheral T-cell lymphoma, unspecified (PTLu) (58 cases), accounted for more than half the T/NK-cell NHL. Angiocentric lymphoma (AL) (which included the three NK-cell lymphomas) and angioimmunoblastic lymphoma (AILD) were the

next most common subtypes of peripheral T-cell lymphomas, with AL showing a male predominance (78%) and all AILDs occurring in the lymph nodes. The incidence of adult T-cell lymphomas (ATL) in our study was 7 cases, 1% of all NHL. The age at diagnosis was younger in T-lymphoblastic lymphomas (TLLs) (median 22 y, ranging from 17 y to 55 y) than in the other types of T/NK-cell lymphoma (median 59 y).

Prognosis Overall survival curves according to cell lineage are presented in Fig. 1. A clear segregation of survival curves was noted: patients with B-cell lymphomas had a significantly better prognosis (5-year survival 60% and 10-year survival 41%) than those with T/NK-cell lymphomas (5 y 38% and 10 y 23%).

Survival curves of patients with B-cell lymphomas according to the REAL classification are presented in Fig. 2. Some subtypes—small lymphocytic, lymphoplasmacytoid, plasmacytoma and high-grade B-cell lymphoma, Burkitt's-like—were excluded from this analysis, because of the small numbers of cases. Each type showed a different survival pattern. The newly recognized MZBL and MCL types, both small sized B-cell lymphomas, appeared to have distinctive clinical courses. MZBL showed a very good prognosis (5 y 92% and 10 y 83%), and MCL had a poor prognosis (5 y 51%), though the number of cases was small. FCL, another small-sized B-cell lymphoma, also demonstrated a good prognosis (5 y 76% and 10 y 67%). DLBL was aggressive (5 y 48% and 10 y 23%) and exhibited relapse 5 years after diagnosis. Burkitt L showed a bad prognosis (5 y 57%) on the whole, but, when analyzed in detail, could be divided into two groups: one (3 cases) with a very aggressive course and death in less than a year; the other (4 cases) with a good prognosis. Statistical

analysis of survival showed significant differences between MZBL and each of the other subtypes—MCL, FCL, DLBL, and Burkitt L—and between FCL and DLBL.

Fig. 2. Survival curves for patients with marginal zone B-cell lymphomas (MZBL), Burkitt's lymphomas (Burkitt), follicle center lymphomas (FCL), mantle cell lymphomas (MCL) and diffuse large B-cell lymphomas (DLBL). Differences in prognosis are statistically significant between MZBL and MCL ($P<0.05$), FCL ($P<0.05$), DLBL ($P<0.0001$), and Burkitt ($P<0.001$); and between FCL and DLBL ($P<0.00001$). —— MZBL, - - - FCL, —— MCL, - - Burkitt, ▬▬ DLBL.
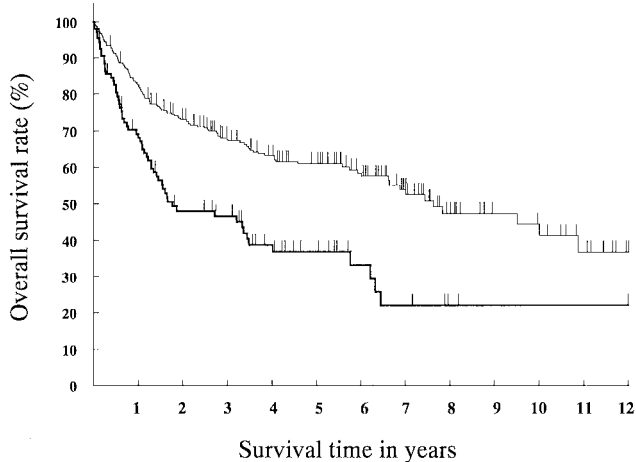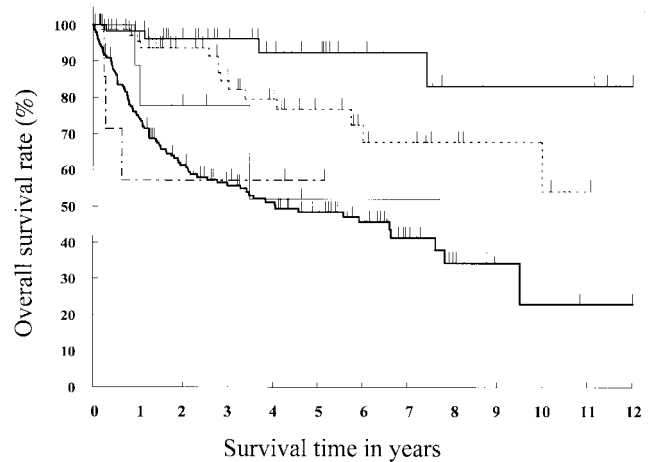

