

## The Role of Radiotherapy in Stage I , II Intermediate Grade Non-Hodgkin's Lymphoma

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Radiotherapy result of 162 patients with stage I , II intermediate grade non-Hodgkin's lymphoma was analyzed to clarify the role and limit of radiotherapy. Of 68 initial failures, 38.2% occurred in field and 61.8% occurred out of field. Proportion of in-field and out-of-field failures in stage I was 30.0% and 70.0%, respectively with involved field treatment and was 43.8% and 56.2% with extended field treatment, respectively; in stage II, was 16.7% and 83.3%, 41.7% and 58.3%, respectively. The disease free survival rate at 5 years was 48.1% for all patients and was 56.3% and 40.4% for patients with stage I and II, respectively. The survival was significantly different by stage. Bulky tumors ( $\geq 10$  cm) and B symptoms didn't influence prognosis significantly. The 5 year disease free survival with extended or wide field was better than that with involved field especially in stage I .

Overall survival rates for all patients, patients with stage I , and II disease were 57.7%, 65.3% and 52.2%, respectively, after survival gain of the salvage chemotherapy was combined. But the overall survival of stage I disease was not better than that of stage II disease. Thus, extended field was required to achieve better disease free survival and relapsed cases might gain with chemotherapy.

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**Key Words:** Radiotherapy, Non-Hodgkin's lymphoma, Intermediate grade, Stage I , II

### INTRODUCTION

The strategy for treatment of localized non-Hodgkin's lymphoma with intermediate grade by Working Formulation has been controversial. Recently, the long-held view that radiation therapy alone is sufficient has been challenged by suggestion that chemotherapy either in combination with radiation therapy<sup>1-4)</sup> or alone<sup>5,6)</sup> could result in superior survival. Because there exist deleterious morbidity<sup>7,8)</sup> as well as benefit of combined therapy, it is needed that establishment of a criteria by which radiotherapy alone or combined with chemotherapy could be delivered. Another issue is the extent of treatment when curative radiation alone is indicated.

We analysed the radiotherapy result of stage I , II non-Hodgkin's lymphoma with intermediate grade to clarify the role and limit of radiotherapy.

### MATERIALS AND METHODS

Between February, 1979 and September, 1987, 162 patients with localized intermediate grade non-Hodgkin's lymphoma received radiotherapy at Seoul National University Hospital. All patients were not treated previously with any modalities. Of these, 130 patients (80.2%) were followed up and 32 patients were lost to follow-up. Median follow-up period of all patients was 50 months. Age ranged from 16 to 73 years and 78 patients (48.2%) were in their fifth to sixth decades. There were 91 males and 71 females.

According to Rappaport classification, diffuse histiocytic (DH) type was 66.0% and diffuse poorly differentiated lymphocytic (DPDL) type was 27.2%. DH type was 50.0% of nodal presentation and 70.6% of extranodal presentation (Table 1). Clinical evaluation included physical examinations, complete blood counts, blood chemistries, and chest radiographs. CT, ultrasound, and lymphangiographic studies were done in some patients. Bone marrow aspirations and biopsies were performed in 82 patients. As staging laparotomy was not

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This work was partly supported by 1990 SNUH Research Fund.

performed routinely, most tumors were clinically staged by Ann Arbor system while gastrointestinal lymphomas were pathologically staged. Numbers of patients with stage I and II were 68 and 94, respectively. B symptoms were present in 33 patients (20.4%): 14 patients (20.6%) with stage I,

**Table 1. Histologic Types by Disease Presentation**

Histologic Type	No. of Patients		
	Nodal	Extranodal	Total (%)
NH	4	2	6 ( 3.7)
DPDL	12	32	44 ( 27.2)
DM	2	3	5 ( 3.1)
DH	18	89	107 ( 66.0)
Total	36	126	162 (100.0)

**Table 2. Distribution of Stage**

Stage	No. of Patients	%
I	68	42.0
IA	21	13.0
IEA	33	20.4
IB	1	0.6
IEB	13	8.0
II	94	58.0
IIA	10	6.2
IIEA	65	40.1
IIB	4	2.5
IIEB	15	9.2
Total	162	100.0

19 patients (20.2%) with stage II, 28 patients (22.2%) with extranodal presentations, and 5 patients (13.9%) with nodal presentations (Table 2).

Treatment methods differed by disease presentation and primary site (Table 3). 80.6% (29/36) of nodal lymphomas were treated with radiotherapy alone and 34.9% (44/126) of extranodal lymphomas were treated with combined modalities. Of 35 patients with gastrointestinal lymphoma 31 patients received operation first and its extent of resection was complete in most cases. Combined radiation and chemotherapy was done in 11 cases but regimen and intensity of chemotherapeutic agents was variable.

