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ORIGINAL ARTICLE

Improved prognosis of extranodal NK/T cell lymphoma, nasal type of nasal origin but not extranasal origin

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Abstract

Extranodal NK/T cell lymphoma (NKTCL), nasal type (ENKL) that shows no apparent nasal involvement, is termed extranasal NKTCL or non-nasal NKTCL. In this study, we aimed to explore therapeutic approaches and outcomes in patients with extranasal NKTCL in current clinical practice. A data set of patients with newly diagnosed NKTCL who were diagnosed at 31 institutes in Japan between 2000 and 2013 was used for analysis. The patients' fitness for steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy was assessed using the major inclusion criteria of the SMILE phase 2 study. Of 358 patients, 47 (13%) had extranasal NKTCL. The most frequent extranodal sites of involvement in extranasal NKTCL were skin/subcutaneous tissue ($n = 18$). Six (13%) of the patients with extranasal NKTCL had localized disease and were diagnosed before 2010. With a median follow-up of 5.8 years, the 2-year overall survival (OS) in patients with nasal and extranasal NKTCL was 70% (95% confidence interval [CI], 65–75%) and 34% (95% CI, 21–47%), respectively. OS in patients with nasal NKTCL had a trend toward better according to treatment era ($P = 0.063$). In contrast, no obvious improvement of OS was observed in extranasal NKTCL ($P = 0.43$). The major inclusion criteria of the SMILE-P2 were met in 21% (10/47) of patients with extranasal NKTCL and 60% (188/311) of those with nasal NKTCL ($P < 0.001$). Despite the advent of new treatments for ENKL, OS remains unfavorable in extranasal NKTCL. A more effective therapy is needed for extranasal NKTCL.

Keywords NK/T cell lymphoma · Extranasal · Chemotherapy · Radiotherapy

Introduction

Extranodal natural killer (NK)/T cell lymphoma (NKTCL), nasal type (ENKL), is a lymphoma entity according to the World Health Organization (WHO) classification that is characterized predominantly by extranodal involvement and its association with Epstein-Barr virus (EBV) [1]. The upper aerodigestive tract is most commonly involved in ENKL, and the nasal cavity is the prototypical site of involvement [1]. More than 60% of patients with ENKL have localized disease [2, 3]. ENKL without any apparent nasal involvement is termed extranasal NKTCL or non-nasal NKTCL, with the skin, soft tissue, and gastrointestinal tract representing common sites of extranasal involvement [4, 5]. Patients with extranasal NKTCL frequently present with advanced-stage disease and have short survival times [4, 6, 7]. The non-nasal type is one of the four risk factors in the prognostic index for NK lymphoma (PINK), which is a modern prognostic model for newly diagnosed ENKL [2].

Current treatment guidelines recommend that the approaches used in advanced nasal NKTCL should be the same as those applied in extranasal NKTCL [8, 9]. Steroid, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) chemotherapy is listed in the guidelines as a reasonable treatment for advanced ENKL based on the excellent overall

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response rate (80%) achieved in a phase 2 trial of SMILE chemotherapy (SMILE-P2) in newly diagnosed stage IV ENKL [10]. Moreover, in patients with newly diagnosed localized nasal NKTCL, chemoradiotherapy with non-anthracycline-containing regimens such as concurrent chemoradiotherapy (CCRT) with radiotherapy and dexamethasone, etoposide, ifosfamide, and carboplatin (RT-DeVIC) [11, 12] is recommended. CCRT with weekly cisplatin followed by etoposide, ifosfamide, cisplatin, and dexamethasone (CCRT-VIPD) [13, 14] and CCRT with etoposide, ifosfamide, dexamethasone, and L-asparaginase (CCRT-VIDL) [14] can be used and have excellent efficacy [15]. These new treatments have been used to treat ENKL for a decade; however, which therapeutic approaches are appropriate and what their outcomes are in patients with extranasal NKTCL in current clinical practice remain poorly explored.

Previously, we conducted a nationwide retrospective study of treatment and therapeutic outcomes in 358 patients diagnosed with ENKL between 2000 and 2013 in 31 institutes in Japan (next-generation therapy for NK/T cell lymphoma in East Asia [NKEA] Part A) [3]. To explore therapeutic approaches and outcomes in patients with extranasal NKTCL in current clinical practice, we analyzed the NKEA Part A data set in two clinical subgroups (nasal vs. extranasal). In extranasal NKTCL, we analyzed the sites of involvement at diagnosis and baseline clinical features with a particular focus on the fitness of SMILE chemotherapy.

