

## Variable Clinical Presentations of Nasal and Waldeyer Ring Natural Killer/T-Cell Lymphoma

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**Abstract Purpose:** To determine the clinical characteristics, prognosis, and treatment outcome for patients with nasal natural killer (NK)/T-cell lymphoma (N-NKTL) and Waldeyer ring NK/T-cell lymphoma (WR-NKTL).

**Experimental Design:** A total of 145 patients with N-NKTL and 95 patients with WR-NKTL were compared.

**Results:** Compared with N-NKTL, WR-NKTL exhibited distinct differences in clinical features with a propensity for nodal involvement, more advanced stages, low elevated lactate dehydrogenase, intermediate chemosensitivity, and a favorable prognosis. Compared with patients with WR-NKTL, patients with N-NKTL were associated with a lower overall response (54% versus 89%) and higher persistent or progressive disease after initial chemotherapy (46% versus 11%;  $P = 0.000$ ). The 5-year overall survival and progression-free survival rates were 67% and 56% for N-NKTL and 65% and 47% for WR-NKTL, respectively. Patients with stage II WR-NKTL showed favorable prognosis compared with those with stage II N-NKTL. Compared with radiotherapy alone, patients with early-stage WR-NKTL that received radiotherapy and chemotherapy showed a superior progression-free survival and improved overall survival. In contrast, the addition of chemotherapy to radiotherapy did not provide any survival benefit for patients with early-stage N-NKTL.

**Conclusions:** N-NKTL and WR-NKTL represent heterogeneous groups with variable clinical features, responses, prognosis, and treatment options.

Extranodal nasal-type natural killer (NK)/T-cell lymphoma (ENNT-NKTL) is a distinct histopathologic entity according to the WHO classification (1, 2). As the prototype of extranodal NK/T-cell lymphoma, nasal-type, nasal NK/T-cell lymphoma (N-NKTL) is a well-defined entity with distinctive morphologic, phenotype, and clinical features (3–8). Extranodal NK/T-cell lymphomas occurring outside the nasal cavity, such as Waldeyer ring, larynx, skin, soft tissue, gastrointestinal tract, and other extranasal sites, may have variable presentations depending on the major site of involvement (9–12).

The nasal cavity and Waldeyer ring are the most common sites of ENNT-NKTL, accounting for 5% to 10% of all lymphoma cases in China (4, 6, 8, 9, 11–16). Due to the close anatomic relationship between the nasal cavity and nasopharynx and the rarity of NK/T-cell lymphomas arising in Waldeyer ring or the extranasal upper aerodigestive tract, these diseases have often been reported together (10, 11, 14–22). The heterogeneous definition of ENNT-NKTL results in variable clinical features and prognosis, thereby making it difficult to distinguish between N-NKTL, NK/T-cell lymphomas of the upper aerodigestive tract, and additionally from Waldeyer ring NK/T-cell lymphoma (WR-NKTL). Previous studies have failed to define the distinct clinical characteristics and outcomes for patients with NK/T-cell lymphomas of the upper aerodigestive tract based on the site of presentation (9–12, 20). Recently, we have observed that patients with WR-NKTL presented with particular clinical features (18). However, the difference of clinical behavior between N-NKTL and WR-NKTL remains largely unknown.

In addition to pathology, primary location is important in determining clinical features and treatment options for non-Hodgkin's lymphoma (20, 23–27). The optimal therapy of extranodal NK/T-cell lymphoma, nasal-type, may vary depending on the primary site of involvement (6, 18, 20). In several previous studies, primary radiotherapy produced a significant improvement in survival, and the addition of chemotherapy to radiotherapy did not provide additional survival benefit for patients with early-stage N-NKTL (3–8,

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### Translational Relevance

Extranodal nasal-type natural killer (NK)/T-cell lymphoma (ENNT-NKTL) represents a heterogeneous group of lymphomas. NK/T-cell lymphomas occurring outside the nasal cavity, such as Waldeyer ring, skin, soft tissue, gastrointestinal tract, and other extranasal sites, have variable presentations depending on the major site of involvement. The clinical features and optimal therapy remain largely unknown. We hypothesize that identifying differences in the clinical behavior of N-NKTL and Waldeyer ring NK/T-cell lymphoma (WR-NKTL) would improve patient treatment and survival. This is first study to successfully identify N-NKTL and WR-NKTL as two distinct subgroups of ENNT-NKTL based on differences in clinical features, response to chemotherapy, prognosis, and treatment strategy. Gene profiling or proteomics analyses will allow for better understanding of biological and clinical characteristics of two subtypes of N-NKTL and WR-NKTL.

14, 15). We have also addressed whether WR-NKTL requires management different from that for N-NKTL (18). Given the lack of information regarding the unique clinical behavior and treatment of extranodal NK/T-cell lymphomas at certain extranasal sites, a specialized evaluation and treatment plan specifically for N-NKTL and WR-NKTL is needed. The goal of this study was to compare the clinical features, responses, prognosis, and treatments in a large group of patients with N-NKTL and WR-NKTL.