Extent of radiation was involved field encompassing involved sites with generous margin in 29 patients, extended field (involved sites and clinically uninvolved adjacent nodes) in 126 patients, and wide field ('mantle' or 'inverted Y') irradiation in 7 patients. The majority of patients received 4,000~5,000 cGy with conventional fractionation. According to field extent, the median dose was 4,660 cGy for involved field, 4,550 cGy for extended field, and 5,000 cGy for wide field irradiation.

Disease free survival and overall survival were calculated by life table method<sup>9)</sup> and comparison between survival was done by log rank test<sup>10)</sup>.

## RESULTS

The disease free survival (DFS) rate at 5 years was 48.1% for all patients and was 56.3% and 40.4% for patients with stage I and II, respectively. The survival was significantly differed by the stage (Fig. 1).

DFS rates at 5 years in patients with nodular histiocytic (NH), diffuse poorly differentiated lymphocytic (DPDL), diffuse mixed (DM), and dif-

**Table 3. Methods of Treatment by Disease Presentation and Primary Sites**

Site	RT	CT + RT	Op + RT	Op + RT + CT	Total
Nodal	29	4	3	—	36
Extranodal	82	4	37	3	126
Gastrointestine	4	—	28	3	35
Waldeyer's ring	49	3	3	—	55
Head and Neck	26	1	4	—	31
Other Site	3	0	2	—	5
Total	111	8	40	3	162

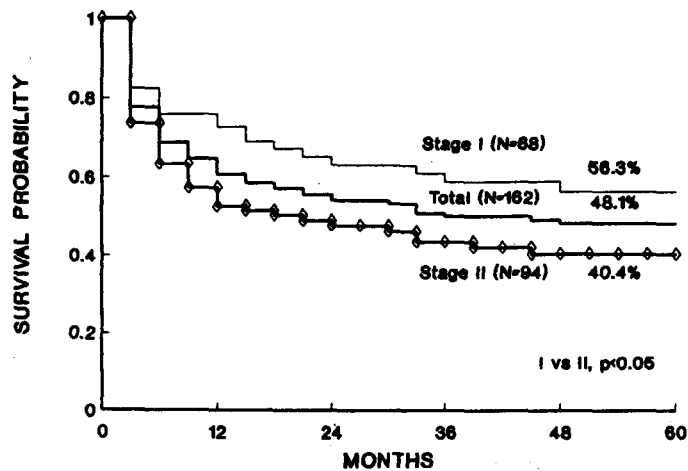


Fig. 1. Disease free survival by stage.

**Table 4.** Survival by Stage and Extent of Radiation Field

Stage and Extent	No. of Patients	5 Year DFS Rate (%)	p Value
<b>Stage I</b>			
Involved	19	36.8	p<0.05
Extended	49	66.8	
<b>Stage II</b>			
Involved	10	12.7	0.05<p<0.1
Extended	77	44.3	
Wide	7	57.1	
<b>All</b>			
Involved	29	28.3	0.05<p<0.1
Extended	126	52.8	
Wide	7	57.1	

**Table 5.** Patterns of Initial Failure

Pattern of Initial Failure	No.	%
<b>In-field</b>		
Persistent Disease	17	25.0
Relapse	9	13.2
<b>Out-of-field</b>		
Nodal	24	35.3
Extranodal	15	22.1
Systemic	3	4.4
<b>Total</b>	<b>68</b>	<b>100.0</b>

fuse histiocytic (DH) type were 60.0%, 55.6%, 60.0%, and 43.7%, respectively. But survival was not significantly influenced by the histology. Five year DFS rates were 53.5% and 47.1% for patients with nodal and extranodal disease, respectively and the difference was not significant. In extranodal lymphomas, survival was not differed by primary sites: 5 year DFS was 46.5% with tumors in Waldeyer's ring, 58.3% with gastrointestinal tumors, and 43.6% with tumors in other head and neck area. DFS at 5 years were 47.5% and 48.3% in patients with and without B symptoms, respectively. DFS at 5 years were 43.1% and 48.6% for 15 patients with bulky disease ( $\geq 10$  cm) and in 147

patients without bulky disease, respectively, and the survival difference was not significant, too.

