Radiotherapy Results of the Non-Hodgkin's Lymphoma in the Head and Neck†

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This is a retrospective analysis of 54 patients with stage I or II Non-Hodgkin's lymphoma involving the head and neck region treated with curative radiotherapy in the Department of Therapeutic Radiology, Seoul National University Hospital during the period of February 1979 through September 1982.

The minimum follow-up period was 24 months.

The review of histologic slides was available in 36 cases. Waldeyer's ring was the most common extranodal sites (46%).

41% of patients were in the stage I and 59% in the stage II by Ann Arbor classification. Of the 44 patients who responded after radiotherapy, 24 patients (54.5%) subsequently relapsed. Regional recurrence rate was 29%, distant metastasis was 54% and simultaneous regional recurrence and distant metastasis was 17%.

The survival rate and disease free survival at 2 years were 57% and 45% respectively. Those patients with a large primary lesion (over 6cm in diameter), multiple conglomerated, extranodal site and diffuse cell type, experienced a high rate of distant metastasis. Therefore it seems desirable to study the use of adjuvant chemotherapy in those patients with a high probability of distant metastasis.

Key Words: Non-Hodgkin's lymphoma, Head and neck region, Radiotherapy, Prognostic factors.

INTRODUCTION

Non-Hodgkin's lymphoma tends to be in more advanced stage at the time of diagnosis and to have severe prognosis than Hodgkin's lymphoma as the former has more frequent extranodal presentation, more unpredictable metastatic patterns, and higher rate of bone marrow and other organ involvement. Furthermore, it has variable natural history and progress patterns so that the treatment should be individualized on the histopathology, stage and site, of origin.[1-6]

NHL in the head and neck area however has a tendency to be confined to that region and to have relatively lower rate of distant metastasis compared to NHL in other areas, makes radiotherapy the preferred treatment of choice, the regional response rate with radiotherapy is 80-98%, and 5-year survival rate is 40-70%.[8-12]

However, there are still debates on the optimum

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dose and field of radiation. Many studies are being done with the combination of radiotherapy and chemotherapy in order to increase the cure rate by lowering distant metastasis which is the main factor of treatment failure.

We analyzed 54 histologically confirmed NHL cases in head and neck region which were treated by radical radiotherapy in Seoul National University Hospital for the last 4 years, and tried to determine the optimum dose, field, of radiation and combination of radiotherapy and chemotherapy.

METHODS AND MATERIALS

This is a retrospective analysis of 54 patients with Non-Hodgkin's lymphoma involving the head and neck region who were treated with radical radiotherapy. Patients were treated between February 1979 and September 1982 in the Department of Therapeutic Radiology, Seoul National University. The minimum follow-up period was 24 months. Seven patients were low to follow-up and 47 patients (87%) were available for this study.

Ages of the patients ranged from 19 to 70 years old with a median age of 41 years. The male to female ratio was 2:1 with 37 males and 17 females.

The primary site of involvement is shown in Table 2. Extranodal presentation was higher than nodal presentation and most common sinus of primary lesion was Waldeyer's ring, nasal cavity, and paranasal sinus in the order of decreasing frequency.

Patients were clinically staged according to the Ann Arbor staging system. The clinical evaluation included complete history, physical examination, complete blood count, liver function test and liver scan for all patients. Bone marrow aspiration and/or biopsy was obtained in 33 patients. Most patients had abdominal CT instead of lymphangiogram to evaluate the para-aortic lymph-nodes. None of the patients had explorative laparotomy.

The histology was classified according to the Working Formulation. Histologic re-examination was possible in 36 of 54 patients. No slides were available in the remaining 18 patients. The distribution by histologic type is presented in Table 3. The most common type was diffuse large cell (Diffuse histiocytic, Rappaport classification).

All of the patients were treated primarily with radiation therapy. The radiation ports were defined to include the primary site with and adequate normal tissue margin plus the regional lymph nodes (regional field) (Fig. 1). Only 7 patients were treated with extended field including mediastinum and para-aortic lymph nodes.

Radiation dose varied depending on the histology and tumor size. Diffuse large cell type received 5,000 rad in six to seven weeks and diffuse small cleaved cell type received 4,500 rad in five to six weeks. A boost dose of 500 to 1,000 rad was given for the residual lesion. Patients were treated with a cobalt

Table 1. NHL: Patient Characteristics (N=54) (1979.2 — 1982.9)

Median age	41	
Sex		
Male	37	(60%)
Female	17	(31%)
Stage		
I	22	(41%)
II	32	(59%)
Follow-up	1-57M	(21.5)*
Followed	47	(26)*
Lost	7	(4)*

* Median period. (month)

Table 2. NHL: Sites of Primary Lesion

Site	No. of Pts.	(%)
Nodal	17	(31)
Extranodal	37	(69)
Waldeyer's ring	25	(46)
Nose & sinus	9	(17)
Thyriod	1	(2)
Parotid gland	1	(2)
Orbit	1	(2)
Total	54	(100)

Table 3. NHL: Pathologic Distribution by NWF*

Subtype	No. of Pts.	(%)
I. Low Grade	3 (6)	
A. Small lymphocytic	3	(6)
B. F. Small cleaved cell	—	(0)
C. F. Mixed	—	(0)
II. Intermediate Grade	49 (91)	
D. F. Large cell	4	(7)
E. D. Small cleaved cell	11	(20)
F. D. Mixed	1	(2)
G. D. Large cell	33	(61)
III. High Grade	2 (4)	
H. Large cell immunoblastic	—	(0)
I. Lymphoblastic	2	(4)
J. Small non-cleaved cell	—	(0)

* New Working Formulation.