### Materials and Methods

Between 1987 and 2007, 240 patients with previously untreated NK/T-cell lymphomas of the nasal cavity and Waldeyer ring were reviewed. Patients were confirmed by histologic features with immunophenotype evaluation (CD3 $\epsilon$ , CD56, TIA-1, Gram-B, CD45RO, CD20/CD79 $\alpha$ , and EBV-encoded RNA *in situ* hybridization; refs. 6, 18). The diagnostic criteria and classification of extranodal NK/T-cell lymphoma, nasal-type, were based on WHO guidelines (1). Lymphoma bulk presenting in the nasal cavity with or without direct extension of adjacent structures was considered primary N-NKTL, whereas lymphoma with Waldeyer ring involvement that was clinically dominant in the nasopharynx, tonsil, base of the tongue, or oropharynx was considered primary WR-NKTL. For patients with lymphoma involving both nasal cavity and nasopharynx, primary location was based on an objective assessment of the tumor center as measured by computed tomography scan or magnetic resonance imaging (Supplementary Figure).

Clinical evaluations included documentation of patient history, physical examination, serum biochemistry, computed tomography and/or magnetic resonance imaging of the head and neck, computed tomography of the chest and abdomen/pelvis, and bone marrow aspiration and/or biopsy. The international prognostic index (IPI) was calculated according to Shipp et al. (28). The clinical features for all patients are summarized in Table 1.

**Treatment.** All patients were treated according to Ann Arbor stage (Table 1). Radiotherapy was considered the primary treatment for localized stage patients. All except 10 patients received radiotherapy alone or a combination of radiotherapy and chemotherapy [com-

bined modality therapy (CMT)]. Overall, 61 patients were treated with radiotherapy alone, 10 patients with chemotherapy alone, and 145 patients with CMT. For the latter patients, 82 received chemotherapy followed by radiotherapy and 63 received radiotherapy followed by chemotherapy. Patients with stage III and IV diseases received primary chemotherapy with or without irradiation to the primary and residual tumor.

Radiotherapy was given with a 6 MV linear accelerator. The median dose was 50 Gy at a dose per fraction of 2 Gy. The clinical target volume and radiation fields for NK/T-cell lymphomas of the nasal cavity and Waldeyer ring were described previously (6, 18). Of the 179 patients receiving chemotherapy, all except 11 patients were treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP plus bleomycin. Eight patients received cisplatin, vincristine, bleomycin, and prednisone and 3 patients received cyclophosphamide, vincristine, procarbazine, and prednisone. Patients received between 1 and 9 cycles of chemotherapy, with a median of 4 cycles. Due to poor initial response, short courses (1-4 cycles) of chemotherapy before radiotherapy were usually applied to early-stage patients.

**Statistical analysis.** Overall survival (OS) was measured from the start of initial treatment until the time of death by any cause or until the last follow-up. Progression-free survival (PFS) was measured from the start of initial treatment until the first progression or relapse or until the last follow-up or any death. OS and PFS were calculated using the Kaplan-Meier method and survival curves from different groups were compared using the log-rank test. Using  $\chi^2$  analysis, comparisons of clinical features and initial response rates were made.

### Results

**Clinical features.** One hundred forty-five patients presented at a primary site of the nasal cavity and 95 patients had a primary WR-NKTL. The locations of WR-NKTL were the nasopharynx ( $n = 53$ ), tonsil ( $n = 35$ ), oropharynx ( $n = 4$ ), and base of the tongue ( $n = 3$ ).

The clinical characteristics between the two groups were compared (Table 1). Patients with WR-NKTL were more likely to present with advanced stage, a low frequency of elevated lactate dehydrogenase (LDH), and a low-risk IPI. The majority (81%) of patients with N-NKTL presented with stage I disease, and dissemination to regional lymph nodes or distant organs was uncommon. In contrast, most patients (82%) with WR-NKTL initially presented with nodal involvement with or without distant extranodal spread. Only 17 (18%) patients had a tumor confined to the primary site without any involvement of lymph nodes or extranodal organs (Ann Arbor stage I). These patients with N-NKTL and WR-NKTL were comparable with respect to sex, age, involvement of adjacent organs, B symptoms, and performance.

We further compared the clinical characteristics between nasopharyngeal NK/T-cell lymphoma and NK/T-cell lymphoma of other Waldeyer ring sites including the tonsil, oropharynx, and base of the tongue. The major clinical features such as age, sex, nodal involvement, stage, LDH, performance, and IPI were found to be comparable between the two groups (data not shown). Patients with nasopharyngeal primary were more likely to present with involvement of adjacent organs (83% versus 31%;  $P < 0.001$ ) and B symptoms (49% versus 17%;  $P = 0.001$ ), respectively.

