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Original Article

Malignant Lymphomas in Yamagata Prefecture : Retrospective Investigation on Incidence and Preferential Sites, and a Re-evaluation According to Newly-Published WHO (World Health Organization) Classification

Kunihiko Maeda[1], Mikio Matsuda[2], Fumiaki Yuda[3] and Hito-aki Saitoh[1]

The incidence and preferential sites of malignant lymphomas were retrospectively investigated by reviewing archived pathological files (1985 to 1996) in 11 major hospitals in Yamagata Prefecture, a HTLV-1-nonendemic area of Japan. In addition, re-evaluation of 212 recent cases based upon the newly-published WHO classification was performed. The following results were obtained : 1) the actual number of lymphoma patients was increasing annually, 2) the incidence rate of extranodal lymphomas was 61.3%, with the gastro-intestinal tract and Waldeyer's ring being the major preferential sites, 3) the incidence of extranodal lymphomas seemed to be increasing annually, whereas that of nodal lymphomas was not, 4) B-cell lymphomas were dominant (69.8%), in a percentage similar to that of a previous nationwide investigation, 5) major categories among the B-cell lymphomas were diffuse large B-cell lymphoma, follicular lymphoma and extranodal B-cell lymphoma of MALT, 6) the percentage of T-cell lymphomas was less than that of the nationwide investigation, 7) angio-immunoblastic T-cell lymphoma was a major subtype of T-cell lymphoma, and 8) the incidence rate of Hodgkin lymphoma was 5.7% of total malignant lymphomas.

Key words *epidemiology, non-HTLV-1 endemic area, B-cell, T-cell, Hodgkin lymphoma*

INTRODUCTION

Malignant lymphoma is a common malignant tumor encountered daily by diagnostic pathologists. It can originate from almost all anatomical sites of the human body, including not only lymphoreticular tissues, but also many other sites such as the skin, digestive organs, bone and soft tissues, and even the central nervous system. In addition, it has an extremely broad spectrum of biological and clinical behaviors. It may, therefore, be somewhat difficult to establish a complete tumor registration system for malignant lymphomas, and there seems to be a limitation regarding general epidemiological studies, which would usually be based upon registry data. A geopathological study or an epidemiological study based upon pathological information may have some advantages in this regard, as described by Nanba[1]. Although several recent papers have described geopathological or patho-epidemiological traits of malignant lymphomas in Japan[1-11], there are only limited reports involving incidence, preferential sites and recent trends of this type of neoplasm in a human T-lymphotropic virus-1 (HTLV-I)-nonendemic area of Japan[3,4,9].

The present study was initially designed to look at changes in the incidence of total malignant lymphoma or disease subgroups, by applying accumulated pathological information from Yamagata Prefecture, which is located in a

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[1]Department of Pathology, Yamagata University School of Medicine, Yamagata, Japan, [2]Department of Nursing, School of Health Science, Yamagata Prefectural University of Health Science, Yamagata, Japan, [3]Department of Clinical Laboratory, Yamagata Municipal Hospital Saisei-Kan, Yamagata, Japan
Address correspondence and reprint request to Kunihiko Maeda, Department of Pathology, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 900-9585, Japan

HTLV-1-nonendemic area of Japan. We analyzed retrospectively the primary anatomical sites, along with the actual patient numbers, by reviewing files of pathological reports archived in the pathological laboratory section of the 11 major hospitals in the Prefecture. In addition, the distribution of each subtype of the newly published World Health Organization (WHO) classification of lymphoid tumors[12] was estimated by a re-evaluation of the recent cases.

Our results suggested some particular trends for malignant lymphomas in the subjected local area, and might contribute to the establishment of a therapeutic strategy against malignant lymphomas in a HTLV-1-nonendemic area of Japan.

