

Original Article

Clinicopathological analysis of sinonasal malignant lymphoma in an HTLV-1 endemic area in Japan -special focus on primary sinonasal diffuse large B-cell lymphoma-

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The present study investigated histological subtypes of lymphoma in patients newly diagnosed with malignant lymphoma in the human T-cell leukemia virus type 1 (HTLV-1) endemic area of Japan, and further analyzed the clinicopathological features and clinical outcomes of patients with primary sinonasal lymphoma. We retrospectively examined 151 patients aged 18-90 years in Fukuoka, Japan. Subtypes of lymphoma were determined according to the WHO classification. Among the 151 patients, 104 were diagnosed with malignant lymphoma, including 96 at the time of initial diagnosis. Ninety-two of the 96 lymphomas (96%) were non-Hodgkin lymphoma. Mature B-cell neoplasms comprised 78% (n = 75). Primary lymphoma of the sinonasal cavity was found in six patients (6%). The histological subtype of sinonasal lymphoma was diffuse large B-cell lymphoma (DLBCL) in all six tumors. Furthermore, overall survival was significantly different among three distinct DLBCL patient groups, including primary sinonasal lymphoma patients ($p = 0.0016$; 3-year overall survival: sinonasal DLBCL group, 53%; DLBCL of the CNS group, 0%; other DLBCL group, 83%). Our study suggests that primary DLBCL of the sinonasal tract is a distinct disease entity of DLBCL.

Keywords: chemotherapy, diffuse large B-cell lymphoma, human T-cell leukemia virus type 1, primary sinonasal lymphoma

INTRODUCTION

The incidence of malignant lymphoma, especially non-Hodgkin lymphoma (NHL), has been gradually increasing worldwide, including in Japan.¹ Cervical lymph node biopsy is recommended for diagnosing NHL, and opportunities for otolaryngologists to diagnose this condition have been increasing. Malignant lymphoma in the World Health Organization (WHO) classification is mainly separated into precursor lymphoid neoplasms, mature B-cell neoplasms, mature T-cell and natural killer (T/NK)-cell neoplasms, and Hodgkin lymphoma.² In Japan, the proportion of Hodgkin lymphoma is smaller than that in Western populations, whereas the percentage of B-cell neoplasms is large, and its subtype classification is characterized by diffuse large B-cell lymphoma (DLBCL) in many cases.³ Additionally, regional differences are large among Japanese cases. In previous reports, the proportion of adult T-cell leukemia/lymphoma


(ATLL) in the Kyushu region was as high as 20%, and the ratio of mature T/NK-cell neoplasms as a whole was higher than that in other areas.⁴ Primary sinonasal lymphoma is rare and accounts for only 0.2% of all lymphomas in Western populations.⁵ The incidence of primary sinonasal lymphoma has been reported to be higher in Asia than in Western populations.⁶ In a previous study performed in a human T-cell leukemia virus type 1 (HTLV-1) non-endemic area of Japan, the ratio of primary NHL in the nasopharynx was reported to be 24% of that in the head and neck region.⁷ However, in Japan, the ratio of primary sinonasal lymphoma to all lymphomas, NHL, and head and neck lymphoma is unclear. In addition, there are no recent statistical reports on malignant lymphoma, including primary sinonasal lymphoma, in the HTLV-1 endemic area of Fukuoka, Japan. Therefore, we conducted a retrospective study on the type of WHO classification based on histopathological diagnosis of patients who were newly diagnosed with malignant lymphoma from April

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2012 until March 2016. We also examined the clinicopathological analysis of primary sinonasal lymphoma.

