Prognostic Factors and Treatment Outcome in Non-Hodgkin's Lymphoma of Waldeyer's Ring

Yasuaki Harabuchi, Hiroshi Tsubota, Shinji Ohguro, Tetsuo Himi, Kohji Asakura, Akikatsu Kataura, Atsushi Ohuchi and Masato Hareyama

From the Departments of Otolaryngology, (Y. Harabuchi, H. Tsubota, S. Ohguro, T. Himi, K. Asakura, A. Kataura), and Radiology (A. Ohuchi, M. Hareyama), Sapporo Medical University School of Medicine, Sapporo, Japan

Correspondence to: Dr Yasuaki Harabuchi, Department of Otolaryngology, Sapporo Medical University School of Medicine, S1W16, Chuo-Ku, Sapporo 060, Japan

Acta Oncologica Vol 36, No. 4, pp. 413–420, 1997

Prognostic factors and treatment outcome of 71 patients with non-Hodgkin's lymphoma of Waldeyer's ring were analyzed retrospectively. In univariate analyses, unfavorable prognosis was associated with primary disease in the base of the tongue, stage III–IV diseases, B-symptoms, high-grade histology, T-cell phenotype, elevated serum LDH levels, decreased peripheral blood lymphocyte counts, and negative response on delayed type hypersensitivity skin reactions. Multivariate analysis showed that stage III–IV and T-cell phenotype were significant independent risk factors for death. In stage I–II lymphomas, patients with unilateral large or bilateral cervical lymph node involvement had a poorer prognosis. In stage I–II lymphomas with intermediate or high-grade histology, patients who had received radiotherapy with MTCOP-P chemotherapy (pirarubicin, cyclophosphamide, vincristine, methotrexate with leucovorin rescue, peplomycin, and predonisolone) showed significantly better 5-year disease-free survival rate compared with patients treated with radiotherapy alone.

Received 24 June 1996
Accepted 20 February 1997

Waldeyer's ring (WR) is known to be commonly involved with extranodal non-Hodgkin's lymphoma (NHL). In general, WR lymphomas are localized but gastrointestinal involvement is occasionally found (1–4). Histologically, diffuse large lymphomas (1–5) with B-cell phenotype (4, 6) are common. Several investigators have reported that the prognosis of WR lymphomas is associated with Ann Arbor stage (1–3, 5, 7), tumor bulk (3), presence or absence of systemic symptoms (3), status of cervical lymph node involvement (5, 7, 8), or histology (2, 3, 8). However, the prognostic value of some factors is a matter of controversy and multivariate analysis was not available in those reports.

In the past, WR lymphomas have been treated with radiotherapy alone. Most lymphomas with low-grade histology have been cured by radiotherapy alone; however, relapse occurred frequently in lymphomas with intermediate or high-grade histology (1, 8–10). Radiotherapy with systemic chemotherapy in the treatment of localized WR lymphomas with intermediate- or high-grade histology has become common (5, 9, 11), but there is still some disagreement about the treatment modality.

In this report, 71 patients with NHL arising from WR were presented, all of whom were treated during the past 18 years in our department. Univariate and multivariate analyses were performed in order to determine the prognostic value of various factors. Furthermore, the results of different types of treatment for early stage diseases, reflecting the gradual change during the period, were compared in order to design an effective treatment plan.

MATERIAL AND METHODS

Patients

Seventy-one Japanese patients, who were newly diagnosed non-Hodgkin's lymphoma primary involving Waldeyer's ring and treated at the Department of Otolaryngology, Sapporo Medical University, were available for this study. Follow-up period of living patients was from 13 to 181 months and the median value was 83 months. Clinical and histopathologic data of 25 patients (including 3 patients with adult T-cell lymphoma) have been partly reported elsewhere (4, 12).

 ISSN 0284-186X

Clinical and histologic evaluation

Pertinent clinical information and follow-up data were obtained from hospital charts for all cases. The clinical stage according to the Ann Arbor system was assessed by physical examination, gallium 67 scintiscan, computerized tomography scan, echogram, roentgenographic and fiberscopic examination of the gastrointestinal tracts, and bone marrow aspiration. The histologic type was classified according to the Working Formulation System. Phenotypic study was performed on formalin-fixed paraffin-embedded sections using the avidin-biotin immunoperoxidase method (13). Monoclonal antibodies UCHL1/CD45RO (Dakopatts, Copenhagen, Denmark) and/or MT1 (Bio-Science, Emmenbrucke, Switzerland) were used for T-cell phenotype, and L26 (Dakopatts) was employed for B-cell phenotype. Phenotype was defined by over 70% positive staining lymphoma cells counted in the area involving atypical mononuclear cells. Cell-mediated immune function was assessed by delayed type hypersensitivity skin reactions against purified protein derivative (PPD) of *Mycobacterium tuberculosis*, extracts of *Candida albicans*, and/or to phytohemagglutinin (PHA). Positive response was defined by ≥ 5 mm of erythema in the PPD or Candida test and by ≥ 15 mm of that in the PHA test after 48 h of each injection. If the responses were heterogeneous among antigens, the corresponding result between the two skin tests was scored.