**Responses.** Table 2 summarizes the responses to radiotherapy and/or chemotherapy for all patients or stage I to II

**Table 1.** Clinical characteristics and treatment of patients with N-NKTL and WR-NKTL

Characteristics	All patients (n = 240), n (%)	N-NKTL (n = 145), n (%)	WR-NKTL (n = 95), n (%)	P (N-NKTL vs WR-NKTL)
Sex				
Male	163 (68)	94 (65)	69 (73)	0.205
Female	77 (32)	51 (35)	26 (27)	
Age (y)				
Median (range)	42 (7-79)	43 (11-72)	38 (7-79)	0.15
≤60	222 (93)	137 (94)	85 (89)	
>60	18 (7)	8 (6)	10 (11)	
Ann Arbor stage				
I	134 (56)	117 (81)	17 (18)	<0.001
II	82 (34)	25 (17)	57 (60)	
III	13 (5)	0 (0)	13 (14)	
IV	11 (5)	3 (2)	8 (8)	
Cervical nodal involvement				
Present	98 (41)	24 (17)	74 (78)	<0.001
Absent	142 (59)	121 (83)	21 (22)	
Nodal involvement				
Present	101 (42)	25 (17)	76 (80)	<0.001
Absent	139 (58)	120 (83)	19 (20)	
Involvement of adjacent organ				
Present	148 (62)	91 (63)	57 (60)	0.667
Absent	92 (38)	54 (37)	38 (40)	
B symptoms	83 (35)	50 (34)	33 (35)	0.968
Elevated LDH level	84 (35)	66 (46)	18 (19)	0.008
Eastern Cooperative Oncology Group score				
0	55 (23)	32 (22)	23 (24)	0.172
1	162 (68)	95 (66)	67 (71)	
2	17 (7)	12 (8)	5 (5)	
3	6 (2)	6 (4)	0 (0)	
IPI				
0	122 (50)	67 (46)	55 (58)	0.017
1	90 (37)	64 (44)	26 (27)	
2	24 (10)	14 (10)	10 (11)	
3	2 (1)	0 (0)	2 (2)	
4	2 (1)	0 (0)	2 (2)	
Treatment for stage I-II	n = 216	n = 142	n = 74	
CMT	145 (67)	89 (63)	56 (76)	
Radiotherapy	61 (28)	47 (33)	14 (19)	
Chemotherapy	10 (5)	6 (4)	4 (5)	
Treatment for stage III-IV	n = 24	n = 3	n = 21	
CMT	13 (54)	2 (67)	11 (52)	
Chemotherapy	11 (46)	1 (33)	10 (48)	

patients. There was a significant difference in overall response [complete response (CR) + partial response (PR)] rate between patients with N-NKTL and WR-NKTL (86% versus 96%;  $P = 0.016$ ).

N-NKTL and WR-NKTL were sensitive to radiotherapy with a CR rate of 85% and 76% ( $P = 0.301$ ). A much lower CR rate after chemotherapy was observed compared with those receiving radiotherapy for N-NKTL (17% versus 85%;  $P = 0.000$ ) and WR-NKTL (34% versus 76%;  $P = 0.000$ ) patients. However, patients with N-NKTL were associated with a lower overall response rate (54% versus 89%) and higher stable disease (SD) and progressive disease (PD; 46% versus 11%) after the initial chemotherapy compared with patients with WR-NKTL. Similar response rates with radiotherapy, chemotherapy, or combination were observed in 216 patients with stage I and II diseases.

No significant differences between the response rates for patients with nasopharyngeal NK/T-cell lymphoma or NK/T-cell lymphoma of other Waldeyer ring sites were observed. Overall, the CR, PR, and SD/PD rates were 81%, 13%, and 6%

for patients with nasopharyngeal NK/T-cell lymphoma and 79%, 19%, and 2% for those with NK/T-cell lymphoma of other Waldeyer ring sites, respectively ( $P = 0.570$ ). In patients with nasopharyngeal NK/T-cell lymphoma, the CR rate was 70% (14 of 20) with radiotherapy compared with 36% (12 of 33) with chemotherapy ( $P = 0.018$ ). For patients with NK/T-cell lymphoma of other Waldeyer ring sites, 85% (11 of 13) had CR following radiotherapy and 31% (9 of 29) had CR following chemotherapy ( $P = 0.001$ ). Similar overall response rate with initial chemotherapy was observed between the two groups, with 85% (28 of 33) of patients with nasopharyngeal primary versus 93% (27 of 29) of patients with NK/T-cell lymphoma of other locations ( $P = 0.305$ ).