Fig. 1. Survival curves for patients with B-cell lymphomas (B) and T/NK-cell lymphomas (T/NK). The difference in prognosis is statistically significant ($P<0.001$). —— B, —— T/NK.
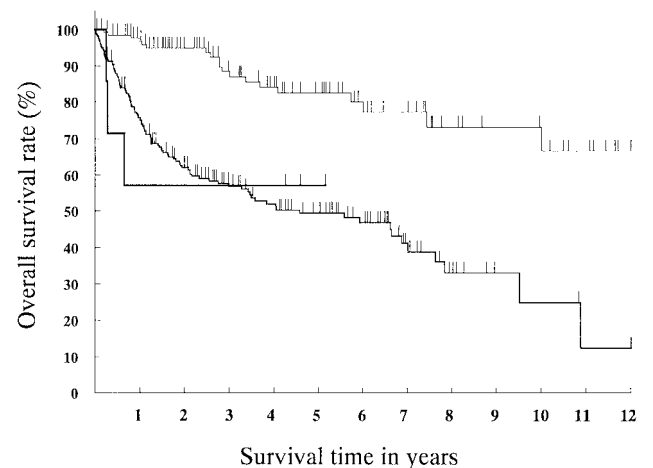

Fig. 3. Survival curves according to the risk group of B-cell lymphoma. High, high risk group; Inter, intermediate risk group; Low, low risk group. Differences in prognosis are statistically significant between Low and Inter ($P<0.0001$) and Low and High ($P<0.01$). However, no difference was observed between high and intermediate groups. —— Low, —— Inter, ▬▬ High.
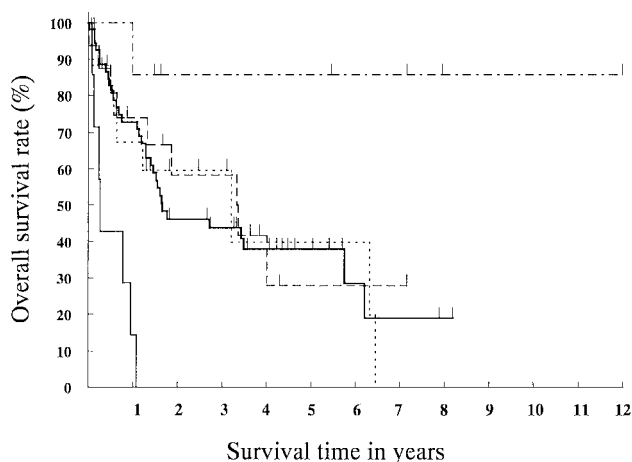
Fig. 4. Survival curves for patients with precursor T-lympho-blastic lymphomas (TLL), angioimmunoblastic lymphomas (AILD), peripheral T-cell lymphomas, unspecified (PTLu), angiocentric lymphomas (AL) and adult T-cell lymphomas (ATL). Differences in prognosis are statistically significant between TLL and PTLu ($P<0.05$), AL ($P<0.05$) and ATL ($P<0.001$); and between ATL and PTLu ($P<0.0001$), AILD ($P<0.005$) and AL ($P<0.01$). - - - TLL, - - - AILD, —— PTLu, —— ATL, ······· AL.

Survival curves according to risk group of B-cell lymphoma are presented in Fig. 3. Although all patients were treated, these with low-risk B-cell lymphoma had a significantly better prognosis (5 y 85% and 10 y 78%) than the intermediate risk (5 y 49% and 10 y 26%) and high risk (5 y 57%) groups, the latter two not differing markedly.

Survival curves of patients with T/NK-cell lymphomas separated according to the REAL classification are presented in Fig. 4, excluding some subtypes (mycosis fungoides, intestinal T-cell lymphoma and anaplastic large cell lymphoma, each of which was low in number). Precursor TLLs had a very good prognosis (5 y 85%) in our study, with differences in outcome from other types (PTLu, AL, and ATL) being statistically significant. ATL had a very aggressive outcome (5 y 0%), as compared with the PTLu, AILD, and AL. The differences in survival between the other subtypes of peripheral T/NK-cell lymphoma were not statistically significant.