Treatment schedule

Patients with stage I–II lymphomas were treated with cobalt 60 irradiation alone or radiotherapy with chemotherapy. The dose of radiotherapy was 40–45 Gy using a lateral opposing field covering Waldeyer's ring. The field was extended to cover the cervical region for patients with cervical lymph node involvement. Chemotherapy regimens used were partially modified from the original regimens. Before 1981, the VEMP regimen (14) (vincristine 0.02 mg/kg intravenously (i.v.) once weekly, cyclophosphamide 1 mg/kg orally every day, 6-mercaptopurine 1 mg/kg orally every day, and predonisolone 0.8 mg/kg orally every day) was employed for 4 or 5 weeks after radiotherapy. Between 1981 and 1987, the VEPA (15) (vincristine 1 mg/m^2 i.v., cyclophosphamide 350 mg/m^2 i.v. each once weekly, doxorubicin 40 mg/m^2 i.v. once every two weeks, and predonisolone 40 mg/m^2 orally for the first three days of each week) or two cycles of the COP regimen (16) (vincristine 1 mg/m^2 i.v., cyclophosphamide 450 mg/m^2 i.v., and predonisolone 40 mg/m^2 orally for 5 consecutive days at 14-day intervals) was administered for 4 weeks before radiotherapy. After 1987, the MTCOP-P regimen modified from the original MACOP-B regimen (17), in which pirarubicin (THP-Adriamycin) and peplomycin were used instead of doxorubicin and bleomycin respectively (pirarubicin 50 mg/m^2 i.v. on days 1 and 15, cyclophosphamide 350 mg/m^2 i.v. on days 1 and 15, vincristine 1.2 mg/m^2 i.v. on days 8 and 22, methotrexate 400 mg/m^2 i.v. with leucovorin rescue on day 8, peplomycin 10 mg/m^2 persistent-subcutaneously on day 22, and predonisolone 40 mg/m^2 orally for the first three days of each week), was administered at two and one cycles before and after radiotherapy respectively. Patients with stage III–IV lymphomas were treated repeatedly with combined chemotherapy regimens, VEMP (before 1981), VEPA (between 1981 and 1987), MTCOP-P or MEPP (18) (mitoxantrone, etoposide, cisplatin, and predonisolone)(after 1987); but those patients older than 70 years and those with multiple medical illness were placed on the COP regimen (between 1981 and 1987) or the VEPA regimen (after 1987). Additional radiotherapy was administered for those patients with bulky tumor region. Salvage therapy for patients who were resistant to initial treatment or experienced relapse after complete remission was performed by a variety of chemotherapy or by radiotherapy if the relapse was localized.

Statistics

Tumor response was assessed by standard criteria. The Kaplan-Meier product-limit method was used to generate disease-free survival (DFS) and overall survival (OS) curves. The DFS time was measured from the date of first complete remission (CR) to the date of first relapse or to the date of last follow-up. The DFS time was set at zero for patients who had not experienced CR. The OS time was measured from the date of diagnosis to the date of death or that of last follow-up visit. The generalized Wilcoxon test was used to compare survival curves. The chi-square test or Fisher's exact test was used to compare CR and relapse rates. Multivariate regression analysis using Cox's proportional hazards model was performed to determine independent prognostic factors.

RESULTS

Patient characteristics

The patients ranged in age from 13 to 82 years and the median age was 45 years. The patient populations comprised 39 males and 32 females. The possible primary sites were palatine tonsil in 56 (79%) patients, nasopharynx in 9 (13%), and base of tongue in 6 (8%). There were 11 (15%) patients with stage I, 42 (60%) with stage II, 7 (10%) with stage III, and 11 (15%) with stage IV disease. Fourteen (20%) patients had B symptoms such as fever, weight loss, and/or night sweating. Decreased number ($<1\,500$/mm^3) of peripheral blood lymphocytes (PBL) was found in 20 (31%) patients. Serum lactate dehydrogenase (LDH) levels were elevated (<400 IU/m) in 17 (27%) of 64 patients examined. Serum albumin levels were decreased (≤ 3.4 g/d) in 12 of 63 patients examined. Of 23 patients in whom

Table 1

Treatment outcome of Waldeyer's ring non-Hodgkin's lymphoma according to patient characteristics