The 5 year DFS with extended or wide field was better than that with involved field especially in stage I (Table 4). Of 68 initial failures, 38.2% occurred in field and 61.8% occurred out of field. Of 26 in-field failures, 65.4% were persistence of disease and 34.6% were in-field relapse. Of 42 out-of-field failures, 57.1% occurred at lymph nodes, 35.7% occurred at extranodal sites, and 7.2% were systemic relapse (Table 5). Among 26 failures in stage I, 38.5% were in-field failures and 61.5% were out-of-field failures. Proportion of in-field and out-of-field failures was 30.0% and 70.0%, respectively with involved field treatment, while was 43.8% and 56.2%, respectively with extended field treatment. Among 42 failures in stage II, 38.1% were in-field failures and 61.9% were out-of-field

**Table 6. Patterns of Initial Failure by Stage and Treatment Extent**

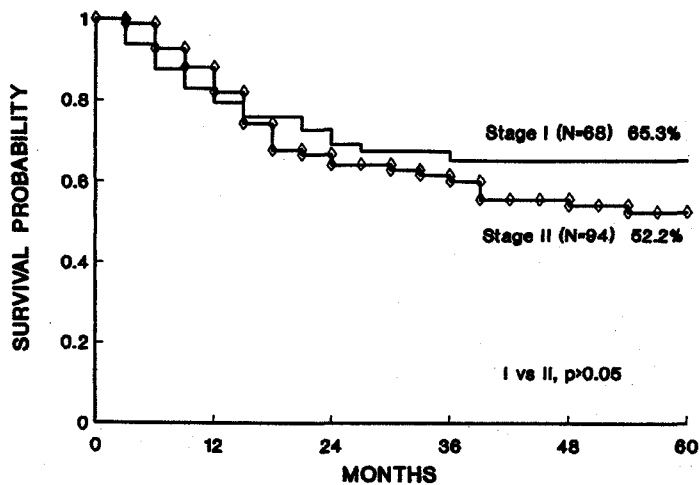
Stage and Treatment Extent	N	In-field Failure		Out-of-field Failure		
		Residual	Relapse	Nodal	Extranodal	Systemic
Stage I	68	7	3	8	7	1
Involved	19	3	0	4	2	1
Extended	49	4	3	4	5	0
Stage II	94	10	6	16	8	2
Involved	10	1	0	2	2	1
Extended	77	9	5	13	5	1
Wide	7	0	1	1	1	0
All	162	17	9	24	15	3
Involved	29	4	0	6	4	2
Extended	126	13	8	17	10	1
Wide	7	0	1	1	1	0

failures. Proportion of in-field and out-of-field failures was 16.7% and 83.3%, respectively with involved field treatment, while was 41.7% and 58.3%, respectively with extended or wide field treatment. Thus overall proportion of in-field and out-of-field failures was 25.0% and 75.0%, respectively with involved field treatment, while was 38.5% and 61.5% with extended or wide field treatment (Table 6). Patterns of initial failures was not influenced by stage, site, or B symptoms.

Of 30 patients who received chemotherapy after failure, 16 patients were salvaged (Table 7). Overall survival rates at 5 years for all patients, patients with stage I, and II disease were 57.7%, 65.3%, and

**Table 7. Effect of Salvage Chemotherapy**

Site of Initial Failure	No. Salvaged / No. Tried
In-field	6/10
Residual	4/7
Relapse	2/3
Out-of-field	10/20
Nodal	6/11
Extranodal	4/8
Systemic	0/1
Total	16/30



**Fig. 2. Overall survival by stage.**

52.2%, respectively, after survival gain of the salvage chemotherapy was combined. But the survival of stage I disease was not better than that of stage II disease (Fig. 2). Overall survival at 5 years was 49.4% in patients with B symptoms and 59.8% without B symptoms, 43.4% in patients with bulky disease ( $\geq 10$  cm) and 59.2% without bulky disease. Presence of bulky disease lowered overall survival without significance.

## DISCUSSION

There were numerous reports on the results of radiotherapy for patients with localized intermediate grade non-Hodgkin's lymphoma which were clinically staged<sup>11-20</sup>. Relapse free survival ranged from 35% to 65% with an average of 58% in stage I patients and ranged from 0% to 47% with an average of 26% in stage II patients. Toonkel et al.<sup>21</sup> and Bitran et al.<sup>22</sup>, in their laparotomy staged studies, reported higher survival rates up to 85% in stage I and II non-Hodgkin's lymphoma. Our relapse free survival data, 58.3% in stage I and 40.4% in stage II were similar to other studies.

Several prognostic factors have been suggested in intermediate grade lymphoma. Kaminski et al.<sup>11</sup> suggested that bulky tumor ( $\geq 10$  cm), B symptoms, and three or more extranodal sites of disease lessened disease free survival significantly. Others also reported that higher LDH level<sup>22,23</sup> and poor performance<sup>23</sup> also influenced disease free survival adversely. B symptoms and tumor bulk ( $\geq 10$  cm) affected prognosis adversely but not significantly in our study. But bulky tumors ( $\geq 10$  cm) that were mainly detected in the gastrointestinal presentation were completely resected in most cases, and it might result in disappearance of prognostic influence of tumor bulk.