MATERIALS AND METHODS

Study design and participants

One hundred and fifty-one patients suspected of malignant lymphoma (82 males and 69 females) aged 18 to 90 years who underwent tissue diagnosis by the Malignant Lymphoma Comprehensive Analysis Test (ML-NET) (SRL, Inc., Tokyo, Japan) from April 2012 to March 2016 at Saiseikai Fukuoka General Hospital in an HTLV-1 endemic area of Fukuoka were retrospectively analyzed. Lymphoma was classified according to the WHO classification (2008).² Patients with main mass lesions in the sinonasal cavity and the chief complaint of accompanying lesions of the sinonasal cavity were diagnosed with primary sinonasal malignant lymphoma. However, accurately defining primary sinonasal malignant lymphoma was difficult because it was often accompanied by lymphadenopathy at multiple sites. The International Prognostic Index (IPI) and the stage (Ann Arbor classification) of malignant lymphoma were determined by hematologists based on the patients' characteristics, performance status, blood chemical values, and imaging findings, including computed tomography (CT), magnetic resonance imaging, positron emission tomography-CT, and bone marrow biopsy results. This retrospective study was conducted according to the principles in the Declaration of Helsinki, and was approved by the institutional ethics committee of Saiseikai Fukuoka General Hospital (number 2017-7-5).

Pathological tissue examination

Malignant lymphoma was diagnosed using the ML-NET (SRL, Inc., Tokyo, Japan), including pathological tissue examinations. These examinations included hematoxylin and eosin staining, special staining (Periodic Acid Schiff and silver bromide), an enzyme antibody method (labeled streptavidin biotin method), flow cytometry (LSMA CD45 gating), and chromosome examination (G-band or FISH).

Laboratory methods

Serum samples were collected from patients before the initiation of therapy and used for routine laboratory testing, including assays for serum lactate dehydrogenase (LDH). Serum soluble interleukin-2 receptor (sIL-2R), β 2-microglobulin (β 2M), anti-HTLV-1 antibody, and anti-HIV antigen/antibody were assessed by another agency (BML Inc., Tokyo, Japan). Increased marker values were established as follows: > 245 U/L for LDH, > 496 U/mL for sIL-2R, and > 2.0 mg/L for β 2M.

Statistical analysis

Statistical analyses, including the nonparametric Mann-Whitney *U*-test and Fisher's exact probability test, were performed using GraphPad Prism 5.0 (GraphPad Software Inc., San Diego, CA). Clinicopathological variables were

compared among three diffuse large B-cell lymphoma (DLBCL) patient groups using the χ^2 test and Fisher's exact probability test. The survival curves were plotted using the Kaplan-Meier method and compared using the log rank method. Statistical comparisons between the 3 DLBCL groups were carried out using JMP software version 9.0.3 (SAS Institute Inc., Cary, NC, USA). Differences were considered significant when the *p*-value was less than 0.05.

RESULTS

Incidence of sinonasal malignant lymphoma

Malignant lymphoma was suspected and 151 biopsies were performed. Among them, 75 were performed on the head and neck area by otolaryngologists. In total, 30 were examined by physicians, 15 by surgeons, 10 by plastic surgeons, nine by brain surgeons, six by gynecologists, three by orthopedic surgeons, two by dermatologists, and one by an ophthalmologist. Among 151 cases, 104 were diagnosed as malignant lymphoma, 96 of which were first-onset lymphoma.

Of the cases of overall malignant lymphoma, 95.8% (n=92) were NHL (Table 1). Mature B-cell neoplasms comprised 78.1% (n=75) of cases, of which DLBCL accounted for 43.7% (42 cases) and follicular lymphoma accounted for 18.7% (18 cases). Mature T/NK-cell neoplasms accounted for 15.6% (15 cases) and 6.2% (6 of these 15 cases) were ATLL. Primary lymphoma in the sinonasal cavity as the main lesion was found in 6.2% (n=6) of cases. According to tissue subtype classification, all of the cases were DLBCL.