Characteristics	Overall cases (n = 72)				Stage I–II diseases (n = 53)			
	No. of cases	CR No. (%)	5-year DFS (%)	5-year OS (%)	No. of cases	CR No. (%)	5-year DFS (%)	5-year OS (%)
Sex								
Female	32	25 (75)	49	62	27	23 (49)	59	70
Male	39	29 (74)	45	44	26	24 (51)	63	63
Age (years)								
< 65	47	36 (77)	52	56	36	33 (92)	68	71
≥ 65	24	18 (75)	36	45	17	14 (82)	45	58
Primary sites								
Tonsil	56	44 (78)	53	56	41	38 (93)	69	72
Nasopharynx	9	8 (89)	30	53	8	7 (88)	33	60
Base of tongue	5	2 (33)*	17*	17*	4	2 (50)	25**	25**
Clinical stage								
I–II	53	47 (89)	61	66				
III–IV	18	7 (39)§	6§	11§				
Symptoms								
A	57	48 (84)	53	60	47	43 (91)	65	71
B	14	6 (43)**	19§	18§	6	4 (67)	33**	25**
Histologic grades								
Low/Intermediate	62	52 (84)	50	56	50¶	46 (92)	62	69
High	9	2 (22)†	22**	22†	3	1 (33)*	33*	33*
Phenotype								
B-cell	63	53 (84)	53	59	50	46 (92)	65	71
T-cell	8	1 (13)§	0§	0§	3	1 (33)*	0**	0†
LDH levels (IU/ml)								
< 400	47	41 (87)	52	60	38	36 (95)	62	70
≥ 400	17	7 (41)†	19**	19†	10	6 (60)*	32	32*
PBL counts (/mm^3)								
> 1 500	45	38 (84)	51	58	35	33 (94)	63	69
≤ 1 500	20	11 (55)*	30*	35*	14	10 (71)*	43*	50*
DTH skin reactions								
Positive	13	11 (85)	61	77	10	10 (100)	79	89
Negative	10	6 (60)	20*	20**	6	5 (83)	33*	33**

CR: complete remission, DFS: disease-free survival, OS: overall survival, LDH: lactate dehydrogenase, PBL: peripheral blood lymphocytes. DTH: delayed-type hypersensitivity. The DFS and OS rates were measured using the Kaplan-Meier product-limit method and compared using the generalized Wilcoxon test. The data of LDH levels, PBL counts, and DTH skin reactions were not available in 7, 8, 6, and 48 cases, respectively. ¶All 50 cases were classified as intermediate grade histology. * $p < 0.05$; ** $p < 0.01$; † $p < 0.001$; § $p < 0.0001$.

delayed-type hypersensitivity skin reactions were tested, 10 (43%) patients showed a negative response (Table 1).

Histologic and phenotypic features of WR lymphomas are summarized in Table 2. Fifty-nine (84%) patients were classified as intermediate-grade histology according to the Working Formulation System. High-grade histology was found in 9 (13%) cases and low-grade histology occurred in only 3 (4%). In phenotypic studies, 63 (89%) tumors were classified as B-cell lymphomas and the remaining 8 (11%) as T-cell lymphomas including 4 adult T-cell lymphomas, 3 other types of peripheral T-cell lymphomas, and one thymic lymphoma.

Prognosis according to variables in overall cases

Of 71 patients, 54 (76%) had complete remission (CR) and 19 (35%) of these showed a relapse after CR. The disease-free survival (DFS) rates at 1, 3, and 5 years, were 63%, 50%, and 47%, respectively. The overall survival (OS) rates at 1, 3, and 5 years were 76%, 60%, and 52%, respectively. The CR rate, 5-year DFS, and OS rates according to patient characteristics are listed in Table 1. Age, sex, and serum albumin levels did not significantly affect the clinical outcome. The CR rate, 5-year DFS, and OS rates of the primary disease in the base of the tongue were significantly lower than those of primary disease in the tonsil (33% vs.