Patients and methods

Patients

This is a multicenter, retrospective study in which we used a data set obtained from the NKEA Part A (clinical trial registration number: UMIN000015491) [3]. In the NKEA Part A project, data were retrospectively collected from consecutive patients diagnosed with ENKL between 2000 and 2013 at 31 participating institutes in Japan. The diagnostic criteria for nasal and extranasal NKTCL were based on criteria described in a previous report [16]. The cut-off values for C-reactive protein (CRP) and serum soluble interleukin-2 receptor (sIL-2R; sCD25) levels were 0.30 mg/dL and 519 U/mL, respectively; these are the same values that were used in a previous analysis [3]. The NKEA project was approved by the institutional review board at each study site and conducted according to the Declaration of Helsinki.

Patients' fitness for SMILE chemotherapy

Among the inclusion criteria applied in the SMILE-P2 study [10], the following six major criteria were used to evaluate fitness for SMILE chemotherapy: age, 15–69 years old; performance status (PS), 0–2; WBC, $\geq 3000/\mu L$; lymphocyte count, $\geq 500/\mu L$; platelets, $\geq 75 \times 10^9/L$ (or $50 \times 10^9/L$ in patients with bone marrow involvement and/or hemophagocytic syndrome); and no serious complications. Patients who fulfilled all six of these criteria were regarded as fit for SMILE chemotherapy.

Statistical analysis

Correlations between the two groups were examined with Fisher's exact test. Survival data were analyzed by the Kaplan-Meier method. Overall survival (OS) was defined as the time from diagnosis until death from any cause or until the date of the last follow-up. Progression-free survival (PFS) was defined as the time from diagnosis until a documented progression or relapse of lymphoma or death resulting from any cause. OS and PFS were calculated according to the Kaplan-Meier method and were compared by the log-rank test. The results of a multicenter nationwide retrospective study performed between 1994 and 1998 in Japan [6] (2-year OS: nasal, $< 50\%$ and extranasal, $< 30\%$) were used as a historical control in the survival analysis. To perform a comparison of OS across treatment era, we applied the same periods that were used in our previous analysis [3]: first era, 2000 to 2004; second era, 2005 to 2009; and third era, 2010 to 2013. All tests were two-sided, and $P < 0.05$ indicated a significant difference. All analyses were performed using IBM SPSS Statistics 23 (IBM Japan).

Results

Clinical characteristics of nasal NKTCL and extranasal NKTCL

Of 358 patients, 311 (87%) had nasal NKTCL, and 47 (13%) had extranasal NKTCL. There was no significant difference in the age at diagnosis or the proportion of male patients between the two groups. At diagnosis, the clinical features of extranasal NKTCL were more aggressive than those observed in nasal NKTCL (Table 1).

The median number of sites of extranodal involvement in extranasal NKTCL was 2 (range, 0–8). Common involved extranodal sites included the skin/subcutaneous tissue ($n = 18$), liver ($n = 16$), bone marrow ($n = 15$), small intestine ($n = 10$), and lungs ($n = 8$). The extranodal sites of involvement in each patient are shown in Fig. 1. Notably, no patients with cutaneous involvement exhibited intestinal involvement. All 6 patients with localized extranasal NKTCL had stage IE disease. The primary sites of involvement in those patients included the testis, duodenum, small intestine, brain, skin, and cervical lymph nodes.

Table 1 Clinical characteristics according to subgroups ($N = 358$)