Physical and laboratory data for first-onset lymphoma

The Eastern Cooperative Oncology Group Performance Status (PS) score, serum tumor marker levels, and viral infections of malignant lymphoma are shown in Table 2. PS was assessed for all 96 patients. Serum LDH, sIL-2R, and β 2M were measured for 95, 88, and 79 patients, respectively, except for those who received best supportive care (BSC) and those transferred to other hospitals. As shown in Table 2, the mean PS for overall malignant lymphoma was 1.0 and the mean levels of LDH, sIL-2, and β 2M were higher than the normal reference values (486 IU/L, 3607 U/mL, and 4.0 mg/L, respectively). Comparing mature B-cell neoplasms and mature T/ NK-cell neoplasms, the PS was slightly higher in mature T/NK-cell neoplasms than in mature B-cell neoplasms (mature T/NK-cell neoplasms vs mature B-cell neoplasms: mean PS 1.6 vs 0.8; *p* < 0.062). In addition, serum levels of LDH, sIL-2R, and β 2M were significantly higher in mature T/NK-cell neoplasms than in mature B-cell neoplasms (mature T/NK-cell neoplasms vs mature B-cell neoplasms: mean LDH 982 vs 389 IU/L, *p* < 0.005; mean sIL-2R 9243 vs 2430 U/ml, *p* < 0.001; and mean β 2 M 8.4 vs 3.3 mg/L, *p* < 0.008).

Regarding virus infection, anti-HTLV-1 antibody was measured in 82 of 96 patients. Anti-HTLV-1 antibody was positive in 8/82 (9.7%) patients with overall malignant lymphoma. For mature B-cell neoplasms, anti-HTLV-1 antibody was

Table 1. Incidence of lymphoid malignancies according to the WHO classification (2008).

	n	%	M/F	Mean age, years (SD)
Mature B-cell neoplasms	75	78.1	37/38	65.2 (16.4)
Diffuse large B-cell lymphoma	42	43.7	22/20	66.5 (15.8)
Follicular lymphoma	18	18.7	7/11	68.3 (11.3)
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue	5	5.2	1/4	59.6 (17.9)
Burkitt lymphoma	2	2.0	2/0	74.5 (6.3)
Mantle cell lymphoma	2	2.0	2/0	53.0 (2.8)
Plasmacytoma	2	2.0	1/1	57.5 (26.1)
Nodal marginal zone B-cell lymphoma	1	1.0	0/1	20.0 (0.0)
B-cell lymphoma, unclassifiable	3	3.1	2/1	60.0 (34.7)
Mature T-cell and NK-cell neoplasms	15	15.6	8/7	65.9 (12.4)
Adult T-cell leukemia/lymphoma	6	6.2	3/3	70.8 (6.1)
Peripheral T-cell lymphoma, not otherwise specified	4	4.1	2/2	67.2 (7.8)
Angioimmunoblastic T-cell lymphoma	3	3.1	2/1	71.6 (9.8)
Anaplastic large cell lymphoma, ALK positive	2	2.0	1/1	40.0 (4.2)
Composite B- and T-cell neoplasms	2	2.0	2/0	72.5 (9.1)
Hodgkin lymphoma	4	4.1	2/2	61.2 (22.1)
Total	96	100.0	49/47	65.3 (15.8)

M, male; F, female; ALK, anaplastic lymphoma kinase; MALT, mucosa-associated lymphoid tissue.

Table 2. Physical and laboratory data for first-onset lymphoma.

	PS (SE)	LDH (IU/L) (SE)	sIL-2R (U/mL) (SE)	β 2M (mg/L) (SE)	% Anti-HTLV-1 antibodypositive (n/N)
Mature B-cell neoplasms	0.8 (0.1)	389 (76)	2430 (639)	3.3 (0.6)	3.2 (2/61)
Diffuse large B-cell lymphoma	1.0 (0.1)	415 (77)	1893 (340)	2.7 (0.2)	5.7 (2/35)
Follicular lymphoma	0.6 (0.1)	224 (27)	4480 (2669)	5.3 (2.6)	0.0 (0/13)
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue	0.2 (0.2)	193 (33)	895 (394)	1.8 (0.2)	0.0 (0/5)
Burkitt lymphoma	1.5 (1.5)	2639 (2302)	3724 (2873)	4.4 (1.9)	0.0 (0/2)
Mantle cell lymphoma	0.0 (0.0)	213 (50)	3488 (2886)	2.6 (1.2)	0.0 (0/2)
Plasmacytoma	0.5 (0.5)	180 (1.0)	334 (0)	2.4 (0.0)	0.0 (0/1)
Nodal marginal zone B-cell lymphoma	0.0 (0.0)	161 (0)	175 (0)	1.4 (0.0)	0.0 (0/1)
B-cell lymphoma, unclassifiable	1.3 (0.8)	197 (30)	1174 (992)	2.4 (1.3)	0.0 (0/2)
Mature T-cell and NK-cell neoplasms	1.6 (0.3)	982 (380)	9243 (3881)	8.4 (3.4)	40.0 (6/15)
Adult T-cell leukemia/lymphoma	1.6 (0.6)	1418 (849)	15082 (9350)	13.3 (10.1)	100.0 (6/6)
Peripheral T-cell lymphoma, not otherwise specified	0.7 (0.2)	1213 (636)	4010 (1387)	6.0 (2.0)	0.0 (0/4)
Angioimmunoblastic T-cell lymphoma	0.3 (0.3)	325 (67)	6533 (4187)	9.5 (6.1)	0.0 (0/3)
Anaplastic large cell lymphoma, ALK positive	2.0 (2.0)	202 (10)	6257 (5371)	2.4 (0.2)	0.0 (0/2)
Composite B- and T-cell neoplasms	3.0 (1.0)	955 (479)	6017 (3553)	5.1 (0)	0.0 (0/2)
Hodgkin lymphoma	0.7 (0.2)	179 (24)	997 (596)	2.6 (0.9)	0.0 (0/4)
Total	1.0 (0.1)	486 (87)	3607 (856)	4.0 (0.7)	9.7 (8/82)