78%, 17% vs. 53%, 17% vs. 56%, respectively; $p < 0.05$ each). Advanced stage (III–IV) disease showed significantly poorer prognosis than early stage (I–II) disease. Of 18 patients with stage III–IV lymphomas, only 7 (39%) had CR, 5 (71%) experienced relapse after CR, and 16 (89%) died of disease; whereas 47 (89%) patients with stage I–II disease had CR ($p < 0.0001$) and only 14 (30%) of them experienced relapse ($p = 0.083$). Both DFS and OS rates at 5 years in stage III–IV disease were significantly lower than those in stage I–II disease (6% vs. 61%, 11% vs. 66%, respectively; $p < 0.0001$ each). The CR rate, 5-year DFS and OS rates of patients with B-symptoms were significantly lower than those of patients without systemic symptoms (43% vs. 84%, $p < 0.01$; 19% vs. 53%, $p < 0.0001$; 18% vs. 60%, $p < 0.0001$; respectively). Patients with high-grade histology showed a significantly lower CR rate, 5-year DFS, and OS rates than patients with low or intermediate histology (22% vs. 52%, $p < 0.001$; 22% vs. 50%, $p < 0.01$; 22% vs. 56%, $p < 0.001$; respectively). Clinical course of T-cell lymphomas was aggressive. Of 8 T-cell lymphomas, only one (13%) experienced CR and no survivor was found at 5 years from diagnosis; whereas 53 (84%) B-cell lymphomas had a CR ($p < 0.0001$). Both DFS and OS of T-cell lymphomas were significantly shorter than those of B-cell lymphomas ($p < 0.0001$, each; Fig. 1). The CR rate, 5-year DFS and OS rates of patients with increased LDH level were significantly lower compared with those of patients with normal LDH levels (41% vs. 87%, $p < 0.001$; 19% vs. 52%, $p < 0.01$; 19% vs. 60%, $p < 0.001$; respectively). Patients with a decreased PBL count showed significantly lower rates of CR, 5-year DFS, and OS than patients with a normal PBL count (55% vs. 84%, 30% vs. 51%, 35% vs. 58%, respectively; $p < 0.05$ each). The negative responders on delayed type hypersensitivity skin reactions showed significantly lower DFS and OS rates at 5 years than the positive responders (20% vs. 61%, $p < 0.05$; 20% vs. 77%, $p < 0.01$; respectively). No significant difference in relapse rate after CR was observed in any comparison between variables. Multivariate analysis of prognostic factors excluding delayed-type hypersensitivity skin reactions showed that stage III–IV and T-cell

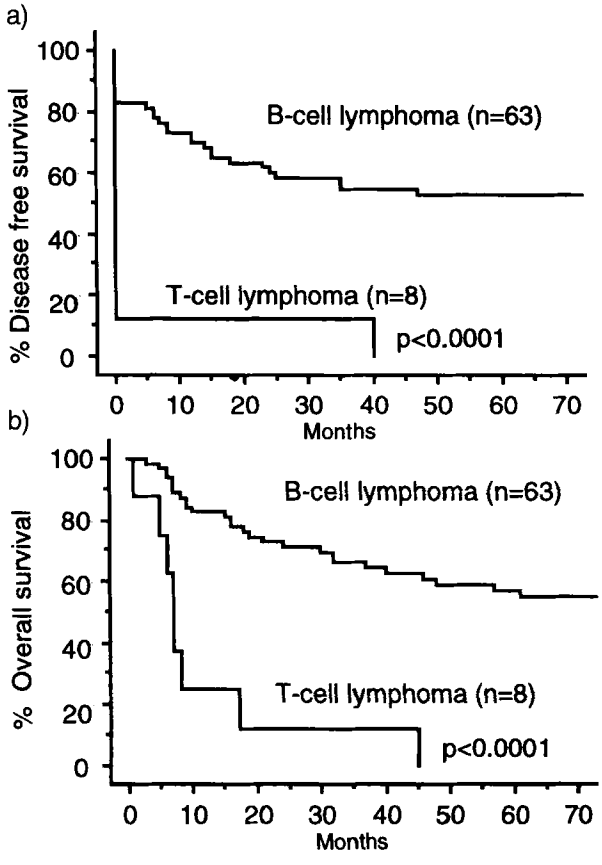

Fig. 1. Disease-free survival (a) and overall survival (b) of B- and T-cell lymphomas of Waldeyer's ring. The Kaplan-Meier product-limit method and the generalized Wilcoxon test were used to generate and compare survival curves.

Table 2

Histologic and phenotypic features of Waldeyer's ring non-Hodgkin's lymphoma according to clinical stage

Characteristics	Clinical stage		Total
	I–II (n = 53)	III–IV (n = 18)	(n = 71)
Histologic type			
Low-grade malignancy			
F. small cleaved cell	0	1	1 (1%)
Small lymphocytic	0	2	2 (3%)
Intermediate-grade malignancy			
F. large cell	1	0	1 (1%)
D. small cleaved cell	8	2	10 (14%)
D. mixed small and large cell	3	2	5 (7%)
D. large cell	38	5	43 (61%)
High-grade malignancy			
LCI plasmacytoid	1	0	1 (1%)
LCI polymorphous	2	4	6 (8%)
Lymphoblastic	0	2	2 (3%)
Phenotype			
B-cell	50	13	63 (89%)
T-cell	3	5	8 (11%)

Data are expressed as number of cases. Histologic type was determined by the Working Formulation System. F.: follicular D.: diffuse, LCI: large cell immunoblastoic.