The 5-year OS and PFS rates were 73% and 62% for patients with CR, with a median OS and PFS of 12 and 5 months for those with non-CR ( $P = 0.000$ ). Similarly, for N-NKTL patients with CR, the 5-year OS and PFS rates were 75% and 66%, with a median OS and PFS rates of 11 and 5 months for patients with non-CR ( $P = 0.000$ ). For WR-NKTL patients with CR, the 5-year OS and PFS rates were 72% and 58%, with a median

**Table 2.** Comparison of patients' initial responses

	All patients, n (%)	N-NKTL, n (%)	WR-NKTL, n (%)	P (N-NKTL vs WR-NKTL)
Stage I-IV				
Response after therapy	n = 240	n = 145	n = 95	
CR	196 (82)	120 (83)	76 (80)	0.001
PR	20 (8)	5 (3)	15 (16)	
SD	4 (2)	3 (2)	1 (1)	
PD	20 (8)	17 (12)	3 (3)	
Response after initial radiotherapy	n = 126	n = 93	n = 33	
CR	104 (83)	79 (85)	25 (76)	0.301
PR	13 (10)	7 (8)	6 (18)	
SD	2 (2)	2 (2)	0 (0)	
PD	7 (5)	5 (5)	2 (6)	
Response after initial chemotherapy	n = 114	n = 52	n = 62	
CR	30 (26)	9 (17)	21 (34)	<0.001
PR	53 (47)	19 (37)	34 (55)	
SD	15 (13)	11 (21)	4 (6)	
PD	16 (14)	13 (25)	3 (5)	
Stage I and II				
Response after therapy	n = 216	n = 142	n = 74	
CR	180 (83)	119 (84)	61 (82)	0.018
PR	13 (6)	4 (3)	9 (12)	
SD	4 (2)	3 (2)	1 (1)	
PD	19 (9)	16 (11)	3 (4)	
Response after initial radiotherapy	n = 124	n = 92	n = 32	
CR	104 (84)	79 (86)	25 (78)	0.288
PR	13 (10)	7 (8)	6 (19)	
SD	2 (2)	2 (2)	0 (0)	
PD	5 (4)	4 (4)	1 (3)	
Response after initial chemotherapy	n = 92	n = 50	n = 42	
CR	20 (22)	8 (16)	12 (29)	0.026
PR	42 (46)	19 (38)	23 (55)	
SD	15 (16)	11 (22)	4 (9)	
PD	15 (16)	12 (24)	3 (7)	

OS and PFS of 15 and 5 months for patients with non-CR ( $P = 0.000$ ).

**Survival and prognostic factors.** The 5-year OS and PFS rates for all patients were 65% and 52%, respectively. The clinical characteristics were evaluated for their prognostic significance of survivals in patients with N-NKTL and WR-NKTL (Table 3).

The 5-year OS rate for patients with N-NKTL and WR-NKTL were 67% and 65% ( $P = 0.539$ ), with the 5-year PFS rate of 56% and 47% ( $P = 0.722$ ), respectively (Fig. 1A). The subgroup analysis for these patients has also no significant differences in OS and PFS for stage I and II diseases or for stage I disease. For stage I and II patients, the 5-year OS rate was 67% for N-NKTL and 77% for WR-NKTL ( $P = 0.104$ ), and the 5-year PFS rate was 57% and 59%, respectively ( $P = 0.516$ ). The 5-year OS and PFS rates for stage I disease were 79% and 65% for N-NKTL and 88% and 66% for WR-NKTL ( $P = 0.381$  for OS and 0.417 for PFS), respectively. However, patients with stage II WR-NKTL had better outcomes compared with patients with stage II N-NKTL. The 5-year OS and PFS rates were 73% and 55% for WR-NKTL and 20% and 18% for N-NKTL, respectively ( $P = 0.000$  for OS and PFS; Fig. 1B).

The 5-year OS and PFS rates were 72% and 50% for nasopharyngeal primary and 58% and 45% for other primary locations, respectively ( $P = 0.267$  for OS and 0.587 for PFS; Fig. 2).

**Treatment outcome according to treatment modalities.** Outcomes according to the treatment were compared between the subsets of patients with N-NKTL and WR-NKTL. The addition

of chemotherapy to radiotherapy did not affect the survivals in patients with stage I and II N-NKTL. The 5-year OS and PFS rates were 71% and 62% for CMT compared with 65% and 55% for radiotherapy alone, respectively ( $P = 0.793$  for OS and 0.921 for PFS; Fig. 3A). Furthermore, the 5-year OS and PFS rates were 82% and 70% for CMT and 73% and 59% for radiotherapy in a large cohort of stage I patients ( $P = 0.752$  for OS and 0.793 for PFS).

The 5-year OS and PFS rates were 82% and 66% for CMT compared with 61% and 43% for radiotherapy in patients with stage I and II WR-NKTL, respectively ( $P = 0.133$  for OS and 0.049 for PFS; Fig. 3B). The corresponding OS and PFS rates were 78% and 65% with CMT compared with 52% and 31% with radiotherapy in a large subgroup of stage II patients ( $P = 0.097$  for OS and 0.028 for PFS).

