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Radiotherapeutic Result of Waldeyer's Ring Lymphoma

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Twenty patients with biopsy-proven Waldeyer's ring lymphoma were treated with radiotherpy between 1984 and 1990 at the Department of Radiation Therapy, Inje University Paik Hospital and seventeen evaluable patients were analysed retrospectively. Dose of radiation ranged from 35 to 50 Gy to Waldeyer's ring structure with an additional 5 and 10 Gy boost dose to the primary site. The lower cervical nodes received 35 to 60 Gy. The median follow-up period was 24 months (range;9 to 80 months). The 5-year overall survival rate was 50.2% and 5-year disease free survival rate was 47.1%. The final local control rate was 82.4%. The relapse developed average 10 months after treatment. Most of relapses were systemic (87.5%). The patients with stage I disease fared better than advance stage. The favorable histology of lymphoma showed better prognosis than unfavorable histology. There was no significant difference in survival rate between radiotherapy alone and combination of chemotherapy and radiotherapy in early stage lymphomas. But of the patients with advanced stage, those who received chemotherapy and radiotherapy had better prognosis than those treated with radiotherapy alone.

Key Words: Waldeyer's ring lymphoma, Radiotherapy, Combined chemotherapy and radiotherapy

INTRODUCTION

Of the extranodal non-Hodgkin's lymphoma, the gastrointestional tract and Waldeyer's ring predominate as primary sites[1]. The involvement of Waldeyer's ring occurs in 66% of the head and neck lymphomas, and the tonsil is the most common site of involvement[2].

Therapy of this group of neoplasm is dependent on stage, pathologic features and extent of disease. In early stage, tumor was controlled locally with radiotherapy alone. In advanced stage, combination of radiotherapy and chemotherapy was needed. The patients with unfavorable histologies were treated with combination therapy. Likewise the patients who had a bulky tumor or presented with systemic symptoms were treated with combination treatment modality.

We analyze retrospectively our experience in the treatment of seventeen patients with primary non-Hodgkin's lymphomas originating in Waldeyer's ring between 1984 and 1990 at Inje University Paik Hospital. The goal of this review was to identify poor prognostic factors and recommend better treatment modality for obtaining the good local control and decreasing the risk of relapse.

MATERIALS AND METHODS

Between 1984 and 1990, 20 patients with non-Hodgkin's lymphoma of Waldeyer's ring were treated at the Department of Radiation Therapy of Inje University Seoul Paik Hospital. Seventeen patients of these were evaluable and were analyzed retrospectively.

The age distribution ranged from 6 to 78 years and median age was 45 years.(Table 1) There were 14 male and 3 female patients. The median follow-up period was 24 months and ranged from 9 to 80

Table 1. Patients Characteristics of Seventeen Patients

Characteristics		No. of patients
Sex	Male	14
	Female	3
Age (years)	Median	45
	Range	6 – 78
Follow-up (months)	Median	24
	Range	9 – 80
Histologic grade	Low	1
	Intermediate	10
	High	3
	Unevaluable	3
Site	Tonsil	15
	Nasopharynx and nose	2
Stage	I	5
	II	10
	III	2

months. The histologic materials were grouped into low, intermediate, and high-grade categories based on the Working Formulation[3], and the Rappaport Classification[4]. The tonsil was the most common site of involvement. Five patients belonged to stage I, 10 stage II and 2 stage III. Histologic review was possible in 14 patients (Table 2). Most patients had tumors that were classified as diffuse histiocytic type in the Rappaport Classification.

A careful physical examination, complete blood cell count, liver function test, chest roentgenograms and biopsy were performed in every patient. Abdominal nodes evaluated by ultrasonography and/or computerized tomography. And, a few patients had bipedal lymphangiogram, bone scan, bone marrow aspiration and gastrofiberscopy as a staging work-up.

Initial treatment consisted of radiotherapy alone in six patients and radiotherapy combined with chemotherapy in eleven patients.