Table 3

*Results of multivariate analysis for survival in Waldeyer's ring non-Hodgkin's lymphoma**

Characteristics	Relative risk	95% CI	p-value
Stage III–IV	5.17	1.86–14.37	0.0016
T-cell phenotype	4.64	1.34–16.11	0.0156

* Proportional hazard model of Cox was used for analysis.
CI: confidence interval.

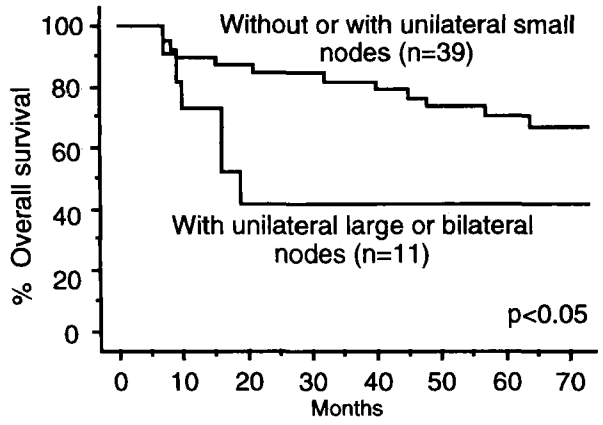

Fig. 2. Overall survival of stage I–II lymphomas according to status of cervical lymph node involvement. Lymph node size was defined as small and large as a maximum diameter <4 cm and ≥4 cm, respectively. The Kaplan-Meier product-limit method and the generalized Wilcoxon test were used to generate and compare survival curves.

phenotype were significant independent risk factors for death (Table 3).

Prognosis of stage I-II disease according to variables

All stage I–II lymphomas were classified histologically as intermediate or high-grade malignancies (Table 2). Unfavorable prognostic factors of stage I–II diseases were similar to those of overall cases. Short 5-year DFS and OS rates were associated with initial involvement of base of tongue, B-symptoms, high grade histology, T-cell phenotype, elevated LDH level, decreased peripheral blood lymphocyte counts, and negative response on delayed-type hypersensitivity skin reactions (Table 1). There was no significant difference on 5-year DFS and OS rates between stages I and II disease (55% vs. 62%, $p = 0.77$; 72% vs. 65%, $p = 0.53$; respectively).

The stage I–II patients were categorized in two groups by cervical lymph node status: no lymph node involvement, unilateral small (<4 cm in diameter) nodes, or single small node in bilateral sides (n = 39) and unilateral large (≥4 cm in diameter) or bilateral multiple (≥3) nodes (n = 11). The data of lymph node size and number were not available in the remaining 3 patients with stage II disease. Patients with large nodes or bilateral nodes showed significantly lower values in both 5-year DFS and OS rates than patients without or with unilateral small nodes (44% vs. 63%, 42% vs. 70%, respectively; $p < 0.05$ each; Fig. 2).

Treatment outcome according to initial therapy

Initial treatments given are listed in Table 4. Of 53 patients with stage I–II lymphomas, 26 (49%) were treated with radiotherapy alone and 27 (51%) received radiotherapy with a variety of combined chemotherapy regimens. Of 18 patients with stage III–IV disease, 10 (56%) were treated with combined chemotherapy alone and 6 (33%) received chemotherapy with additional radiotherapy to bulky tumor region. The remaining 2 patients with stage III–IV lymphomas were treated with radiotherapy alone because of advanced age with multiple medical illness. All patients who experienced CR had received a full dose of irradiation and/or of chemotherapy reagents on any schedule. Any patients, who was resistant to initial treatment schedule, failed to achieve CR by salvage therapies. Salvage therapies were successful in only 2 patients who had experienced relapse in localized lymph nodes. Nobody died of treatment toxicity. No significant difference was found in clinical outcome of patients with stage III–IV disease according to treatment protocol.