**Patterns of failure.** A total of 75 patients developed progression or relapse. Of these, 44 (30%) were patients with N-NKTL and 31 (33%) were patients ( $P = 0.709$ ) with WR-NKTL. Ten patients with N-NKTL and 9 patients with WR-NKTL had multiple sites of failure. Distant extranodal dissemination was the primary pattern of failure for patients with N-NKTL, whereas patients with WR-NKTL showed both lymph node involvement and extranodal dissemination. Thirty-three (79%) patients with N-NKTL and 18 (60%) patients with WR-NKTL experienced disease progression or relapse at extranodal sites ( $P = 0.087$ ). However, node involvement was observed more frequently for patients with WR-NKTL than for patients with N-NKTL (57% versus 19%;  $P = 0.001$ ). Local recurrence was

observed in 10 patients with N-NKTL and 5 patients with WR-NKTL (24% versus 17%;  $P = 0.462$ ).

## Discussion

The location of a primary tumor is recognized as an important criterion for definition of the clinical features and classification of NK/T-cell lymphomas (1, 2). Extranodal NK/T-cell lymphoma, nasal-type, is a heterogeneous group of lymphomas rather than a single clinicopathologic entity. Patients with NK/T-cell lymphomas occurring in a variety of extranasal sites have variable clinical presentations (11, 12, 20). However, N-NKTL or NK/T-cell lymphomas of the upper aerodigestive tract have many definitions, which obscure the identification of the clinical characteristics or independent subtypes (11, 12, 20, 29). Identification of WR-NKTL also remains difficult due to a lack of available information in the literature (18, 20). Several studies incorporated nasopharyngeal primary into N-NKTL and did not find difference in clinical characteristics and outcomes between NK/T-cell lymphomas of the nasal cavity/nasopharynx and NK/T-cell lymphomas of the other upper aerodigestive tract (9, 20). Therefore, this study specifically addresses the clinical features, prognostic factors, initial responses, and treatment outcomes of N-NKTL and WR-NKTL as stratified by primary tumor location. The clinical characteristics identified several similarities and differences between the two groups. Patients with N-NKTL and WR-NKTL are characterized by a young male predominance, good performance, a large proportion of early-stage diseases, high

frequency of involvement of adjacent organs and B symptoms, low-risk IPI, and sensitivity to radiotherapy. However, compared with N-NKTL, WR-NKTL was associated with distinctive clinical features that included a propensity for regional nodal involvement, more advanced stage, less frequent elevations in LDH levels, intermediate chemosensitivity, and favorable prognosis. Correspondingly, N-NKTL and WR-NKTL differed substantially in their prognostic factors and treatment options.

Analysis of response in our series has revealed an inferior CR rate after chemotherapy and a superior CR rate after radiotherapy for patients with N-NKTL and WR-NKTL. Most patients with N-NKTL had persistent or refractory disease (46%) after initial chemotherapy. However, the majority of patients with WR-NKTL had a high PR rate (55%) and low SD/PD (11%) after chemotherapy, which may reflect intermediate sensitivity to conventional chemotherapy. As observed by others, patients with N-NKTL or NK/T-cell lymphomas of the extra-upper aerodigestive tract have been shown to be refractory to chemotherapy (3–11, 14–17, 30–37). Due to the disease rarity, variable definitions, and different treatments, the optimal therapy for N-NKTL, extranasal NK/T-cell lymphomas, or WR-NKTL has not been clearly defined yet (3–8, 18, 19, 34). In recognition of radiosensitivity and relative chemoresistance, the majority of our patients with localized stage disease received primary radiotherapy, and only a few patients received chemotherapy alone. As a retrospective study, it is difficult to make a definitive conclusion. However, treatment options of WR-NKTL seemed to differ from that of N-NKTL. Compared with radiotherapy alone, CMT showed a significantly superior

**Table 3.** Univariate analysis of prognostic factors for patients with N-NKTL and WR-NKTL

Factors	N-NKTL				WR-NKTL			
	5-y OS (%)	P	5-y PFS (%)	P	5-y OS (%)	P	5-y PFS (%)	P
Sex								
Male	67	0.221	56	0.319	67	0.8	45	0.483
Female	64		56		59			
Age (y)								
≤60	69	0.515	59	0.407	70	0.009	50	0.077
>60	36		25		36			
Eastern Cooperative Oncology Group score								
0	77	0.025	67	0.003	95	0.017	68	0.11
1	67		59		56			
2-3	44		23		NA*			
B symptoms								
No	66	0.573	58	0.448	75	0.001	58	<0.001
Yes	67		54		40			
LDH								
Normal	58	0.863	54	0.361	70	0.03	55	0.109
Elevated	67		53		45			
Involvement of adjacent organs								
Present	58	0.013	48	0.001	63	0.869	44	0.508
Absent	78		73		67			
Stage								
I	79	<0.001	65	<0.001	88	0.003	66	0.003
II	20		18		73			
III/IV	NA*		NA*		33			
IPI								
0	72	0.431	72	0.092	81	0.001	61	0.003
1	67		52		55			
>1	54		43		25			

\*Not available for analysis due to small number of patients.