Overall survival curves according to risk group showed no statistically significant variation (data not shown).

DISCUSSION

It is sometimes difficult to determine whether the primary site of a lymphoma is nodal or extranodal, since nodal lymphomas commonly spread to extranodal sites, and, conversely, extranodal lymphomas infiltrate into the lymph nodes. We therefore used the operational definition[13] of this, as described in "Materials and Methods."

The incidence rate of extranodal origin in all NHL was 59% in this study, slightly higher than previous Japanese figures, which ranged from 42 (278/684 cases) to 52% (440/850 cases).[21, 22] The reason for the higher incidence may be partly related to institutional specificity: in the local medical situation, a practitioner usually introduces a patient with malignant lymphoma of the otorhinopharyngeal field to our cancer center. The frequencies of extranodal lymphoma in European and American countries have ranged from 20 to 36%[23-27] (except for 48% in Italy[28]), so a high extranodal manifestation is characteristic of NHL in the Japanese population. Our most common extranodal sites were the oropharynx (33% of extranodal lymphomas), followed by the stomach (20%) and nasal cavity and nasopharynx (13%), consistent with other Japanese data.[22]

The REAL classification divides NHL into two cell lineages, B and T/NK, based on the phenotype determined by immunohistochemical examination, as the Kiel classification did,[2] whereas previous classifications, such as LSG,[8] Working Formulation's (WF)[29] and others, rely entirely on morphologic criteria.

Comparison of the incidence of T/NK-cell lymphomas with previous reports of T-cell lymphomas, NK-cell neoplasms being very infrequent in this study, revealed a regional difference in Japan associated with the overall incidence of HTLV1 infection[30-34]: high in endemic areas of HTLV1 and low in nonendemic areas. Our cancer center is located in the Kanto area at the center of Honshu, which is an HTLV1-nonendemic area. The T/NK-cell lymphoma rate in our institute was 21.4% compared with 33% on average[31] in Honshu. In Kyushu, which is an endemic area of HTLV1, the rate is 70–75%.[31, 32] In Europe and the USA, where HTLV1 is nonendemic, the rate ranges from 12 to 20%.[2, 5, 7, 35, 36] Thus, a high occurrence of the T/NK-cell lineage in Japan may be characteristic even in HTLV1-nonendemic areas.

So far, only a few studies have been performed on the world-wide distribution of subtypes of NHL with the REAL classification. The data from one of the most representative reports,[5] mainly from European and American populations, are presented in Table VI along with our results, slightly modified from those in Tables II and III for the purpose of comparison, i.e., one case of primary mediastinal B-cell lymphoma was excluded from DLBL, along with one case of nodal MZBL.

The incidence rate of DLBL in this study was slightly higher than in another study (39%) of the same Kanto area[37] in Japan. One reason may be that, since DLBL is the major subtype in the otorhinopharyngeal field, the number of patients was more numerous in our study, as previously mentioned. It was also higher than that of European and American populations (31%).

The value for the PTL category (19%), which included several types of peripheral T/NK-cell lymphomas, was

Table VI. Distribution of Non-Hodgkin's Lymphoma

Subtypes	Saitama Cancer Center	ILSG[a]
Diffuse large B-cell	237 (46.0)	422 (30.6)
Peripheral T-cell	98 (19.0)	96 (7.0)
Unspecified	58 (11.3)	53 (3.8)
Angiocentric	18 (3.5)	19 (1.4)
Angioimmunoblastic	14 (2.7)	17 (1.2)
Adult T-cell	7 (1.4)	1 (<1)
Intestinal T-cell	1 (<1)	5 (<1)
Hepatosplenic	0 (0)	1 (<1)
Follicle center	75 (14.6)	304 (22.1)
Grade 1	25 (4.9)	131 (9.5)
Grade 2	29 (5.6)	85 (6.2)
Grade 3	21 (4.1)	88 (6.4)
Marginal zone B-cell, MALT	60 (11.7)	105 (7.6)
Mantle cell	9 (1.7)	83 (6.0)
Precursor T-cell	7 (1.4)[b]	23 (1.7)
Burkitt	7 (1.4)	10 (<1)
Other types[c]	22 (4.3)	335 (24.3)
Total	515 (100.0)	1378 (100.0)

a) From reference 5.
b) Excluding leukemia cases without biopsy.
c) Other types: anaplastic large-cell, high-grade B, Burkitt-like, mycosis fungoides, lymphoplasmacytoid, small lymphocytic,[b] primary mediastinum, marginal zone B-cell (nodal) and others.