Eastern Cooperative Oncology Group Performance Status (PS), serum lactate dehydrogenase (LDH), soluble interleukin-2 receptor (sIL-2R), and β 2-microglobulin (β 2M) data are shown as the mean \pm SE.

ALK, anaplastic lymphoma kinase; MALT, mucosa-associated lymphoid tissue; PS, Eastern Cooperative Oncology Group Performance Status; sIL-2R, soluble interleukin-2 receptor; β 2M, β 2-microglobulin; n.a., not assessed.

positive in 2/61 (3.2%) patients, and it was positive in 2/35 (5.7%) with DLBCL. For mature T/NK-cell neoplasms, anti-HTLV-1 antibody was positive in 6/15 (40%) patients, and all of them had ATLL. Anti-HIV antigen/antibody was measured in 78 of 96 all malignant lymphoma patients, and

they were all negative for anti-HIV antigen/antibody.

Clinical course of sinonasal malignant lymphoma

The clinical characteristics and prognoses of six primary

sinonasal malignant lymphoma patients are shown in Table 3. The age at the first visit ranged from 48 to 86 years, and the ratio of males and females was 1:1. The histological subtype of all of the six sinonasal lymphomas was DLBCL according to the WHO classification (Table 3). Regarding the risk factors for NHL, the PS score was 0 to 1, and two of six patients had greater serum LDH levels than the upper limit of normal. One patient had a higher value of serum β 2M than the reference value. HTLV-1 antibody was negative in the patients examined. The observation period ranged from 1.5 to 23 months. Chemoimmunotherapy with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) was administered to five sinonasal lymphoma patients as initial treatment, whereas one patient (patient no. 4) received BSC because of their age (Table 3). Two patients (patient nos. 1 and 2) whose tumors had recurred in the brain died 1-2 years after diagnosis. Two (patient nos. 5 and 6) of three patients who had complete response (CR) after R-CHOP therapy are alive without relapse. One patient (patient no. 3) who received R-CHOP therapy followed by involved-field radiotherapy is also alive without relapse.

Next, the clinical outcomes were compared between DLBCL patients with sinonasal tumors and those without the tumor phenotype. We separated DLBCL patients into three groups according to lesion type at the time of diagnosis, *i.e.* DLBCL patients with sinonasal lesions: primary sinonasal DLBCL (SN DLBCL), those who had central nervous system (CNS) involvement (CNS DLBCL), and those without lesions in the sinonasal tract or CNS (non-SN/CNS DLBCL). The clinicopathological variables, including age, sex, Ann Arbor stage, PS, serum LDH, and International Prognostic Index, were not significantly different among the three groups (data not shown). The overall survival (OS) for the patients who received chemotherapy was then assessed using the Kaplan-Meier method (Figure 1). The patient survival was significantly different among the three DLBCL patient groups ($p = 0.0016$; 3-year overall survival: non-SN/CNS DLBCL, 83%; SN DLBCL, 53%; CNS DLBCL, 0%).