MATERIALS AND METHODS

Case registration

A total of 807 cases of malignant lymphoma and related disorders were obtained from a comprehensive review of the archived files of the pathological diagnostic reports from 1985 to 1996, which were in the custody of the pathological/cytological laboratory sections of the eleven major hospitals in Yamagata Prefecture: Yamagata University Hospital (Yamagata), Yamagata Prefectural Central Hospital (Yamagata), Yamagata Prefectural Nihon-Kai Hospital (Sakata), Yamagata Prefectural Shinjo Hospital (Shinjo), Yamagata Prefectural Kahoku Hospital (Nishi-Murayama County), Yamagata Municipal Hospital Saisei-kan (Yamagata), Yonezawa Municipal Hospital (Yonezawa), Nagai Municipal Hospital (Nagai), Tsuruoka Municipal Sho-nai Hospital (Tsuruoka), and Tsuruoka Kyoritsu Hospital (Tsuruoka). The patient's age, sex, the anatomical site of the excised specimen, and brief clinical information such as manifestations, physical/laboratory findings and data from image examinations, along with the pathological diagnosis of each case were registered. Plural numbers of specimens from the same patient were counted as one case if they were taken within a year. To improve the reproducibility of data, myeloid leukaemia, histiocytic/dendritic cell tumor and related diseases were excluded because of the difficulty for our reviewing system to accurately define the incidence of these cases.

Re-evaluation of recent cases based upon newly-published WHO classification

212 recent cases (1996 to 2001), which were diagnosed as malignant lymphomas or related diseases at the Department of Pathology, Yamagata University School of Medicine, including consulting cases sent from other hospitals, were re-examined for the application of the newly established WHO classification of tumors of the haematopoietic and lymphoid tissues[12]. For this examination, re-consideration of the clinical and laboratory information, conventional morphological observation by hematoxylin and eosin sections, and immunohistochemical phenotyping were undertaken. Phenotyping was achieved in principle using formalin-fixed, routinely-processed paraffin sections and the labeled streptavidin-biotin (LSAB) labeling system described below. The antibodies used are listed in Table 1. In addition, flow-cytometry examination, chromosomal analysis, southern blot analysis of immunoglobulin and T-cell receptor genes, and polymerase chain reaction (PCR) analysis of the variable regions of the immunoglobulin heavy chain genes were conducted where possible.

Immunohistochemical phenotyping

The immuno-phenotypes of the tumor cells were examined immunohistochemically by the LSAB immunohistochemical system, as previously reported[13,14]. Briefly, the routinely-processed paraffin sections were dewaxed in xylene, rehydrated through a graded series of ethanol and submerged in methanol containing 0.3% H_2O_2 to quench endogenous peroxidase activity. Then, if needed, they were processed by suitable antigenic retrieval procedures, such as microwave irradiation in 0.01 M citrate buffer or proteolytic digestion with trypsin. After being thoroughly rinsed with phosphate-buffered saline (PBS), they were incubated with a protein blocking agent (UltraTech HRP Streptavidin-Biotin Universal Detection System, Immunotech, Marseilles, France) to prevent non-specific binding of the antibodies. They were then incubated overnight with each primary antibody at 4°C. The following day, they were washed three times in PBS and incubated with biotinylated secondary antibody

TABLE 1. Monoclonal antibodies used in the present study.

Antibodies (Recognizing molecules)	Isotype	Working dilution	Antigenic retrieval	Source
PS1 (CD3)	Mouse IgG2a	Ready to use	MW[5]	Nichirei[6]
4C7 (CD5)	Mouse IgG1	1 : 50	MW	NCL[7]
56C6 (CD10)	Mouse IgG1	1 : 50	MW	NCL
LeuM1 (CD15)	Mouse IgM	1 : 10	—	B-D[8]
L26 (CD20cy)	Mouse IgG2a	1 : 50	—	DAKO[9]
1F8 (anti-CD21/CR2)[1]	Mouse IgG1	1 : 20	Trypsin	DAKO
BU38 (anti-CD23/FcεRII)[2]	Mouse IgG1	1 : 200	Trypsin	BDS[10]
BerH2 (CD30)	Mouse IgG1	1 : 25	Trypsin	DAKO
Ber-MAC-DRC(anti-CD35/CR1)[3]	Mouse IgG1	1 : 10	Trypsin	DAKO
MT-1, DF-T1, Leu22/L60(CD43)	Mouse IgG1	1 : 50	—	Cosmo-Bio[11], DAKO B-D
UCHL-1 (CD45RO)	Mouse IgG2a	1 : 50	—	DAKO
MB-1, 4KB5, DBB42(CD45RA)	Mouse IgG1	1 : 10 1 : 25ready-to-use	—	BioGenex[12] DAKO MBL/IMT[13]
123C3 (CD56)	Mouse IgG1	1 : 200	MW	SAN[14]
LN-2, DND53 (CD74)	Mouse IgG1, IgM	Ready-to-use 1 : 25	—	Nichirei MBL/IMT
LN-1, DNA7 (CDw75)	Mouse IgM	Ready-to-use 1 : 10	—	Nichirei MBL/IMT
HM57 (CD79a)	Mouse IgG1	Ready-to-use	MW	Nichirei
LN-3 (HLA-DR)	Mouse IgG2a	Ready-to-use	—	Nichirei
124 (bcl-2 oncoprotein)	Mouse IgG1	1 : 50	MW	DAKO
5D4 (PRAD1/cyclinD1 geneproduct)	Mouse IgG2a	1 : 100	MW	IMT
DBA44 (not determined)	Mouse IgM	Ready-to-use	Trypsin	MBL
8A3 (βchain of TCR[4]/βF1)	Mouse IgG1	1 : 50	—	ENDOGEN[15]
Anti-S100 protein α subunit	Mouse IgG1	1 : 200	MW	JIMRO[16]
Anti-human terminal deoxynucleotidyl transferase (TdT)	Rabbit polyclonal	1 : 20	MW	DAKO
Anti-each isotype of human immunoglobulins	Rabbit polyclonal	1 : 100–1 : 800	Trypsin	DAKO