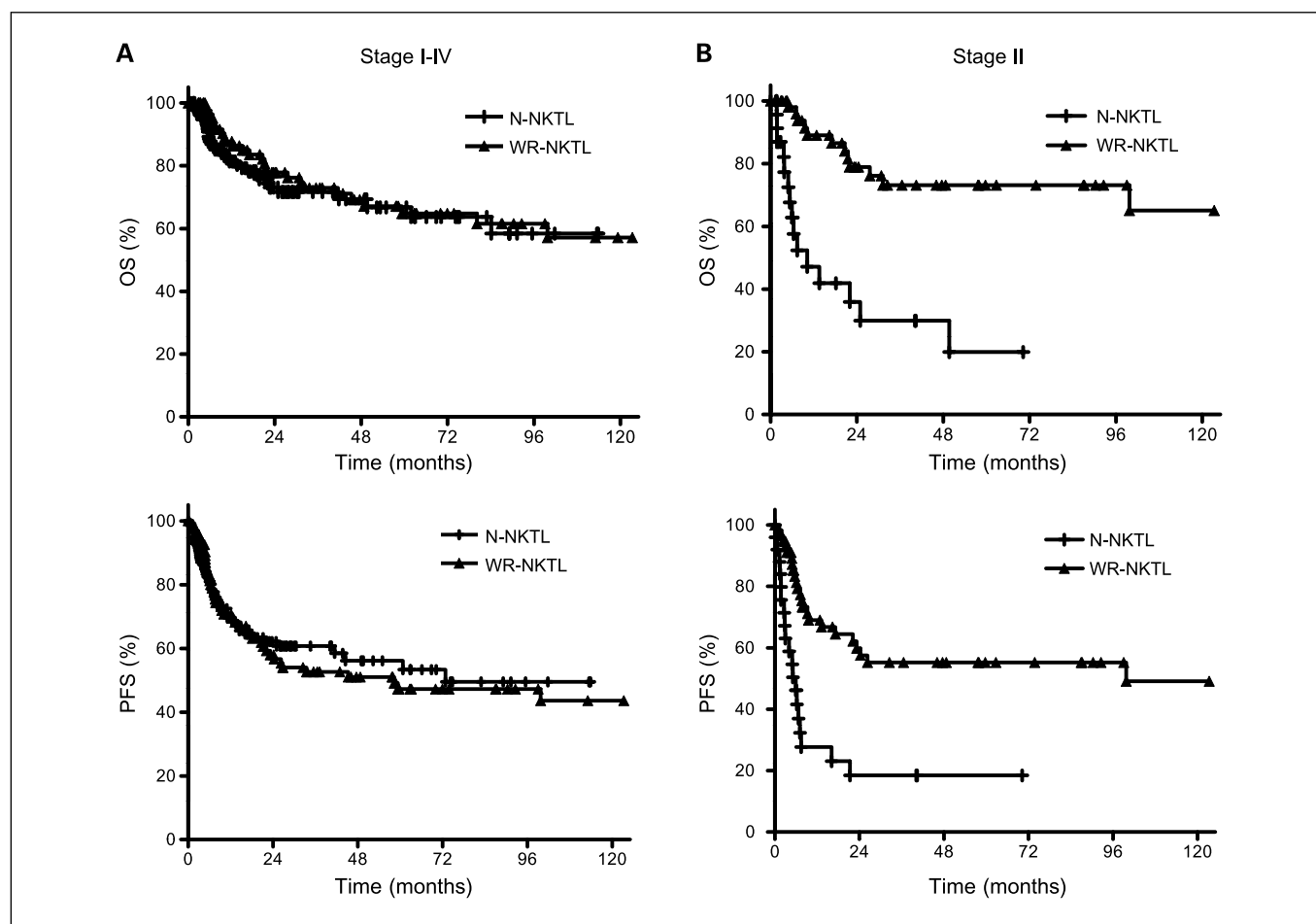


Fig. 1. OS and PFS curves for N-NKTL and WR-NKTL cases cumulatively (stage I-IV; A) and specifically for patients with stage II disease (B).

PFS and tended to improve OS for patients with early-stage WR-NKTL. In contrast, the addition of chemotherapy to radiotherapy did not provide further survival benefit in patients with early-stage N-NKTL, which was consistent with other large studies (3, 6, 15, 33, 34). Radiotherapy appears to be the most effective treatment option for N-NKTL, whereas patients with

WR-NKTL may derive benefit from a combination of chemotherapy and radiotherapy.