All the patients were treated with a 4 MV linear accelerator. The patients received 180 to 200 cGy per fraction, five times per week. The treatment volume was determined by extent of disease and nodal involvement status. The Waldeyer's ring field consisted of parallel opposed lateral fields, which included primary lesion and upper cervical nodes. The remaining lower neck lymph nodes were treated through an en face portal (Fig 1). The total dose ranged from 3500 to 6100 cGy for primary sites and 3500 to 6000 cGy for anterior lower neck nodes. Chemotherapy was used in combination with radia-

Table 2. Histological Classification of Fourteen Patients

Histologic classification		No. of patients
RAPPAPORT CLASSIFICATION		
Nodular	2	
Histiocytic		1
Poorly differentiated lymphocytic		1
Diffuse	11	
Histiocytic		8
Poorly differentiated lymphocytic		1
Lymphoblastic	2	
Not classified	1	
WORKING FORMULATION		
Low	1	
Follicular small cleaved		1
Intermediate	10	
Small cleaved		1
Follicular large		1
Large cleaved		8
High	3	
Large cell immunoblastic		1
Lymphoblastic		2

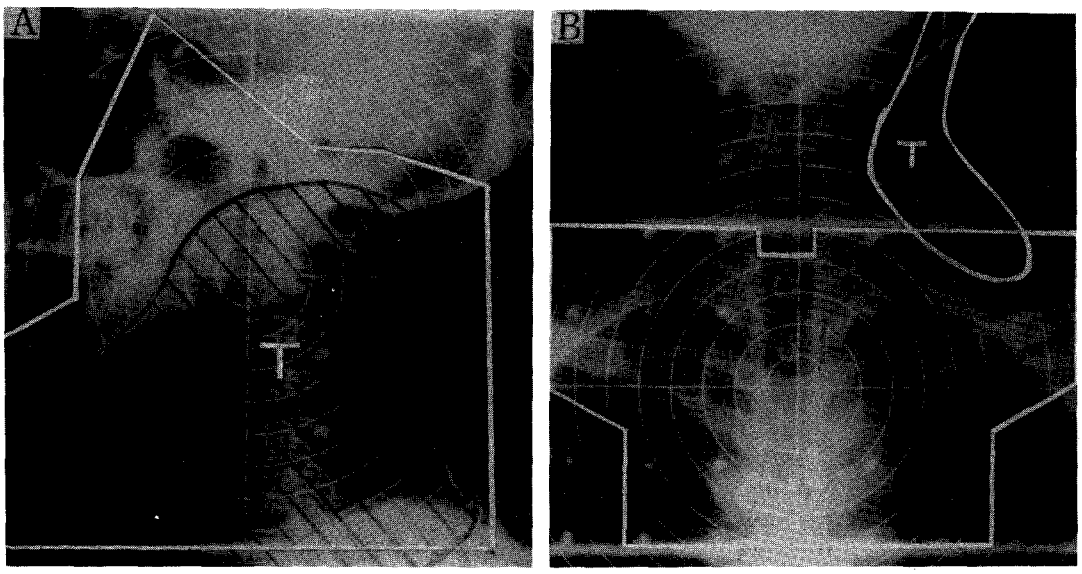

Fig. 1. Radiation portals for non-Hodgkin's lymphoma presenting in Waldeyer's ring.
A. Opposit lateral portals for Waldeyer's ring. B. Anterior portal for lower cervical nodes.

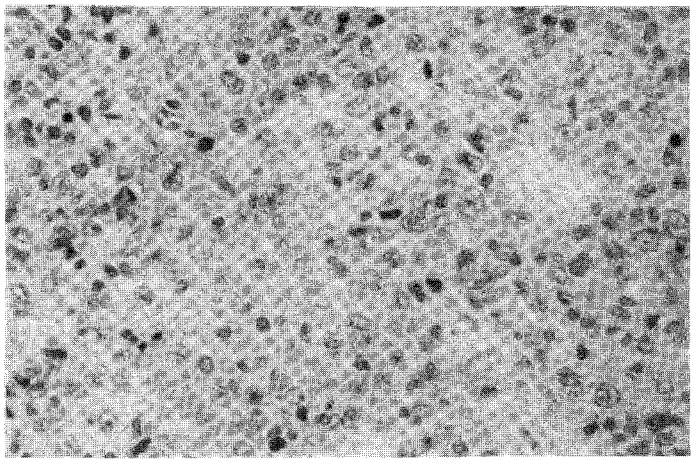

Fig. 2. Histopathologic feature of diffuse large cell lymphoma, (H & E, original magnification ×400).

tion therapy in 11 patients, of whom 2 had stage I disease, 7 stage II and 2 stage III. Most of these patients received combination chemotherapy consisting of BACOP (Bleomycin, Adriamycin, Cyclophosphamide, Vincristine, Prednisone) or CHOP (Cyclophosphamide, Adriamycin Vincristine, Prednisone). Survival and freedom from relapse were calculated from date of initiation of therapy using the Kaplan-Meier method[5].