DISCUSSION

Although malignant lymphoma has been more precisely grouped and classified,² there have been no recent statistical reports on malignant lymphoma in Fukuoka, Japan. The recent incidence and clinical features of malignant lymphoma in the sinonasal cavity as the main lesion are also unknown. Therefore, in this study, we investigated the pathological classification of patients who were newly diagnosed with malignant lymphoma and examined sinonasal malignant lymphoma in detail.

We found that 95.8% (92) of the patients with overall first-onset malignant lymphoma had NHL, as previously reported in Japan.³ Of these patients, those with mature B-cell neoplasms accounted for a large proportion, among which the proportions of those with DLBCL and follicular lymphoma were high. This finding is similar to that of central diagnosis of pathology reported by an adult lymphoma

treatment group in 2005, except for that medical institutions in Kyushu and Shikoku districts are in HTLV-1 endemic areas.⁸ However, the proportion of ATLL patients among those with overall malignant lymphoma was 6.2% (6 patients), which was lower than that (approximately 20%) in previous reports from the Kyushu district.^{3,4,9} The islands of Kyushu and Okinawa in southwestern Japan are hyper-endemic areas for HTLV-1, and 15% of the healthy adult population carries this virus.¹⁰ Screening pregnant women and abstaining from breastfeeding, which is the most common route of transmission of HTLV-1, were found to markedly reduce the prevalence of HTLV-1.¹¹ Therefore, the number and percentage of carriers at a young age have decreased. However, taking into account the low birth rate and rapidly aging population, the number of carriers of HTLV-1 in the entire population has not significantly changed from 20 years ago. Many carriers of HTLV-1 do not develop lymphoma or leukemia. However, after 40 to 50 years, a small percentage of carriers develop lymphoma. The proportion of carriers of HTLV-1 and the incidence of ATLL in older people has not changed.¹² Therefore, the decrease in ATLL observed in our study may be considered a relative decrease because of an increase in the prevalence of malignant lymphoma in recent years, particularly B-cell lymphoma (DLBCL and follicular lymphoma). Consequently, in the current study, the proportion of patients with ATLL and mature T/NK-neoplasms among all malignant lymphoma patients has been approximated to that in other regions of Japan except for HTLV-1-endemic areas, unlike in previous reports.^{3,8,9}

HTLV-1 carriers were reported to have a high incidence of malignant lymphoma and solid tumors.¹³ In our study, we were unable to assess whether HTLV-1 infection played a role in the development of other lymphomas except for ATLL because of the small number of patients; there were only 2 HTLV-1 carriers among patients with DLBCL. In addition, HTLV-1 infection was reported to exacerbate the prognosis of B-cell lymphoma;¹⁴ however, in 5 primary sinonasal lymphoma patients, excluding those with BSC, anti-HTLV-1 antibody was negative and there was no effect of HTLV-1 infection on the clinical course.

A previous study reported the percentage of primary NHL in the nasopharynx to be 24% of that in the head and neck region.⁷ However, the proportion of primary sinonasal malignant lymphoma among overall malignant lymphoma is unclear. In our study, the proportion of primary sinonasal malignant lymphoma was 6.2% of overall malignant lymphoma. Therefore, the proportion of primary sinonasal malignant lymphoma was estimated to be 12.5% among head and neck malignant lymphoma because 6/48 patients were biopsied from the head and neck area by otolaryngologists and diagnosed with first-onset malignant lymphoma.

The tissue subtype of primary sinonasal malignant lymphoma in this study was DLBCL, and extranodal NK/T-cell lymphoma, nasal type (ENKTL) was not detected. In Western populations, the majority of lymphoma in the sinonasal region is DLBCL.^{1,15-17} However, ENKTL, which is

Table 3. Patient characteristics, physical and laboratory data, and treatment and outcome of primary sinonasal malignant lymphoma.