Abbreviations: 1) CR2: complement receptor type 2, 2) FcεRII: low affinity Fc receptor for IgE, 3) CR1: complement receptor type1, 4) TCR: T-cell receptor, 5) MW: microwave irradiation, 6) Nichirei: Nichirei Bio-Science Business Division (Tokyo, Japan), 7) NCL; Novocastra Laboratories Ltd. (Newcastle upon Tyne, UK), 8) BDI: Becton Dickinson Immunocytometry Systems (San Jose, CA), 9) DAKO; DAKO A/S (Copenhagen, Denmark), 10) BDS; The Binding Site Ltd. (Birmingham, UK), 11) Cosmo-Bio; Cosmo-Bio Co. Ltd., (Tokyo, Japan), 12) BioGenex; BioGenex Laboratories (San Ramon, CA), 13) MBL/IMT; Medical & Biological Laboratories Co. Ltd. (Nagoya, Japan) & Immunotech S. A. (Marseilles, France), 14) SAN; Sanbio B. V. /Monosan (Uden, The Netherlands), 15) ENDOGEN; Endogen (Woburn, MA), 16) JIMRO: Japan Immunoresearch Laboratories Ltd. (Takasaki, Japan).

(UltraTech HRP Streptavidin-Biotin Universal Detection System) for one hour at ambient temperature. Sections were then washed three times in PBS and incubated with peroxidase (PO)-labeled streptavidin (UltraTech HRP Streptavidin-Biotin Universal Detection System) for one hour at ambient temperature. After the incubation, sections were washed in PBS and in Tris-HCl buffer (0.05 M, pH 7.6) and the PO activity was developed using 0.05% diaminobenzidine with 0.03% H_2O_2 as described by Graham & Karnovsky[15]. Sections were next counterstained with hematoxylin and mounted with Permount (Fisher Scientific, Fair Lawn, NJ) for light microscopic observation.

As a control, inappropriate antibodies of the same isotype were used instead of the primary antibody. In addition, control experiments were performed to determine the reactivity of the biotinylated secondary antibody and PO-labeled streptavidin, and to quantify endogenous peroxidase activity.

RESULTS AND DISCUSSION

Actual patient numbers and primary anatomical sites of malignant lymphomas in Yamagata Prefecture from 1985 to 1996

A total of 807 cases of malignant lymphomas or related disorders were registered from a retrospectively review of the archived files of patho-

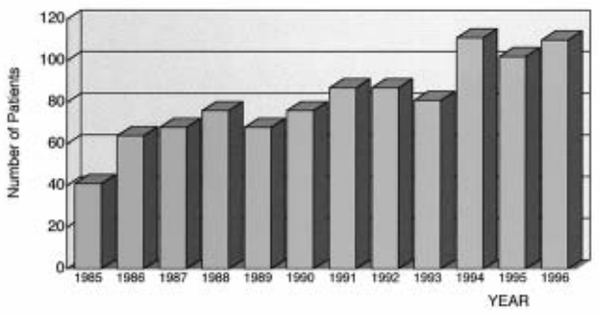

Fig. 1. Change in annual number of patients with malignant lymphoma in Yamagata Prefecture from 1985 to 1996.