almost the same as in an earlier Japanese study (22%),[37] but higher than in European and American populations (7%).[5, 7] While this neoplasm is generally considered to be related to HTLV1 in Japan, the location of our institute in a nonendemic area suggests an association with other factors.

There are geographic or racial differences in the incidence of the FCL,[38, 39] which corresponds to the follicular lymphoma of the LSG classification,[8] malignant lymphoma (follicular) in the WF classification,[29] and centroblastic-centrocytic lymphoma (follicular) in the Kiel classification.[2] The rate ranges from 20 to 40% in the USA, is approximately 20% in Europe, but only about 10% in Asia and Africa. In this study it was also low (15%). Furthermore, FCL grade I cases constituted only 33% (25/75), as reported in other Japanese studies (17–35%),[37, 40, 41] compared with 43% (131/304) in European and American populations. FCL grade I was known to have frequent t(14;18) translocation,[42] which is strongly related to bcl-2 rearrangement. This may be linked to the fact that *bcl-2* gene rearrangement in FCL is low in Japan and high in the USA.[43] The higher frequency of MZBL (12%) (approximately the same as in the other Japanese study[37]) compared with 8% in European and American cases,[5] was also characteristic.

There was clear segregation of survival curves according to the cell lineage: patients with B-cell lymphoma had a better prognosis than those with T/NK-cell lymphomas, as in other studies.[6, 44–46] Therefore, this division has clinical utility. The marked differences in survival between subtypes of B-cell lymphoma, especially between the new categories in small-sized B-cell lymphomas, with MZBL and MCL, respectively showing a very good and a poor prognosis, are in line with earlier reports.[5, 6, 47] However, survival did not significantly vary with the subtype of T/NK-cell lymphoma except between TLL and ATL, one of the reasons possibly being the small number of cases for each subtype. TLL showed a very good prognosis in this study, although it is classified in the high risk group.[18, 19] This might have been due mainly to the fact that T-cell acute lymphocytic leukemia cases without tissue biopsy were excluded, meaning most were probably in an early phase, i.e., without infiltration to peripheral blood and bone marrow. ATL showed an especially poor prognosis and an acute outcome, as already reported.[48, 49]

Survival of lymphomas may vary by primary site even among the same category of lymphoma, but the number of cases examined was insufficient for subdivision by sites in this study, so further analysis is warranted in the future.

The division of prognosis into three risk groups—low, intermediate and high—was performed at first in the WF classification, in which lymphomas were not divided into two phenotypes. However, the importance of phenotyping became clear for evaluation of prognosis of lymphomas from many studies, and the proposed clinical grouping with the REAL classification[18, 19] divides risks into three groups in each phenotype. We examined the utility of the grouping and found that subdivision of B-cell lymphomas was practical even with treatment, since differences in survival were observed, at least between low and intermediate and/or high groups. However no difference was observed between intermediate and high groups, which may be due to the fact that the latter, Burkitt L, consisted of two types, a poor and a rather good prognosis, although the examined numbers were small. Recently the presence of cases with a more optimistic prognosis if treated has been suspected. Therefore, further study on the prognosis of Burkitt L with a sufficient number of cases is needed for grouping of intermediate and high groups. With T/NK-cell lymphomas, in contrast, no difference in survival curves was observed.

Considering all of the above, we can conclude that, clinicopathologically, the REAL classification is very useful, although some problems do exist with its application for Japanese. DLBL was found to be the most numerous subtype, constituting around a half of all NHL in Japan, and this is known to consist of heterogeneous groups showing varying clinical behavior and prognosis.[1, 50–53] Here, it was associated with aggressive behaviors in some

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cases and late-phase death in others, but we feel the sub-classification of DLBL should be retained. The clinical utility of each subtype in the PTL category could not be analyzed sufficiently, because of the small number of cases. Since there are few studies[6, 49] in the world examin-ing this point, further investigations are needed to clarify the necessity for a PTL sub-classification.

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