Patient no.	Age (y)	Sex	Signs and symptoms	Invasive lesions (sinus etc.)	Histological subtype	Stage*	IPI†	PS	LDH (IU/L)	sIL-2R (U/ml)	β2M (mg/L)	Anti-HTLV-1 antibody	EBER	Initial treatment	Response	Outcome
1	48	F	Rt cheek pain, and watery eye	<u>Rt nasal cavity, ethmoidal, and maxillary sinus, orbital medial wall, submandibular, and bilateral cervical lymph nodes</u>	DLBCL (non-GC type)	IV with bulky lesion (B symptom -)	Low	0	193	354	1.4	-	-	R-CHOP 6 cycles	PD	DOD, 1 year 11 months
2	77	F	Nasal obstruction, It submandibular swelling, and diminished vision	<u>Bilateral ethmoidal, sphenoidal, and rt maxillary sinus, pleura, lt intraorbital, chest subcutaneous tissue, bilateral submandibular, cervical, and mediastinal lymph nodes, and bone marrow</u>	DLBCL (GC type)	IV (B symptom -)	High	1	271	402	1.4	-	-	R-CHOP 6 cycles	CR	DOD, 1 year
3	55	F	Rt cheek uncomfortable feeling	<u>Rt maxillary sinus, cheek subcutaneous tissue, intraorbital, bilateral cervical lymph nodes, and bone marrow</u>	DLBCL (GC type)	IV (B symptom -)	Low	0	160	179	1.0	-	-	R-CHOP 6 cycles + RT	CR	AD-, 1 year 4 months
4	86	M	Lt ocular, cheek pain, and cheek numbness	<u>Lt ethmoidal, and maxillary sinus, intraorbital, pterygopalatine fossa, cavernous sinus, and middle cranial fossa</u>	DLBCL (GC type)	IV (B symptom -)	High	1	262	795	n.a.	n.a.	-	BSC	n.a.	DOD, 1.5 months
5	59	M	Rt cheek swelling, and submandibular swelling	<u>Lt nasal cavity, rt ethmoidal and maxillary sinus, intraorbital, cervical, and supraclavicular lymph nodes, bilateral palatine tonsil, and bone marrow</u>	DLBCL (GC type)	IV (B symptom -)	Low	0	199	641	1.9	-	-	R-CHOP 6 cycles	CR	AD-, 1 year 4 months
6	65	M	Nasal obstruction, It nasal ala, and cheek swelling	<u>Lt nasal cavity, and mediastinal and hilar lymph nodes</u>	DLBCL (GC type)	II (B symptom -)	Low	0	203	682	2.6	-	-	R-CHOP 6 cycles	CR	AD-, 1 year 1 months

Underlined parts indicate nasal cavities and paranasal sinuses. Dotted lined parts indicate values ≥ 245 U/L for lactate dehydrogenase (LDH), > 496 U/mL for soluble interleukin-2 receptor (sIL-2R), and > 2.0 mg/L for β 2-microglobulin (β 2M). *Ann Arbor classification; †IPI, International Prognostic Index. M, male; F, female; Rt, right; Lt, left; DLBCL, diffuse large B-cell lymphoma; PS, Eastern Cooperative Oncology Group Performance Status; sIL-2R, soluble interleukin-2 receptor; β 2M, β 2-microglobulin; n.a., not assessed; R-CHOP, chemoimmunotherapy with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, radiation therapy; BSC, best supportive care; CR, complete response; PD, progressive disease; DOD, died of disease; AD-, alive without disease.