Our study shows that independent factors associated with OS and PFS were substantially diverse between patients with N-NKTL and WR-NKTL. In patients with N-NKTL, performance, involvement of adjacent organs, and stage were prognostic

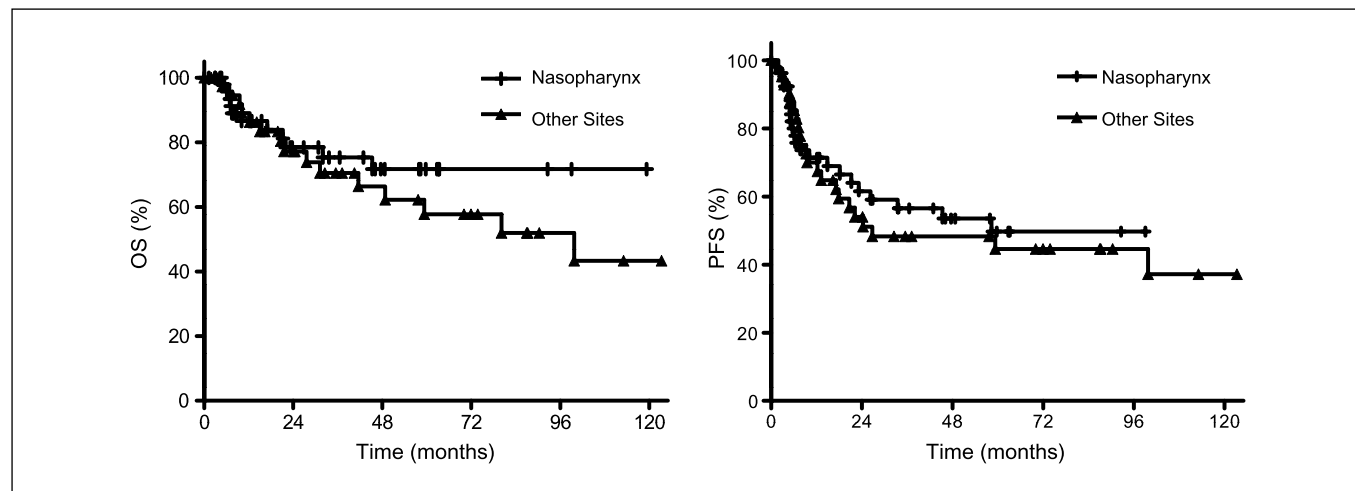


Fig. 2. OS and PFS curves for nasopharyngeal NK/T-cell lymphoma and NK/T-cell lymphoma of other Waldeyer ring sites.