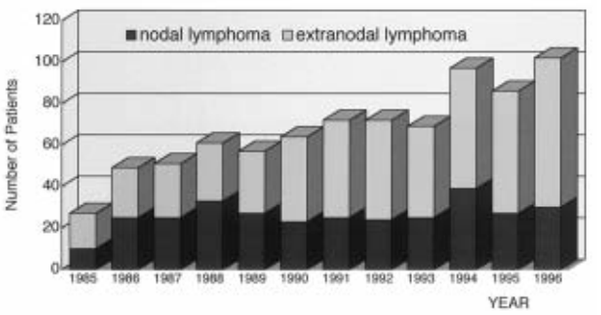

Fig. 2. Change in annual number of patients with nodal or extranodal lymphoma in Yamagata Prefecture from 1985 to 1996.

Table 2. Percentage of nodal and extra-nodal lymphoma in Yamagata and comparison with data from other areas and countries.

Country (Publication year)		Reference	Rate of nodal lymphoma (Case number)	Rate of extranodal lymphoma (Case number)
Japan	Yamagata (2002)	Current study	38.7% (313)	61.3% (496)
	Saitama (2000)	9	40.8% (239)	59.2% (305)
	Hiroshima (1983)	7	55.0% (326)	45.0% (267)
	Tokyo (1983)	4	54.5% (539)	45.4% (45.4)
Korea (1985)		20	45.0% (134)	55.0% (164)
USA*(2000)		18	72.7% (43677)	27.3% (16380)
USA (1972)		21	82.4% (10,253)	17.6% (2,194)
Norway (1968)		22	80.0% (248)	20.0% (62)
Greece*(1996)		23	54.4% (173)	45.6% (145)

*, the data were limited to non-Hodgkin lymphoma.

logical diagnostic reports from 1985 to 1996 in the eleven major hospitals in Yamagata Prefecture.

The annual change in the number of patients who were diagnosed with malignant lymphoma or related disorders is shown in Fig. 1. This graph shows that the actual number of patients gradually increased annually. The data did not indicate an epidemiologically rigorous incidence of malignant lymphoma because data were not sampled evenly, nor were they adjusted by age or population. Nevertheless, the data suggested that the incidence of malignant lymphoma showed a trend to increase in this local area over the applicable 10 years, since the population of this area actually decreased slightly[16]. Several other investigations have also indicated that the incidence of malignant lymphoma has been increasing significantly in recent years in Japan[7,11] and in Western countries[17–19]. It seems certain that the increasing incidence of malignant lymphoma is a worldwide trend. Although the definitive causes of this trend are uncertain, the following reasons could be considered: 1) novel concepts, such as extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), extranodal natural killer (NK)/T-cell lymphoma, nasal type and anaplastic large cell lymphoma have been established, 2) better examination techniques have been developed, especially high-resolution image analysis devices and endoscopic equipments, 3) diagnostic methods have markedly improved, especially highly sensitive immunohistochemical techniques using conventional paraffin sections and the application of molecular biological methods, and 4) the population profile is aging.

It was sometimes difficult to determine whether the primary site of a lymphoma was nodal or extranodal, since nodal lymphoma commonly spread to the extranodal region and, conversely, extranodal lymphomas infiltrated into the lymph nodes. Therefore, we used the following operational definitions: a lymphoma was considered to be extranodal when the main bulk and/or primary lesion was found to be present at an extranodal site in the preliminary examination using various clinicopathological procedures. Table 2 indicates the nodal and

Table 3. Primary anatomical sites of extra-nodal malignant lymphoma in Yamagata and comparison with those of other reports.

Site	Yamagata (current study)	Tokyo (4)*	Hiroshima (7)*	Saitama (9)*	USA (21)*	USA (18)*
GI tract	37.9%	20.0	35.5	20.3	38.0	27.5
Waldeyer ring	19.8	39.0	19.5	33.1	14.0	—
Skin, soft tissue	10.1	15.0	13.7	10.5	13.0	22.0
Nose, paranasal sinus & mouth	5.0	11.0	7.6	16.4	2.0	—
CNS	5.2	1.0	3.8	—	—	9.6
Orbita, eyelid	1.0	5.0	3.0	—	1.6	3.3
Thyroid	1.0	4.0	5.0	2.3	—	3.1
Mediastinum	1.6	—	—	1.0	2.0	—
Breast	0.4	—	1.5	—	2.0	—
Bone	1.2	1.0	1.9	—	2.0	—
Others	16.8	4.0	8.4	—	5.0	34.6