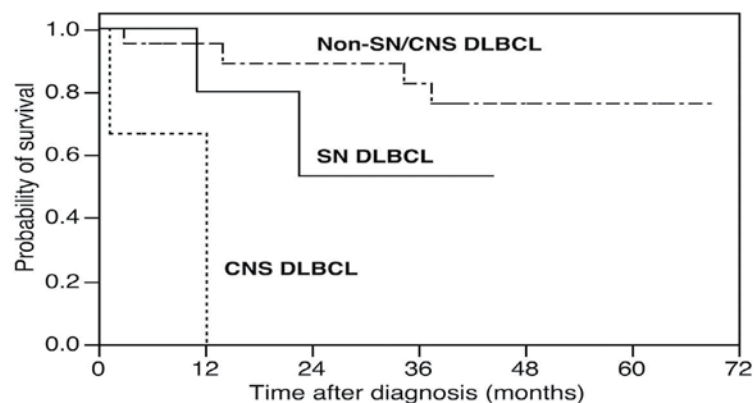


Fig. 1. Overall survival of DLBCL patients with/without sinonasal lesions. The overall survival for each group was evaluated using the Kaplan-Meier method. SN DLBCL: DLBCL patients with sinonasal lesions, primary sinonasal DLBCL; CNS DLBCL: those with central nervous system lesions; non-SN/CNS DLBCL: those without sinonasal tract and central nervous system lesions.

related to Epstein-Barr virus infection, is more common in East Asia and South America.^{1,15,16,18} However, previous studies in Japan have reported that rate of ENKTL among overall malignant lymphoma to be approximately 2%,^{8,9} which is much lower than that in China in East Asia.¹⁸ Additionally, this rate is the same as that reported in Kyushu and other Japanese regions, except for Okinawa, which is close to China.^{8,9} Due to the small number of patients in this study, ENKTL may not have been detected.

Recently, primary sinonasal DLBCL has been recognized as a distinct disease entity of DLBCL. Oprea C *et al.* reported 14 patients with primary DLBCL of the paranasal sinuses who received CHOP-like chemotherapy.¹⁹ Of the 14 sinonasal DLBCL patients, 10 (71%) achieved CR and seven (50%) relapsed or progressed. Five of the seven patients (36%, 5/14) had lesions in the CNS when their tumors progressed. On the other hand, all of five patients that received adjuvant radiotherapy (40-45 Gy to local sinonasal sinuses) had CR, and thus achieved long-term survival despite relapse in one patient. The 3-year OS was approximately 70% for the 14 patients. These results were consistent our findings. However, they investigated primary DLBCL of the paranasal sinuses alone, and did not compare the clinicopathological features or clinical outcomes of sinonasal DLBCL with those of other DLBCL. Toda H *et al.* examined 39 patients with localized nasal/paranasal DLBCL.²⁰ Of 25 patients that were treated using antineoplastic agents, 15 (60%) received chemotherapy followed by involved-field radiotherapy in the study. The 3-year OS for the patients who received chemotherapy was approximately 70%. The OS did not significantly differ between the patients with localized nasal/paranasal DLBCL and those with localized nodal DLBCL. On the other hand, the OS was better in those with localized nasal/paranasal DLBCL than in those with other localized extranodal DLBCL such as DLBCL of the CNS. From these observations, they concluded the prognosis of localized nasal/paranasal DLBCL to be good. This study focused on

localized sinonasal lymphoma, whereas our study included patients with all stages. Thus, the OS for our patients was poorer because there were more patients with advanced stages. Furthermore, radiotherapy may have played an important role in treating patients with localized lesions as localized treatment in their study.²¹ Our present study clarified the incidence and outcomes of patients with primary sinonasal DLBCL among all lymphomas. In particular, the survival curve of primary sinonasal DLBCL patients was located in the middle among three DLBCL patient groups (Figure 1). The patient survival may have been poor in our sinonasal DLBCL group because two sinonasal DLBCL patients had recurrence in the CNS. Some reports also described CNS involvement at the time of relapse,¹⁹ similar to our present report. Therefore, prophylactic treatment for CNS involvement, such as radiotherapy for the involved sinonasal cavity and intrathecal injection of methotrexate, may improve sinonasal DLBCL patient survival.²²⁻²⁴ There are some limitations in our present study. This was a retrospective study at only one facility. As the number of patients in our study was small, further studies with a larger number of patients is necessary.

In summary, primary sinonasal lymphomas, all of which were DLBCL, accounted for 6.2% of all malignant lymphomas. CNS recurrence of sinonasal DLBCL with standard chemotherapy has a poor prognosis. Therefore, in addition to standard chemotherapy, the combination of involved-field radiotherapy or intravenous and/or intrathecal administration of methotrexate with other blood-brain barrier-crossing agents should be considered.

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CONFLICT OF INTEREST

All authors have read the journal's policy on conflicts of interest and have none to declare.

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