	All patients	Subgroup		
	($N = 358$) No. (%)	Nasal ($n = 311$) No. (%)	Extranasal ($n = 47$) No. (%)	*P*
Median age, years	58	58	59	
Range	16–88	16–88	20–85	
Age > 60	155 (43)	133 (43)	22 (47)	0.64
Male sex	240 (67)	212 (68)	28 (60)	0.25
Stages III and IV	101 (28)	60 (19)	41 (87)	< 0.001
Elevated LDH	157 (44)	118 (38)	39 (83)	< 0.001
ECOG PS > 1	79 (22)	50 (16)	29 (62)	< 0.001
Extranodal sites > 1	105 (29)	74 (24)	31 (66)	< 0.001
Involvement of the nasal cavity	286 (80)	286 (92)	0 (0)	< 0.001
B symptom (+)	156 (44)	121 (40)	35 (75)	< 0.001
Unknown	5	5	0	
Hb < 11 g/dL	77 (22)	52 (17)	25 (53)	< 0.001
Elevated CRP	204 (59)	171 (57)	33 (72)	0.076
Unknown	11	10	1	
Elevated sIL-2R	171 (57)	140 (54)	31 (84)	0.001
Unknown	60	50	10	
IPI low	207 (58)	201 (65)	6 (13)	< 0.001
Low-intermediate	48 (13)	45 (14)	3 (6)	
High-intermediate	41 (12)	29 (9)	12 (26)	
High	62 (17)	36 (12)	26 (55)	
PINK low	146 (41)	146 (47)	0 (0)	< 0.001
Intermediate	127 (35)	124 (40)	3 (6)	
High	85 (24)	41 (13)	44 (94)	

ECOG, Eastern Clinical Oncology Group; *IPI*, international prognostic index; *LDH*, lactate dehydrogenase

First-line treatment in patients with ENKL according to the two clinical subgroups

Of the 47 patients with extranasal NKTCL, 7 (15%) received SMILE as a first-line therapy. Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)–like chemotherapy was selected in 14 patients (30%), and DeVIC-like therapy was selected in 11 patients (23%) (Table 2). Six out of the 25 patients treated with CHOP-like chemotherapy or DeVIC-like therapy received SMILE after one course of initial chemotherapy. Three patients received RT-DeVIC therapy, and 7 received no therapy. Among the 40 patients with extranasal NKTCL who received any therapy, the complete response (CR) rate and overall response rate were 40% and 58%, respectively. Fourteen patients underwent hematopoietic stem cell transplantation in the first CR or partial response (PR).

Of the patients with nasal NKTCL, the proportion of patients who received RT-DeVIC or non-anthracycline-containing chemotherapy increased according to treatment era. In contrast, in patients with extranasal NKTCL, there was no obvious difference in treatment choice among the three eras (data not shown).

Fitness for SMILE chemotherapy

All 6 of the major inclusion criteria in the SMILE-P2 were used in this analysis and were met in 21% (10/47) of patients with extranasal NKTCL, 60% (188/311, $P < 0.001$) of those with nasal NKTCL, and 38% (23/60, $P = 0.091$) of those with advanced nasal NKTCL. The fitness for SMILE chemotherapy of each patient with extranasal NKTCL is shown in Fig. 1. In patients with extranasal NKTCL, 27 patients (57%) did not meet multiple inclusion criteria.

Notably, no patients with liver involvement were fit for SMILE chemotherapy (Fig. 1). Among patients with intestinal involvement, only one (10%) was fit for SMILE, while 5 out of 18 patients (28%) with cutaneous involvement were fit for SMILE. Of 18 patients with cutaneous involvement, 7 (39%) were > 69 years old, and 8 (44%) had a poor PS (> 2).

Among 10 patients with extranasal NKTCL who were fit for SMILE, three patients actually received SMILE