*, reference number

extranodal ratio of malignant lymphoma in Yamagata Prefecture and other areas, including Saitama, Hiroshima, Tokyo, Korea and Western countries. In the current study, 313 cases (38.7%) had a nodal manifestation, and 496 cases (61.3%) were extranodal. The incidence rate of extranodal disease in all malignant lymphomas was quite similar to a recent report from Saitama Prefecture, but slightly higher than previous Japanese figures, which had indicated an almost 45% frequency. The frequencies of extranodal lymphoma in European and American countries have ranged between 17.6 and 45.6%, so a high extranodal manifestation seems to be characteristic of lymphoma in the Japanese and Korean populations, especially those in northeastern Japan (a HTLV-1-nonendemic area).

Fig. 2 illustrates the annual change in patient numbers with nodal or extranodal lymphomas. The number of patients with extranodal lymphomas gradually increased annually, whereas those with nodal lymphomas did not change significantly. Thus, the above-mentioned increasing trend of incidence of malignant lymphoma seems to be based upon the increasing incidence of extranodal diseases.

The most common extranodal site was the gastro-intestinal (G-I) tract (37.9% of all extranodal lymphoma) followed by Waldeyer's ring (19.8%), skin and soft tissue (10.1%), nasal and oral cavity (5.0%) etc, as shown in Table 3. It is somewhat difficult to directly compare the data, regarding the preferential sites of extranodal lymphomas, from the different reports because there are some discrepancies in the working classifications of anatomical sites among the reports. Nevertheless, it is obvious that the G-I tract and Waldeyer's ring (nasopharyngeal region) are the major anatomical sites of extranodal lymphoma, not only in Japan but also in Western countries.

Distribution of subtypes by re-evaluation of 212 recent cases based upon the newly published WHO classification

Table 4 indicates the incidence of each subtype of the newly published WHO classification for lymphoid neoplasms by re-evaluation of 212 recent cases and comparison with other reports in Japan. In our area, B-cell lymphoma was dominant (69.8%) as well as other reports, but the incidence rate was relatively higher.

Among the subtypes of B-cell lymphoma, diffuse large B-cell lymphoma (DLBCL) constituted almost half of the B-cell lymphomas. This category indicated the highest frequency in all other reports because it is not a uniform disease entity and must be composed of a heterogeneous population. Actually, the WHO classification[12] described DLBCL to include several variants (centroblastic, immunoblastic, T-cell/histiocyte-rich and anaplastic) and several subtypes (mediastinal (thymic) large B-cell lymphoma, intravascular large B-cell lymphoma and primary effusion lymphoma). In addition, de novo CD5-positive DLBCL has been recently received much attention as a clinically and pathogenetically distinct subgroup of DLBCL[25–27]. Indeed, five CD5+ cases were included in our cases classified into DLBCL (6.1% of all DLBCL). Although there are some problems to distinguish between *de novo* CD5-positive DLBCL and the pleomorphic-blastoid variant of mantle cell

TABLE 4. Incidence of each category of the new WHO classification for malignant lymphoma and comparison with previous reports.