Stage I–II diseases were divided into 3 groups according to treatment modalities: radiotherapy alone (n = 26), radiotherapy with MTCOP-P chemotherapy (n = 8), and radiotherapy with combined chemotherapy other than MTCOP-P (n = 19). There was no significant difference on distribution of prognostic factors such as primary sites, B-symptoms, histologic grades, phenotype, LDH levels, and PBL counts, among the three groups. Of 26 patients who were treated with radiotherapy alone, 4 (16%) failed to achieve CR and 9 (41%) experienced relapse after CR. Relapse occurred outside the radiation field: mediastnum, axilla, and/or inguinal lymph nodes (4 patients), gastrointestinal tracts including paraortic lymph nodes (4 patients), and bone marrow and spleen (1 patient). Relapse never occurred inside the radiation field. On the other hand, of 8 patients who received radiotherapy with MTCOP-P chemotherapy, all had CR and none experienced relapse or died of disease. Most frequent toxicity of MT-

Table 4

Initial treatment of Waldeyer's ring lymphoma

	Stage I (n = 11)	Stage II (n = 42)	Stage III–IV (n = 18)
Radiotherapy alone	9	17	2
Radiotherapy with chemotherapy	2	25	6
VEMP		7	1
COP	1	1	
VEPA		10	4
MTCOP-P	1	7	1
Chemotherapy alone			10
COP			4
VEPA			3
MTCOP-P			1
MEPP			2

Data are expressed as number of cases. VEMP: vincristine, cyclophosphamide, 6-mercaptopurine, and predonisolone. COP: vincristine, cyclophosphamide, and predonisolone. VEPA: vincristine, cyclophosphamide, doxorubicin, and predonisolone. MTCOP-P: pirarubicin, cyclophosphamide, vincristine, methotrexate with leucovorin rescue, peplomycin, and predonisolone. MEPP: mitoxantrone, etoposide, cisplatin, and predonisolone.

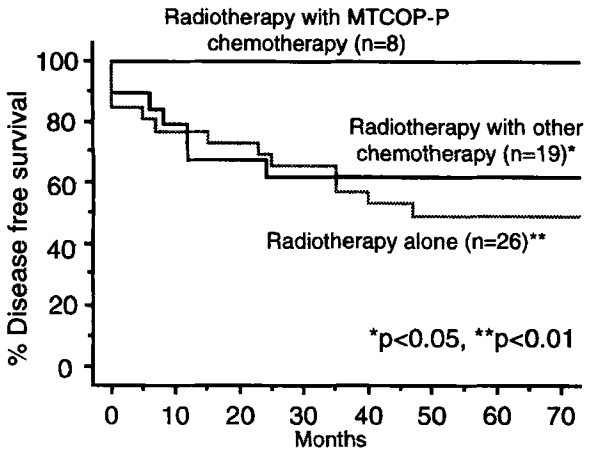

Fig. 3. Disease-free survival of stage I–II lymphomas according to treatment manner. The Kaplan-Meier product-limit method and the generalized Wilcoxon test were used to generate and compare survival curves. MTCOP-P: pirarubicin, cyclophosphamide, vincristine, methotrexate with leucovorin rescue, peplomycin, and predonisolone.

COP-P chemotherapy was leukocytopenia as found in 6 (75%) cases, but all those recovered within about 1–2 weeks by prolonging the schedule interval and/or by administering human granulocyte-stimulating factor. Mild oral mucositis was also found in all patients, but it was alleviated by local treatment. The 5-year OS rate of the MTCOP-P group (100%) was not statistically significant compared with that of the radiotherapy alone group (60%) and of the group with radiotherapy plus other chemotherapy (62%) because of a limited number of cases. However, the 5-year DFS rate of radiotherapy of the MTCOP-P group (100%) was significantly better than that of the radiotherapy alone group (49%, $p < 0.01$) and of the radiotherapy plus other chemotherapy group (62%, $p < 0.05$; Fig. 3).

DISCUSSION

In this study, the prognostic factors of non-Hodgkin's lymphoma (NHL) of Waldeyer's ring (WR) were examined retrospectively. Although our treatment has not been uniform over the years, the management protocol did not differ substantially from the standard treatment of NHL.

In our series, follicular lymphomas comprised only 2% of all cases. This feature was in agreement with previous reports from Japan (6, 7). It is generally accepted that the frequency of follicular lymphomas in Asia appears to be relatively low compared with that in western countries. The histologic grade is reported to be one of the most useful prognostic factors for WR lymphomas (2, 3, 8). Although our multivariate analysis failed to demonstrate histologic grade as an independent prognostic factor because of a limited number of cases with low-grade histology, univariate analysis showed that high-grade histology was associated with unfavorable outcome.

Recently, a number of phenotypic studies showed poor prognosis of T-cell lymphoma. With regard to NHL in head and neck lesions, we and other investigators showed poorer prognosis of nasal T-cell lymphoma (4, 6, 19). In this study T-cell lymphomas arising from WR have been shown to have an aggressive clinical course compared with B-cell lymphomas. Furthermore, our multivariate analysis showed that expression of T-cell phenotype is one of the significant independent risk factors for death. The International Lymphoma Study Group (20) has suggested that peripheral T-cell lymphomas show a more aggressive course compared with B-cell lymphomas of similar histologic grade. We propose that phenotypic studies should become part of the grading process at the time of WR lymphoma diagnosis.