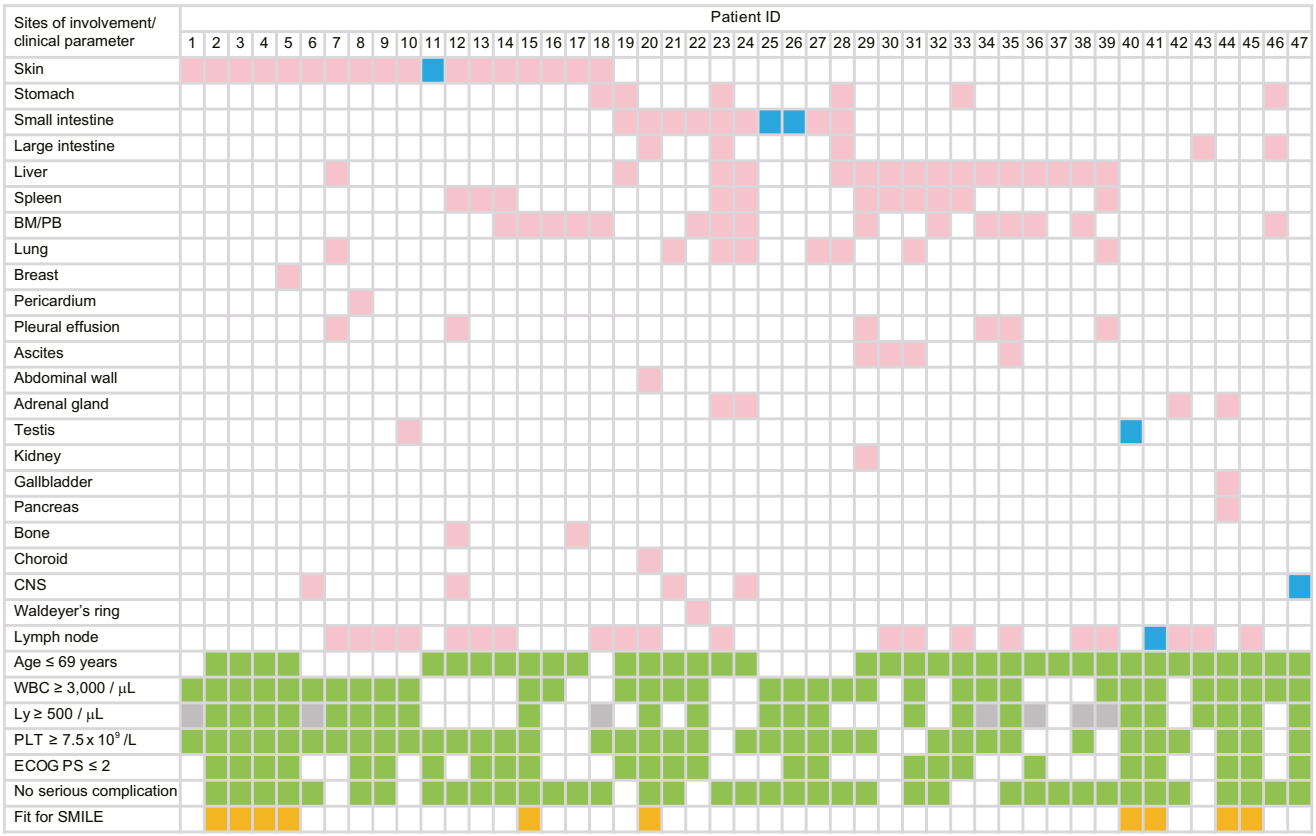

Fig. 1 Extranodal sites of involvement at diagnosis and fitness for SMILE chemotherapy in each patient ($n = 47$). Pink cells indicate the presence of involvement. Blue cells indicate the presence of involvement in patients with localized disease ($n = 6$). Orange cells indicate patients who fulfilled all 6 major inclusion criteria of the SMILE-P2 study. Gray cells indicate data not available

Table 2 Treatments according to disease stages among patients with newly diagnosed ENKL ($N = 358$)

	All stage		Localized stage		Advanced stage	
	($N = 358$)		($n = 257$)		($n = 101$)	
Treatment	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)
Nasal NKTCL ($n = 311$)						
RT-DeVIC	175	(56)	168	(67)	7	(12)
RT alone	25	(8)	22	(9)	3	(5)
SMILE-like chemo. ± RT	26	(8)	5	(2)	21	(35)
Sequential RT-DeVIC	20	(6)	19	(8)	1	(2)
Sequential RT-CHOP	20	(6)	17	(7)	3	(5)
RT-CHOP	15	(5)	13	(5)	2	(3)
DeVIC-like chemo.	14	(5)	1	(0)	13	(22)
CHOP-like chemo.	12	(4)	5	(2)	7	(12)
None	4	(1)	1	(0)	3	(5)
Extranasal NKTCL ($n = 47$)						
CHOP-like chemo.	14	(30)	2	(33)	12	(29)
DeVIC-like chemo.	11	(23)	1	(17)	10	(24)
SMILE-like chemo.	7	(15)	0	(0)	7	(17)
None	7	(15)	1	(17)	6	(15)
RT-DeVIC	3	(6)	1	(17)	2	(5)
Others	5	(11)	1	(17)	4	(10)

chemo., chemotherapy

chemotherapy as a first-line treatment. Other three patients received SMILE after RT or one cycle of DeVIC chemotherapy, two had localized disease and were treated as described in Table 3 (46 F, 34 M), and the remaining 2 patients who were diagnosed in 2006 and 2007 received CHOP therapy.