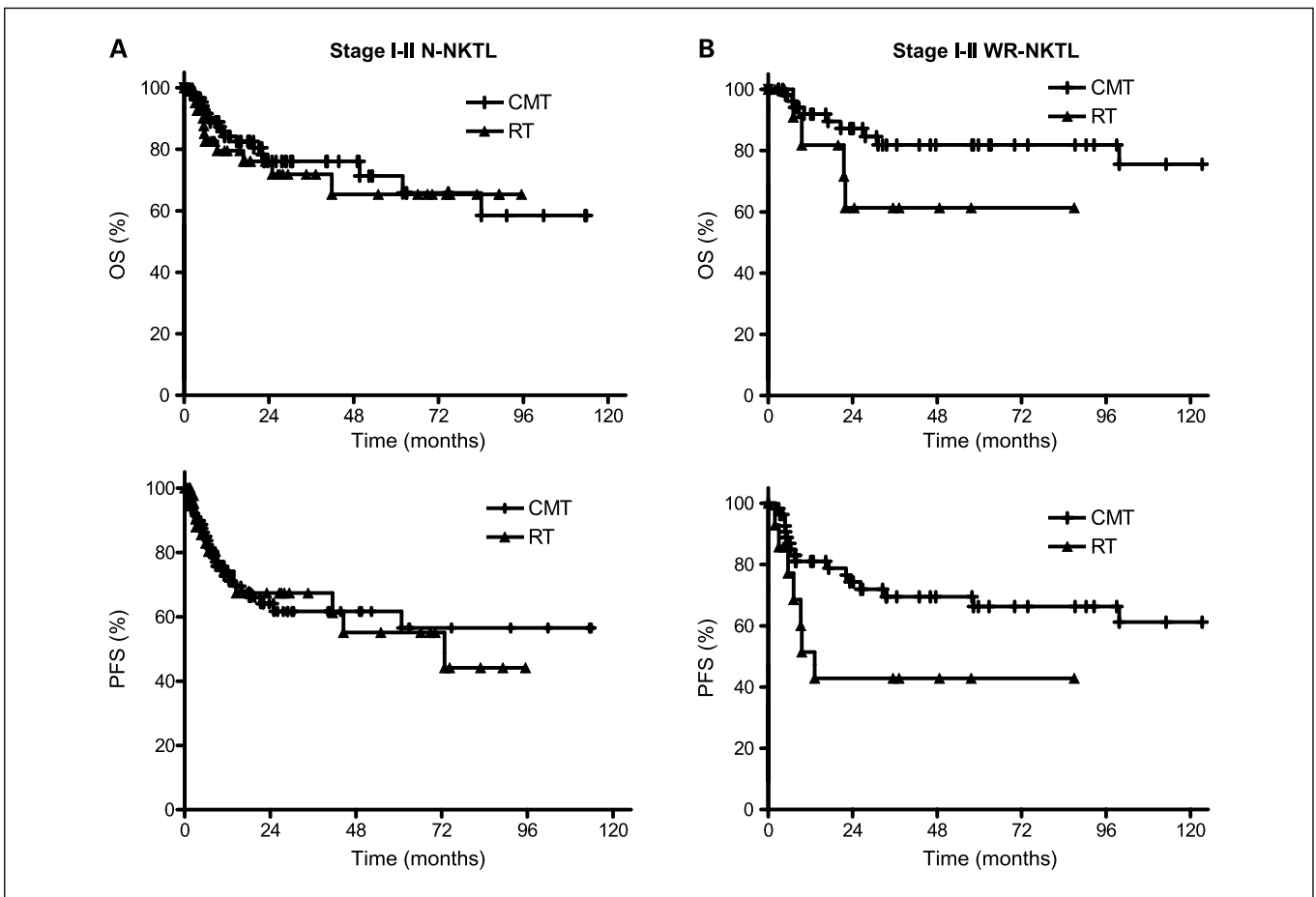


Fig. 3. OS and PFS curves associated with CMT or radiotherapy alone (RT) for patients with stage I to II N-NKTL (A) and stage I to II WR-NKTL (B).

predictors of disease. For patients with WR-NKTL, age, performance, B symptoms, elevated LDH, stage, and IPI were predictors of OS. Patients with stage I N-NKTL or stage I to II WR-NKTL had superior OS and PFS, whereas patients with stage II N-NKTL or stage III/IV WR-NKTL carried a worse prognosis. Although patients with WR-NKTL were more likely to present with advanced stages, survival of these patients was similar to or better compared than those with N-NKTL. The 5-year OS and PFS rates were comparable between two group patients with stage I to IV, for both stage I and II, and for stage I disease. However, patients with stage II WR-NKTL had better survivals than those with stage II N-NKTL. Coincidentally, previous studies also showed an equivalent or superior outcome in patients with NK/T-cell lymphomas of the upper aerodigestive tract outside the nasal cavity and nasopharynx versus patients with NK/T-cell lymphomas of the nasal cavity and nasopharynx, where most of the former patients were WR-NKTL (14, 19, 34). Another important finding from this series was that patients with N-NKTL and WR-NKTL showed a plateau in their survival curves after treatment. Conversely, survival of patients with NK/T-cell lymphomas of the extra-upper aerodigestive tract continued to decline (11). Compared with NK/T-cell lymphomas of the upper aerodigestive tract, NK/T-cell lymphomas of the extra-upper aerodigestive tract was associated with a highly aggressive clinical behavior, with a median survival time of

3.5 to 19 months (9–11, 17–19, 29, 34). Furthermore, this poor outcome was also validated by other studies in patients with cutaneous presentation (31, 32, 35).

The most common site of treatment failure was both nodal and extranodal dissemination for WR-NKTL, whereas it was distant extranodal dissemination only for N-NKTL. The propensity for regional nodal involvement at presentation and primary patterns of failure in lymph nodes after treatment of WR-NKTL may reflect the primary draining of Waldeyer ring as lymphoid tissues. Moreover, extranodal dissemination for WR-NKTL and N-NKTL is also an identical characteristic of extranodal N-NKTL (9–11, 31, 32).

Our study is the first to successfully identify N-NKTL and WR-NKTL as two subgroups of extranodal NK/T-cell lymphomas, nasal-type. In recent Korea studies, patients with extranodal NK/T-cell lymphoma, nasal-type, were divided into two different groups according to presentation in the upper aerodigestive tracts versus in the extra-upper aerodigestive tract (9, 10, 17, 20). Differing prognosis and treatment outcomes were observed for each group. However, no significant difference was found in clinical features and survivals between NK/T-cell lymphomas of the nasal cavity/nasopharynx and NK/T-cell lymphomas primarily involving the upper aerodigestive tract outside the nasal cavity and nasopharynx (9, 20). Our data clearly show that patients with N-NKTL were different from those with WR-NKTL by their clinical characteristics, response

to chemotherapy, prognosis, pattern of failure, and treatment. Furthermore, the major clinical features of patients with nasopharyngeal primary were similar to those with NK/T-cell lymphoma of other Waldeyer ring sites. There was no significant difference in the initial response or treatment outcome between the two groups. Therefore, it should be pointed out that nasopharyngeal NK/T-cell lymphoma needs to be separated differently from the prototype of N-NKTL and to be considered as WR-NKTL.

In conclusion, the data from our study emphasize the clinical heterogeneity of ENNT-NKTL and the need to consider WR-NKTL and N-NKTL as two different groups when evaluating clinical features, new prognostic factors, response to chemotherapy, and treatment strategies.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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