RESULT

Analysis of the sex distribution represented male preponderance (4.7:1). The peak incidence was during the fifth decade (52.9%). But two patients were aged under twenty.

Based on the Rappaport Classification, subclassification of diffuse histiocytic type was the most common pattern (50%). The morphologic pattern of this type was typified by a monomorphic proliferation of large lymphoid cells with variably prominent nucleoli (Fig 2).

The final local control was acheived in 82.4% (14/17) of patients (Fig 3) and was influenced by Ann Arbor staging[6]; 100% (5/5) for stage I, 90.0% (9/10) for stage II and 0% (0/2) for stage III (Fig 4). It was also influenced by lymph nodal status. The patients with no nodal involvement or ipsilateral involvement showed 90.9% (10/11) of local control rate (Fig 5), whereas the patients with bilateral nodal involvement showed 66.7% (4/6). Histology influenced local control. By the Rappaport Classification, the local control was achieved in 100% (2/

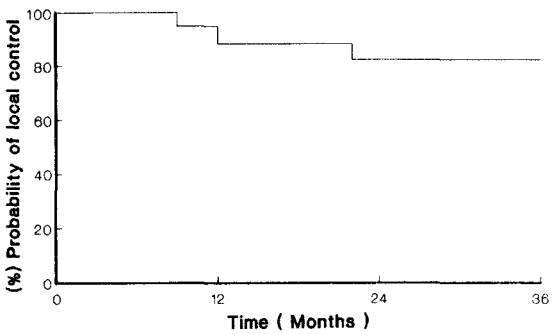

Fig. 3. Final local control of seventeen patients with Waldeyer's ring lymphoma.

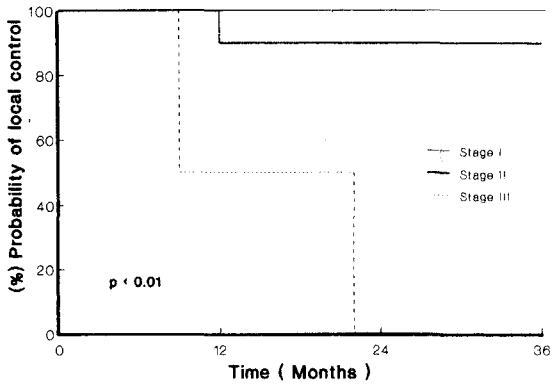

Fig. 4. Local control by stage.

2) of the patients with nodular histologies and 81.8% (9/11) of the patients with diffuse histologies (Fig 6).

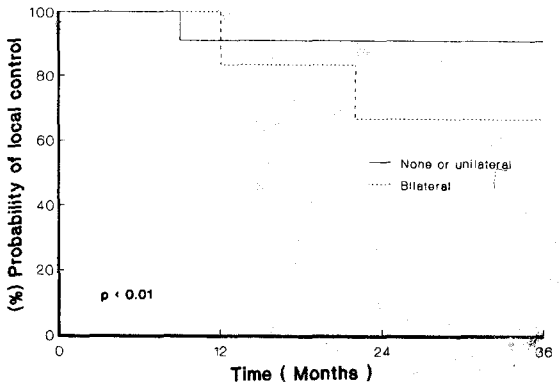

Fig. 5. Local control by nodal involvement state.

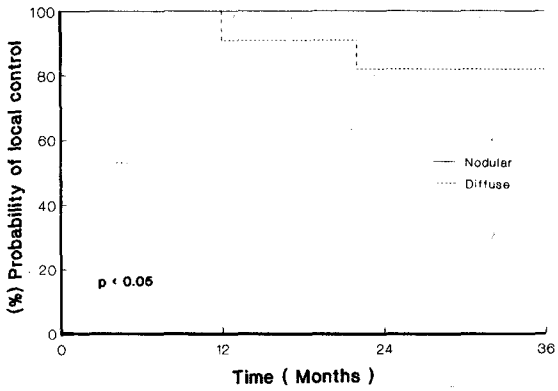

Fig. 6. Local control by histologic type.

The median duration of remission was 12 months (range; 3 to 17 months). Table 3 shows the sites of relapse. Six out of 7 patients failed at distant sites. Among these, two patient failed at both local and distant site. The common sites of distant failure was distant nodal structure (57.1%) and gastrointestinal tract (28.6%). Survival following relapses was poor and half of relapsed patients refused salvage procedure. For salvage procedure, two patients received radiotherapy and the remaining two patients received chemotherapy. Three out of four patients died of disease.