The Ann Arbor staging classification has been popular and beneficial for predicting prognosis of WR lymphomas (1–3, 7). Indeed, we found significant differences in prognosis between stages I–II and III–IV diseases by multivariate analysis as well as univariate analysis. However, we failed to find any difference in prognosis between stages I and II diseases. When our stage I–II patients were further classified according to status of cervical lymph node involvement, patients with unilateral large nodes or bilateral nodes showed significantly poorer prognosis than patients with unilateral small nodes or without any nodes. Similar significance has also been reported (5, 7, 8). The number, locations, and sizes of the cervical nodes are regarded as good criteria for establishing the degree of malignancy as well as the treatment policy of these tumors.

Increased serum LDH levels, decreased serum albumin levels, decreased peripheral blood lymphocyte (PBL) counts, or impaired cell-mediated immunity have all been reported to be associated with poor prognosis of NHL (21). However, this is still uncertain in WR lymphomas. Although serum albumin levels did not affect outcome in our series, elevated serum LDH levels and decreased PBL counts were correlated with poor prognosis. A negative delayed-type hypersensitivity skin response, which reflects impaired cell-mediated immune function, was associated also with unfavorable prognosis.

Among primary sites, base of tongue lymphomas showed a significantly poorer outcome than tonsil lymphomas. We cannot explain the reason for this prognostic significance because of a limited number of cases. This is possibly due to much inclusion of patients of high age or elevated LDH in base of tongue lymphomas; every 4 (67%) of 9 patients showed high age or elevated LDH. There was no significant difference for sex, clinical stage, histologic grade, phenotype, and B-symptoms between these two sites. On the other hand, Jacobs et al. (22) and Liang et al. (23) stated poorer prognosis of primary disease in the nasopharynx.

In the past, radiotherapy alone has been the mainstay of treatment for stage I–II WR lymphomas, but results were dependent on histologic grades. The 5-year DFS and OS of lymphomas with low-grade histology have been re-

ported to be over 85% each; but those of lymphomas with intermediate- or high-grade histology were around 40% and 50%, respectively (1, 8–10). In our series, the 5 year DFS and OS of stage I–II diseases treated with radiotherapy alone, all of which had an intermediate- or high-grade histology, were 49% and 60%, respectively. Most relapse occurred outside the radiation fields, such as in systemic lymph nodes and in the gastrointestinal tracts, similar to other reports (1, 8, 9). Recently, radiotherapy with systemic chemotherapy in the treatment of localized WR lymphomas with aggressive histologic types has become common (5, 9, 11). In our series, radiotherapy with mild chemotherapy using VEMP, CVP, or VEPA failed to make the outcome significantly better than radiotherapy alone. This may be due to failure to prevent relapse in patients with large or bilateral cervical lymph nodes; out of 6 of these patients, 3 experienced relapse and 4 died of disease. On the other hand, out of 8 stage I–II patients who had received radiotherapy with MTCOP-P chemotherapy, all achieved CR and none experienced relapse or died even though 3 patients had unfavorable lymph node status. Although the OS rate was not statistically significant because of a limited number of cases, this treatment resulted in a significantly better DFS than the treatment with radiotherapy alone. The original MACOP-B regimen has been reported to be effective for stage II lymphomas with unfavorable histology, but the toxicities were often severe and not curable in 5–10% of cases (17, 24). In our treatment, there were no severe infections and toxic death. This may be due to decreased dose and replacement of reagents administered. Therefore, we believe that our treatment schedule using radiotherapy with a modified MACOP-B regimen is safe and effective for stage I–II WR lymphomas with intermediate or high-grade histology. Recent reports also showed good results with use of three courses of CHOP and involved field radiation for WR lymphomas with intermediate or high-grade histology (9, 11). However, our material is small and the analysis is retrospective. Randomized prospective studies are needed to address survival and relapse rates and quality of life.

ACKNOWLEDGEMENTS

The authors express their appreciation to Professor Howard Faden, Department of Pediatrics, State University of New York, School of Medicine and Children's Hospital of Buffalo, for helpful comments on the manuscript. This work was funded by a grant in aid of scientific research from the Ministry of Education, Science and Culture of Japan.