Category/subtype	Yamagata 212 cases (current study)	Japan 3,184 cases (24)*	Kyushu 990 cases (24)*	Saitama 544 cases (9)*
B-cell neoplasms	69.81	68.75	53.84	78.64
T-cell neoplasms	19.34	25.00	40.00	21.36
Hodgkin lymphoma	5.66	4.43	4.14	5.33
Undetermined	5.19	1.82	2.02	—
Precursor B-cell lymphoblastic leukemia/lymphoma	0.94	2.36	0.51	0.00
B-cell CLL/SLL	2.36	1.32	0.20	0.19
B-cell prolymphocytic leukemia	0.00	0.06	0	—
Lymphoplasmacytic lymphoma	0.00	0.69	0.30	0.39
Mantle cell lymphoma	2.36	2.80	2.42	1.75
Follicular lymphoma	12.26	6.72	5.25	14.56
Marginal zone B-cell lymphoma of MALT type	6.60	8.48	8.28	11.65
Nodal marginal zone lymphoma	2.36	1.01	0.30	0.19
Splenic marginal zone B-cell lymphoma	0.00	0.13	0.00	0.00
Hairy cell leukemia	0.00	0.16	0.00	—
Diffuse large B-cell lymphoma	38.68	33.45	28.38	46.80
Burkitt's lymphoma/leukemia	0.94	1.01	0.91	1.36
Extraosseous plasmacytoma/myeloma	1.89	9.17	6.36	1.75
Precursor T-cell lymphoblastic leukemia/lymphoma	0.94	1.73	1.72	1.36
T-cell prolymphocytic leukemia	0.00	0.06	0.00	—
T-cell large granular lymphocytic leukemia	0.47	0.15	0.00	—
Aggressive natural killer cell leukemia	0.00	0.09	0.10	—
Adult T-cell leukemia/lymphoma	0.00	7.47	19.29	1.36
Extranodal NK/T-cell lymphoma, nasal-type	0.94	2.61	2.83	3.50
Enteropathy-type T-cell lymphoma	0.00	0.25	0.00	0.19
Hepatosplenic T-cell lymphoma	0.00	0.06	0.00	—
Subcutaneous panniculitis-like T-cell lymphoma	0.00	0.06	0.00	—
Mycosis fungoides/Sézary syndrome	0.47	1.16	0.91	0.39
Primary cutaneous CD30+ T-cell lymphoproliferative disorders	0.94	0.25	0.30	—
Peripheral T-cell lymphoma, unspecified	5.66	6.69	8.38	11.26
Angioimmunoblastic T-cell lymphoma	7.08	2.42	3.84	2.72
Anaplastic large-cell lymphoma	3.77	1.54	2.22	0.58
Nodular lymphocyte-predominant Hodgkin lymphoma	0.00	0.16	0.10	—
Nodular sclerosis classical Hodgkin lymphoma	4.72	1.79	2.02	—
Lymphocyte-rich classical Hodgkin lymphoma	0.00	0.25	0.20	—
Mixed cellularity Hodgkin lymphoma	0.94	1.63	1.01	—
Lymphocyte-depleted Hodgkin lymphoma	0.00	0.25	0.20	—
Unclassifiable Hodgkin lymphoma	0.47	0.34	0.61	—

*, reference number

lymphoma (MCL) or transformed MCL, they may contain some cases of de novo CD5-positive DLBCL. Further attempts to subdivide the DLBCL cases would be expected to obtain more specific and informative results.

Follicular lymphoma was the second most common subtype, and marginal zone B-cell lymphoma of the MALT type, the third common subtype of B-cell lymphoma. Such a distribution pattern was quite similar to the investigation in Saitama Prefecture[9]. The frequency of follicular lymphoma in these reports was considerably higher than nationwide investigation, as indicated in Table 4. The cause of this discrepancy is unidentified. A westernized living environment may have caused the recent increment of follicular lymphoma. The low frequency of plasmacytoma/myeloma seems to suggest that the pathological diagnostic system may contribute poorly to the diagnosis of such diseases in our local area.

We had a lower percentage of T-cell lymphomas than that in other reports, especially those in Kyushu, as indicated in Table 4. This obviously depended upon the much lower incidence of adult T-cell leukemia/lymphoma (ATLL). In addition, peripheral T-cell lymphoma and extranodal NK/T-cell lymphoma, nasal type, also indicated a lower incidence. In contrast, angioimmunoblastic T-cell lymphoma revealed a higher incidence rate in Yamagata. This may represent one of the particular features

of T-cell lymphoma in the HTLV-1-nonendemic area even if it may be partly related to institutional bias.

The incidence of Hodgkin lymphoma in Yamagata was only slightly more frequent than in previous reports as indicated in Table 4. Although nodular sclerosis classical Hodgkin lymphoma occupied over 80% of the total cases of Hodgkin lymphoma in Yamagata, the number of patients was too small to estimate the real incidence of subtypes of Hodgkin lymphoma in this area.

Because of limited information and materials, we have not yet obtained sufficient and conclusive results on the incidence and distribution by a subtype of malignant lymphoma in Yamagata Prefecture. Nevertheless, the present results suggest some particular features of malignant lymphoma in a HTLV-1-nonendemic area of Japan and should contribute to the verification of the usefulness of the WHO classification. Further accumulation of cases, the introduction of epidemiological utilities, such as age adjustment and statistical processing, more objective improvement of the diagnostic system and the establishment of a case registration system will be required to obtain a complete conclusion.

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