Considerable controversy still exists concerning volume to be irradiated. Fuks et al.<sup>19</sup> reported that 57% of initial failures were detected in lymph nodes, 30% in contiguous nodes and 27% in non-contiguous nodes in stages I and II diffuse lymphoma. On the other hand, Chen et al.<sup>15</sup> reported that, in diffuse histology, 13% of all failures occurred in contiguous lymphatic sites only. It seems certain that non-Hodgkin's lymphoma shows random patterns of relapse, but, in some extent, they represent contiguous spread of disease. Our study showed that the survival difference according to field extent was significant in stage I and marginally significant in stage II. Kaminski et al.<sup>11</sup> reported that survival differed significantly

between treatment with limited field and extensive field including areas in both sides of diaphragm, but that survival didn't differ between treatment with involved field and extended field. But Timothy et al.<sup>14</sup> asserted that there was significant difference in survival between treatment with involved field and extended field especially in stage I disease. In our series, larger portion of tumors failed out of field and 57% of out-of-field failures were nodal failures, and most tumors treated with involved field relapsed out of field. Considering these we could assume that considerable proportion of failures might occur at contiguous area when treatment was delivered with involved field.

Since 1980, encouraging results have been obtained with the use of either chemotherapy alone or in combination with radiation therapy. Miller et al.<sup>5</sup> reported 85% disease free survival with chemotherapy alone and nearly same result was obtained by Cabanillas et al.<sup>6</sup>. By a randomized prospective trial in clinical stage I and II lymphoma with extended field radiotherapy alone or radiotherapy plus chemotherapy<sup>1</sup>, relapse free survival after combined treatment was superior to that after radiotherapy alone, but there was no difference in overall survival. Landberg et al.<sup>3</sup> showed similar results. But higher morbidity after combined treatment was observed<sup>7,8</sup>. These results suggest that combined modality may be helpful in certain subset of tumors.

Although currently available chemotherapeutic regimens have been reported to be effective in previously untreated patients with intermediate grade lymphoma, result of salvage chemotherapy have been usually poor<sup>24-27</sup>. Recently, several groups reported encouraging results using high dose chemotherapy with or without total body irradiation followed by autologous bone marrow transplantation<sup>28</sup>. Some reported that results of second line chemotherapeutic regimen for tumors which relapsed after initial chemotherapy were by far poorer than those of initial chemotherapy<sup>25,26</sup>. These findings might be related with good salvage effect of chemotherapy tried on tumors that failed after radiotherapy alone.

In summary, generous extended field was required to achieve better disease free survival in stage I, II intermediate grade non-Hodgkin's lymphoma with radiotherapy and relapsed cases might gain with chemotherapy.

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## = 국문초록 =

**I, II기 Intermediate Grade 임파종에서 방사선 치료의 역할**

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I, II기 intermediate grade 악성 임파종에서 방사선 치료의 역할을 확인하기 위하여 서울대학교 병원 치료 방사선과에서 치료받은 162 예의 방사선 치료 성적을 분석하였다. 초기의 치료 실패 양상이 확인 가능한 68 예 중 38.2%는 조사야 내에서 61.8%는 조사야 밖에서 치료 실패 또는 재발 하였다. I기에서는 조사야 내 및 외에서 발생한 치료 실패 양상은 국소 조사야 치료시 각각 30.0%와 70.0%였고, 확대 조사야 치료시는 각각 43.8% 와 56.2%였다. II기에서는 각각 16.7% 와 83.3% 및 41.7%와 58.3%였다. 5년 무병 생존율은 전 환자에서 48.1%였고, I기 및 II기에서 각각 56.3%와 40.4%로 병기에 따른 유의한 차이가 있었다. 10 cm 이상의 종괴나 전신적 증상은 무병 생존율에 영향을 미치지 못하였다. 방사선 치료 범위가 큰 경우에 5년 무병 생존율이 양호하였고 특히 I기에서는 유의하였다. 재발 후에 시행한 전신 화학 요법의 효과를 감안한 5년 생존율은 I, II기에서 각각 65.3% 및 52.2%였으며 병기에 따른 유의한 차이는 없었다. 따라서 5년 무병 생존율을 향상시키기 위해서는 원발 병소와 인접한 임파절 부위를 포함하는 확대 조사야로 치료할 필요가 있으며 재발된 경우에는 전신 화학 요법이 유용할 것으로 시사된다.