The probabilities of survival and disease-free survival for the entire population are shown in figure 7. Five-year overall survival rate was 50.2%, and disease-free survival rate was 47.1%. Figure 8 shows the survival rate according to stage. Two-year survival rate was 80.0% in stage I, 53.3% in stage II and 0% in stage III. Five-year survival rate was 53.3% in stage I and II.

The therapeutic results was influenced by treatment modalities (Table 4). Two-year survival rates of stage I patients treated with radiotherapy alone and combination of raditherapy and chemotherapy were 66.7% and 50%, In stage II, none of the patients received radiotherapy alone was alive.

Table 3. The Sites of Relapses

Failure sites		No. of patients (%)
Local		1 (14.3%)*
Nodal		4 (57.1%)
Supradiaphragmatic	1**	
Infradiaphragmatic	3	
Extranodal		2 (28.6%)
Gastrointestinal tract	2	

* Excludes two loco-regional failure
** Involves axillar lymph node

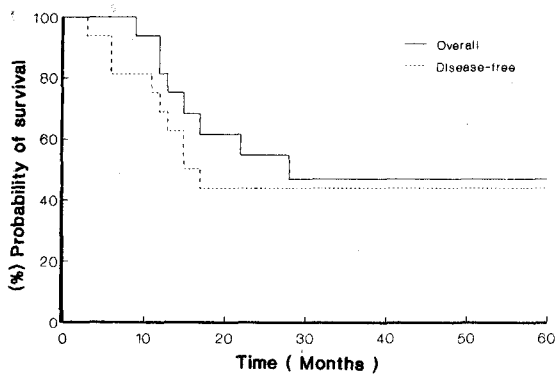

Fig. 7. Overall survival and disease free survival rates of seventeen patients with Waldeyer's ring lymphoma.

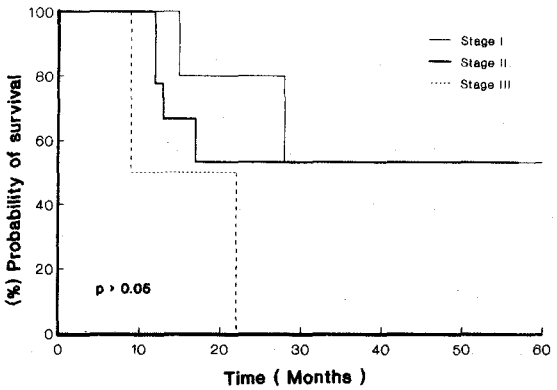

Fig. 8. Overall survival rates by stage.

Table 4. Difference of Two-Year Survival Rate of Radiotherapy Alone and Combination of Radiotherapy and Chemotherapy (17 Patients)

	RT alone	RT plus CT
Stage I	66.7%	50.0%
Stage II	0%	71.4%
Stage III	–	0%

RT : Radiotherapy CT : Chemotherapy

Two-year survival rate of stage II patients received combination therapy was 71.4%. Two patients with stage III patients had received combination therapy, but all died of systemic failure. Therefore, in early stage, the treatment result between radiotherapy alone and combination of radiotherapy and chemotherapy did not show significant difference. However, in advanced stage, combined chemotherapy and radiotherapy showed better prognosis than radiotherapy alone.

Complications of treatment were within acceptable range. Most patients experienced mild to moderate degree of mucositis during radiation therapy.

DISCUSSION

In head and neck lymphoma, Waldeyer's ring, particularly the tonsil, is the most common site of involvement[7]. The majority of patients presents with symptoms of local masses and 64.7% of patients complained of palpable cervical mass. The systemic symptoms were rare (17.6%)[2].

By univariate analysis, stage, histologic group and addition of multiple agent chemotherapy has been reported to be prognostic factors[2].

The extent of disease is of major prognostic importance. Mill et al reported that acturial five-year survival rate was 61% for stage I and 53% for stage II[7]. In our result, survival of stage I fared better than that of stage II and III. Mauch et al reported that the patients with extended stage I-II disease treated with radiotherapy alone had a 6-year acturial survival rate of 46%, as compared with 82% for patients with minimal disease[8]. Therefore, in same stage, the bulkiness of disease influenced survival.

The majority of Waldeyer's ring lymphoma had unfavorable histologies[9]. The preponderance of a diffuse pattern in our patients (87.5%) is consistent with other report scheme[10~12]. Likewise, the histiocytic cell type, present in fifty six percent of our cases, has usually been reported to be the most common type.