REFERENCES

1. Hoppe RT, Burke JS, Glatstein E, Kaplan HS. Non-Hodgkin's lymphoma: involvement of Waldeyer's ring. Cancer 1978; 42: 1096–104.
2. Saul SH, Kapadia SB. Primary lymphoma of Waldeyer's ring. Clinicopathologic study of 68 cases. Cancer 1985; 56: 157–66.
3. Jurga L, Vladimir A, Kulikova M, Klimo J, Berc A. Non-Hodgkin's lymphomas of Waldeyer's ring. Neoplasma 1985; 32: 729–35.
4. Yamanaka N, Harabuchi Y, Sambe S, et al. Non-Hodgkin's lymphoma of Waldeyer's ring and nasal cavity. Clinical and immunologic aspects. Cancer 1985; 56: 768–76.
5. Kondo M, Mikata A, Ogawa K, et al. Prognostic factors in stage I and II non-Hodgkin's lymphoma of Waldeyer's ring. Acta Radiol Oncol 1985; 24: 153–8.
6. Shima N, Kobashi Y, Tsutsui K, et al. Extranodal non-Hodgkin's lymphoma of the head and neck. A clinicopathologic study in the Kyoto–Nara area of Japan. Cancer 1990; 66: 1190–7.
7. Hayabuchi N, Jingu K, Matsui M, et al. Non-Hodgkin's lymphomas involving Waldeyer's ring: a proposal for clinical categorization. Radiat Med 1984; 2: 252–9.
8. Shimm DS, Dosoretz DE, Harris NL, Pilch BZ, Linggood RM, Wang CC. Radiation therapy of Waldeyer's ring lymphoma. Cancer 1984; 54: 426–31.
9. Takagi T, Sampi K, Iida K. Stage I malignant lymphoma of Waldeyer's ring: frequent relapse after radiation therapy. Ann Oncol 1992; 3: 137–9.
10. Mill WB, Lee FA, Franssila KO. Radiation therapy treatment of stage I and II extranodal non-Hodgkin's lymphoma of the head and neck. Cancer 1980; 45: 653–61.
11. Uematsu M, Kondo M, Hiramatsu H, et al. Stage IA non-Hodgkin's lymphoma of the Waldeyer's ring. Limited chemotherapy and radiation therapy versus radiation therapy alone. Acta Oncol 1993; 32: 675–8.
12. Ohguro S, Himi T, Harabuchi Y, Suzuki T, Asakura K, Kataura A. Adult T-cell leukaemia-lymphoma in Waldeyer's ring: a report of three cases. J Laryngol Otol 1993; 107: 960–2.
13. Harabuchi Y, Yamanaka N, Kataura A. Identification of lymphocytes subsets and natural killer cells in head and neck cancers. An immunohistological study using monoclonal antibodies. Arch Otorhinolaryngol 1985; 242: 89–97.
14. Kimura K, Sasaki Y, Konda C, et al. Chemotherapy of the malignant lymphoma. Saishin Igaku 1972; 24: 816–24 (in Japanese).
15. Lymphoma Study Group. Combination chemotherapy with vincristine, cyclophosphamide (Endoxan), predonisolone and Adriamycin (VEPA) in advanced adult non-Hodgkin's lymphoid malignancies: relation between T-cell or non-T-cell phenotype and response. Jpn J Clin Oncol 1979; (Suppl 9): 397–406.
16. Canellos GP, Lister TA, Skarin AT. Chemotherapy of the non-Hodgkin's lymphomas. Cancer 1978; 42: 932–40.
17. Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. Ann Intern Med 1985; 102: 596–602.
18. Ohnoshi T, Hayashi K, Ueoka H, et al. Salvage chemotherapy for non-Hodgkin's lymphoma with a four-drug combination of mitoxantrone, etoposide, cisplatin and predonisolone (MEPP). Jpn J Cancer Chemother 1987; 14: 626–9 (in Japanese).
19. Harabuchi Y, Imai S, Wakashima J, et al. Nasal T-cell lymphoma causally associated with Epstein-Barr virus: clinicopathologic, phenotypic, and genotypic studies. Cancer 1996; 77: 2137–49.
20. Chan JK, Banks PM, Cleary ML, et al. A revised European–American classification of lymphoid neoplasms proposed by the International Lymphoma Study Group. A summary version. Am J Clin Pathol 1995; 103: 543–60.

21. The International Non-Hodgkin's Lymphoma Prognostic Factor Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987–94.
22. Jacobs C, Hoppe RT. Non-Hodgkin's lymphomas of head and neck extranodal sites. Int J Radiat Oncol Biol Phys 1985; 11: 357–64.
23. Liang R, Chiu E, Todd D, Chan TK, Choy D, Loke SL. Combined chemotherapy and radiotherapy for lymphomas of Waldeyer's ring. Oncology 1991; 48: 362–4.
24. Schneider AM, Straus DJ, Schluger AE, et al. Treatment results with an aggressive chemotherapeutic regimen (MA-COP-B) for intermediate and some high-grade non-Hodgkin's lymphomas. J Clin Oncol 1990; 8: 94–102.