Survival analysis

After a median follow-up of 5.8 years, patients with nasal NKTCL exhibited better OS and PFS than in those with extranasal NKTCL (Fig. 2; $P < 0.001$). The 2-year OS of patients with nasal NKTCL was 70% (95% CI, 65–75%), and this was superior to the historical control (< 50%). In contrast, the 2-year OS of patients with extranasal NKTCL was 34% (95% confidence interval [CI], 21–47%). The 5-year OS was 61% in the nasal group and 12% in the extranasal group. At the last follow-up, three patients with extranasal NKTCL had survived > 5 years, and two of them had primary cutaneous NKTCL. The OS of patients with nasal NKTCL tended to improve with treatment era progression ($P = 0.063$, Fig. 3a). In contrast, in extranasal NKTCL, there was no obvious improvement in OS according to treatment era ($P = 0.43$, Fig. 3b).

In localized NKTCL, the OS of patients with extranasal NKTCL tented to be worse than that of patients with nasal NKTCL ($P = 0.062$, Fig. 4a). In contrast, there was no difference in OS between advanced nasal NKTCL and advanced extranasal NKTCL ($P = 0.14$, Fig. 4b). The treatments and outcomes reported in 6 patients with localized extranasal NKTCL are summarized in Table 3. All patients were diagnosed before 2010. One patient with primary testicular NKTCL received RT-2/3DeVIC with contralateral RT after surgical resection. One patient with duodenal NKTCL died without any therapy.

Four patients with extranasal NKTCL experienced relapse at the nasal cavity (#20, #33, #40, and #41 in Fig. 1). The sites of extranodal involvement at diagnosis were the liver and stomach in one patient; the small and large intestine, abdominal wall, and choroid in one patient; only the cervical lymph node in one patient; and the testis in one patient. Two of these four patients received a non-anthracycline-containing first-line therapy.

Discussion

In the present study, we used the NKEA Part A data set and found that there was no obvious improvement in the survival of patients with extranasal NKTCL, whereas the prognosis of patients with nasal NKTCL improved to 70% (95% CI, 65–75%) from the < 50% reported in a previous study in Japan (1994–1998, $n = 149$) [6].

Several reports have summarized the clinicopathologic features of extranasal NKTCL [4, 6, 7, 16, 17]. The present study is unique in the following two ways. First, in our study, we visualized extranodal sites of involvement in each patient with extranasal NKTCL (Fig. 1). Of note, most patients had multiple sites of extranodal involvement. Only 13% (6/47) of patients with extranasal NKTCL had localized disease in the present study (2000–2013). This incidence was lower than the rate found in our previous study performed in Japan (37% [10/27]; 1985–2008) [16] as well as the rate found in an international T cell lymphoma project study (32%; 1990–2002) [7]. In the present study, no patient had localized extranasal NKTCL after 2010. One possible reason for this change is the advent of more rigorous staging procedures, including PET-CT, which have been introduced to pretreatment evaluation in ENKL. Second, in our study, we evaluated fitness for SMILE chemotherapy using a detailed data set that included pretreatment clinical features and laboratory data (Fig. 1). We found that only 21% of patients with extranasal NKTCL were fit for SMILE chemotherapy. In fact, SMILE

Table 3 Treatment and outcome in patients with localized extranasal NKTCL ($n = 6$)

Age/sex (year at diagnosis)	Site of involvement	Treatment, response, and sites of relapse/progression	Outcome
85/M (2005)	Brain	50% DeVIC (SD)	0.8 years, DOD
46/F (2006)	Cervical LN	THP-COP, HD-CY (CR) ➔ HD-AHSCT (CR, relapsed in the nasal cavity) ➔ THP-COP, RT, DeVIC (CR) ➔ allo HSCT (CR, cGVHD, infection)	4.1 years, DND
20/F (2002)	Skin	THP-COP, ESHAP, CHASE (PR) ➔ CBT (CR)	13.6 years, AND
70/F (2003)	Small intestine	Surgery, CCRT (45 Gy)-THP-COP (CR, lost to follow-up)	1.2 years, AND
71/F (2008)	Duodenum	None	0.4 years, DOD
34/M (2009)	Testis	Surgery (CR) ➔ RT-2/3DeVIC, MTX/AraC IT (CR, relapsed in subcutaneous tissue in extremities, cervical LN, nasal cavity) ➔ HD-AHSCT (PD, PB involvement) ➔ DeVIC, CBT (PD, CNS involvement)	2.6 years, DOD