Histologic type was the important prognostic factor. Kim et al reported that five-year acturial survival rates were 84% for lymphocytic tumors, 52% for histiocytic tumors[13]. All of our patients with nodular and low-grade histologies was disease-free state. Three patients with high grade histologies by the criteria of Working Formulation showed better prognosis than those with intermediate grade. This result seemed to be due to the small number of patients with high grade histologies.

Malignant lymphoma localized to Waldeyer's ring, with or without involvement of cervical lymph nodes, can be cured with involved field radiation therapy[14]. In our report, the local control rate was 82.4%. Wang et al reported that 64% of patients who received radiation therapy for stage I and II lymphomas survived five year[14]. But, the majority of patients failed had disseminated disease[15]. So by adding multiagent chemotherapy early in the course of treatment might improve the overall disease-free survival[2,9,16]. Monfardini et al reported that the five-year relapse-free survival was 46.3% after radiation therapy and 72.1% after radiation therapy plus chemotherapy[17]. Nissen et al reported that local control rate of stage I was 68.4% in the radiotherapy alone and 92.3% in the combination of radiotherapy and chemotherapy, and that of stage II was 14.3% and 85.7%; local control rate of the patients who had B symptoms was 40% in the radiotherapy group and 83.3% in the combination therapy group[18]. They suggested that the favorable effects of adjuvant chemotherapy on relapse-free survival were statistically significant in stage I patients with the bulky tumor mass, histiocytic histologic subgroup or B symptoms, and stage II patients[19]. Thus, Monfardini et al recommended to start chemotherapy before or simultaneously with radiation therapy in order to avoid early relapse[17].

The incidence of relapses is highest in the first year after treatment[14]. In our cases, 71.4% of relapse developed within a year. Most relapses were systemic. In our study, the sites of distant failure were distant nodal structures and gastrointestinal tract. Banfi et al reported that gastrointestinal involvement was 17.6% of cases[20]. Gastrointestinal involvement occurs in a greater portion of patients with malignant lymphoma of Waldeyer's ring, in spite of the absence of direct lymphatic connection between these two sites. This fact may

be represented by the homing tendency of the gut-associated lymphoid tissue[21]. Due to high incidence of systemic failure, a thorough work up, including physical and biological investigations, chest roentgenography, bipedal lymphangiography, abdominal computerized tomography and sonography, gastrofiberoscopy, bone scintigraphy and bone marrow aspiration, is indicated. The controversial role of diagnostic laparotomy is discussed in other reports[16]. It is not being used in the routine staging procedure in our series.

Survival following initial relapse is poor. All relapsed patients died of disease within an average of 10 months. Bartons et al reported that the relapsing patients who received no therapy died of disease within an average of 4.6 months from the first evidence of relapsed disease[17]. Only 14% of patients with recurrent disease was without evidence of disease, who received combination chemotherapy alone or with the addition of irradiation. In our result, one out of 7 relapsing patients (14.3%) treated with combination chemotherapy for salvage procedure was alive.

In conclusion, early stage of Waldeyer's ring lymphoma can be cured by radiation therapy, but in the patients with B symptoms, bulky mass or unfavorable histologies, failed at combination treatment modalities. In advanced disease, most of patients failed at distant sites, thus we recommend combined modality of radiotherapy and chemotherapy.

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국문초록 =

Waldeyer's Ring 임파종 : 방사선 치료의 결과

인제의대 서울백병원 치료방사선과학교실

김 주 리·서 현 숙

인제 대학교 백 병원 치료 방사선과 교실에서는 1984년에서 1990년 까지 조직학적으로 확진된 Waldeyer's ring 임파종 환자 20명이 치료를 받았으며 이 중 17명의 환자가 조사기능하여 후향성으로 분석하였다. 방사선 조사량은 Waldeyer's ring에 35내지 50 Gy를 조사하였고 원발 병소 부위에 5내지 10 Gy를 첨가로 조사하였다. 경부 하부 임파절은 35내지 60 Gy를 조사 받았다. 관찰기간은 9개월에서 78개월(중앙값 : 23개월)이었다. 5년 생존율은 46.8%이고 5년 무병 생존율은 43.8%였다. 재발은 치료 후 평균 10개월에 발견되었으며 대부분의 재발은 전신적으로 발생하였다. 1기 환자는 병소가 진행된 경우보다 경과가 좋았으며, 세포 유형도 예후에 영향을 나타내었다. 조기 병기의 환자에서는 방사선 조사의 결과와 방사선 조사와 화학요법을 병행한 결과의 차이가 거의 없었으나 진행된 병기의 환자에서는 병행요법이 단독 치료 방법에 비해 예후가 좋았다.