AND, alive with no evidence of disease; *CBT*, cord blood transplantation; *cGVHD*, chronic graft versus host disease; *CHASE*, cyclophosphamide, high-dose cytarabine, dexamethasone, and etoposide; *CNS*, central nervous system; *DOD*, died of disease; *DND*, died of no evidence of disease; *ESHAP*, etoposide, methylprednisolone, cytarabine, and cisplatin; *HD-AHSCT*, high-dose chemotherapy with autologous hematopoietic stem cell transplantation; *HD-CY*, high-dose cyclophosphamide; *LN*, lymph node; *PB*, peripheral involvement; *PD*, progressive disease; *SD*, stable disease; *THP-COP*, pirarubicin, cyclophosphamide, vincristine, and prednisolone

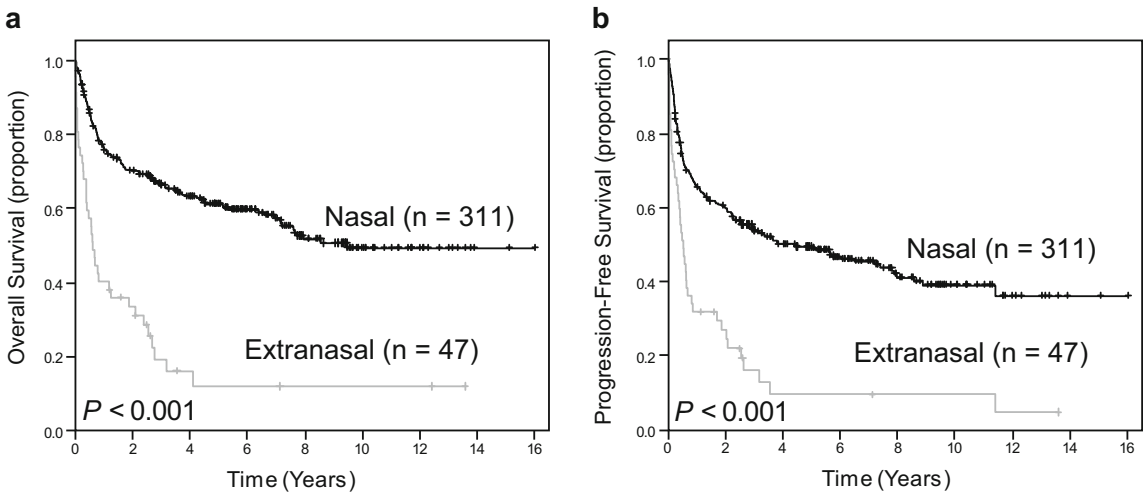

Fig. 2 Survival curves for all patients with ENKL ($N = 358$). OS (**a**) and PFS (**b**) were compared between the nasal and extranasal subgroups

was used as a first-line therapy in only 7 patients with extranasal NKTCL (15%) and after one cycle of CHOP-like or DeVIC-like chemotherapy in 6 patients (13%). These results clearly indicate that more feasible systemic treatments need to be developed for extranasal NKTCL.

The skin and soft tissues are the second most common sites of involvement in NKTCL. The prognosis of cutaneous NKTCL has been reported to be more favorable than that of other extranasal NKTCL types [18]. In the present study, two of three patients who survived more than 5 years had primary cutaneous NKTCL, supporting previous findings. One explanation for the favorable prognosis observed in these patients is that cutaneous NKTCL may be diagnosed earlier than other NKTCL types because skin abnormalities are easy to find and the skin is easy to biopsy. Another possible reason is that the skin can tolerate 50 Gy of RT [19]. A retrospective study of 48

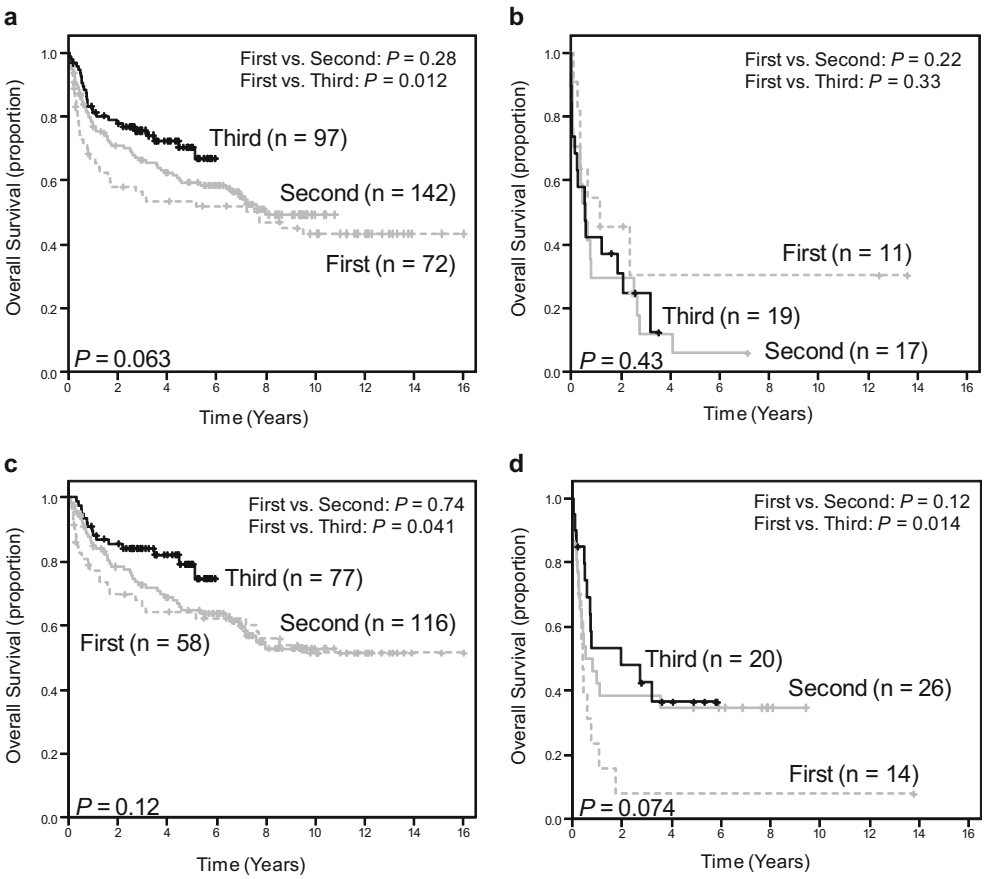

Fig. 3 OS curves for patients with ENKL according to treatment era (N = 358). **a** Nasal NKTCL ($n = 311$). **b** Extranasal NKTCL ($n = 47$). **c** Stage I/II nasal NKTCL ($n = 251$). **d** Stage III/IV nasal NKTCL ($n = 60$). First era, 2000 to 2004; second era, 2005 to 2009; and third era, 2010 to 2013

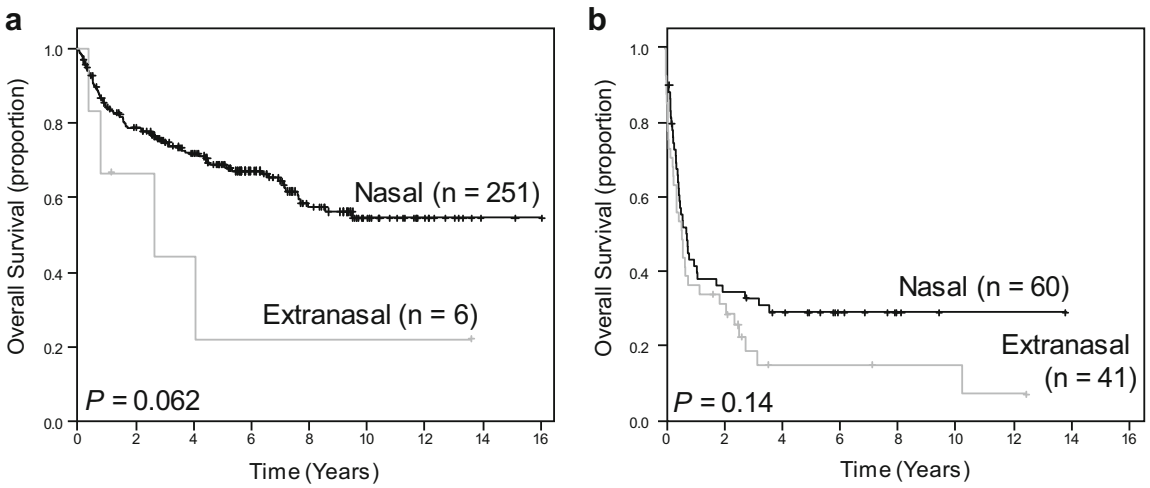

Fig. 4 OS curves for patients with ENKL according to stages ($N = 358$). **a** Localized NKTCL ($n = 257$) either nasal ($n = 251$) or extranasal ($n = 6$). **b** Advanced NKTCL ($n = 101$) either nasal ($n = 60$) or extranasal ($n = 41$)

patients suggested that RT provided survival benefits in patients with only localized cutaneous involvement [18]. The results of the present study suggest an additional explanation: patients with cutaneous involvement in NKTCL rarely exhibited intestinal involvement, which is often complicated by perforation. Skin and gastrointestinal involvement appear to be almost mutually exclusive. This phenomenon has been also documented in previous reports [4, 17, 20, 21] and was highlighted in our present study. Nevertheless, a more specific treatment strategy should be developed for cutaneous NKTCL because almost half of the patients with cutaneous involvement were > 69 years old and had poor PS in the present study.

The gastrointestinal tract is the third most common site of involvement in ENKL [17, 22]. Intestinal NKTCL is frequently complicated by perforation during therapy, and this complication is often fatal [17, 21]. Some reports have described patients who underwent surgical resection of intestinal lesions to prevent fatal complications during chemotherapy [23]. While this approach may be reasonable, we found that all but two patients with intestinal involvement also had additional extranasal involvement, such as hepatic lesions, indicating that surgical resection of intestinal lesions is not sufficient to obtain disease control. Innovative drug or cellular therapies that do not induce perforation are needed to treat intestinal NKTCL.

There is a consensus that RT of 50 Gy is required to achieve local control of ENKL [15]. In the present study, we found that the incidence of localized extranasal NKTCL was low (6/47, 13%), with two of the affected patients having involvement in sites that cannot be feasibly treated with high-dose RT (duodenum, $n = 1$; small intestine, $n = 1$). Therefore, innovative therapies are also needed to treat patients with localized extranasal NKTCL.

Some reports have described patients with extranasal NKTCL who have experienced a relapse in the nasal area, suggesting that nasal and non-nasal NKTCL are different clinical forms of the same disease process [24]. In the present study, four patients with extranasal NKTCL experienced relapse in the nasal cavity. Among these patients, two received non-anthracycline treatments. A longer follow-up study could determine whether this phenomenon continues to be observed in the non-anthracycline era.

In conclusion, OS remains unfavorable in patients with extranasal NKTCL despite the advent of new treatments for ENKL. Patients with ENKL, especially with advanced extranasal disease, should ideally be treated in an expert center, especially in countries where the incidence is low. SMILE chemotherapy and high-dose RT are not indicated for most patients with extranasal NKTCL because of frequent multiple extranodal involvement, contraindications to radiotherapy, and impaired organ functions. Less toxic L-asparaginase-containing regimens such as AspaMetDex (L-asparaginase, methotrexate, and dexamethasone) [25] and platinum-based regimens such as GDP (gemcitabine, dexamethasone, and cisplatin) [26] may be a good therapeutic option for those patients, warranting further evaluation. A more effective therapy should be explored for extranasal NKTCL.

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Author's contribution Conception and design: M Yamaguchi, R Suzuki, and M Oguchi.

Financial support: M Yamaguchi and R Suzuki.

Data analysis and interpretation: M Yamaguchi, R Suzuki, M Oguchi, and N Asano.

Provision of study materials or patients, collection and assembly of data, manuscript writing, and final approval of manuscript: All authors.

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Compliance with ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of interest RS received honoraria from Kyowa Hakko Kirin. YM and NK received a research grant from Kyowa Hakko Kirin. All remaining authors have no conflicts of interest.

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