60 teletherapy unit and 9-12 MeV electrons.

A statistical comparison of survival rates was performed by the Log-Rank test.

RESULTS

1. Treatment failure

Of the 44 patients who had completely responded, 24 patients (54.5) subsequently relapsed.

There were 8 failures in the irradiated field, all of which had primary lesion larger than 6cm in diameter of multiple conglomerated. 18 of the 24 failures (71%) were in distant metastasis. The most common sites of distant metastasis were absomen and inguinal nedes (Table 5). Most of the failures with locoregional or distant metastasis received chemotherapy without further work-up to define additional sites of failure.

The time of relapse in the 24 patients is presented in Table 6. The median time of relapse was 5 months in stage 1 and 3 months in stage II which meant that the current work-up study for staging was not enough to evaluate the small gross or microscopic lesion at the time of diagnosis. Ninety-two percent of the failures occurred within 24 months.

2. Survivals

Analysis of survival by the life table method demonstrated improved survival for those with the favorable histology, nodal origin, and early stage. The actuarial survival rate at 2 years was 57% and disease free survival rate was 45% (Fig. 2). The actuarial survival rates at 2 years for low, intermediate and high grade were 100%, 55%, and 25% respectively (Fig. 7).

Analysis by stage is shown in Figure 3 and 4. At 2 years, the actuarial survival is 59% for stage I and 56% for stage II, the disease free survival is 49% for stage I and 42% for stage II.

Analysis by site is shown in Fig. 5. A actuarial survival at 2 years was 71% for nodal origin and 52% for extranodal origin.

3. Treatment after failures

4 out of 10 patients who had residual disease after completion of radiotherapy received adjuvant chemotherapy such as BACOP, CHOP, and C-

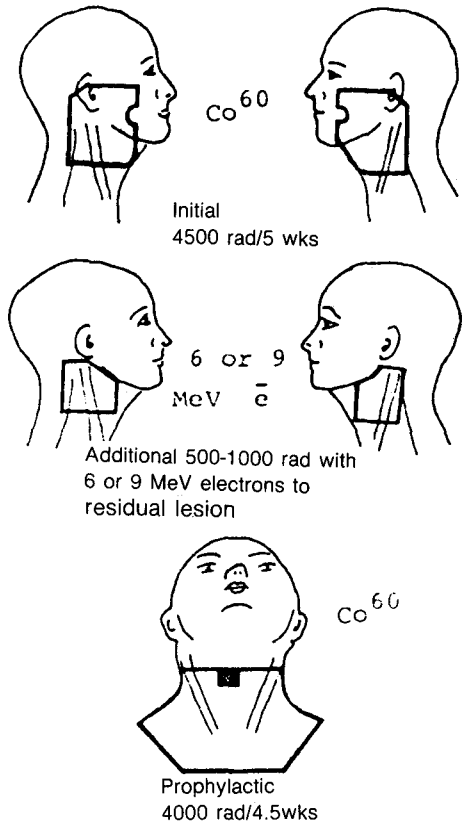

Fig. 1. NHL: Radiation therapy: Field & Dose

Table 4. Response & Relapse Rate by Histology

Histology	CR	Relapse	Median time to Relapse
	No. of Pts. (%)	No. of Pts. (%)	
Small lymphocytic (N=3)	3 (100)	1 (33)	—
F. Large cell (N=4)	3 (100)	3 (75)	6 m
D. Small cleaved cell (N=11)	10 (91)	5 (50)	7 m
D. Mixed (N=1)	1 (100)	—	—
F. Large cell (N=33)	24 (73)	15 (63)	3 m
Lymphoblastic (N=2)	2 (100)		

*CR: Complete response

MOPP. One patient is still alive with NED status, the other patient was lost to follow-up and the rest two of them dies at 3 months and 4 months.

On the other hand, 2 out of 6 patients who refused to receive chemotherapy are still alive without any evidence of the disease.

One patient who had residual lesion after radiotherapy received 2 cycles of chemotherapy and subsequently was found to have fibrosis of mass by biopsy and still lives in a disease-free. Two patients who were disease-free without re-treatment were confirmed to have complete remission in 2 months and in 7 months after radiotherapy respectively.

13 out of 24 failures received chemotherapy and 3 out of 24 cases received combination of chemotherapy and radiotherapy but 5 of them refused further treatment.

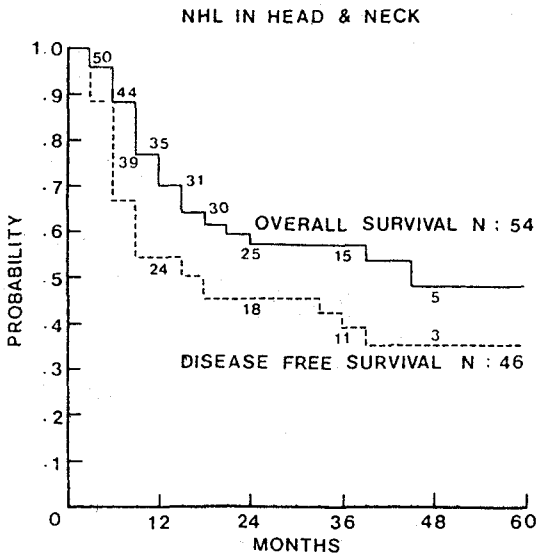

Fig. 2. Actuarial overall and disease free survival

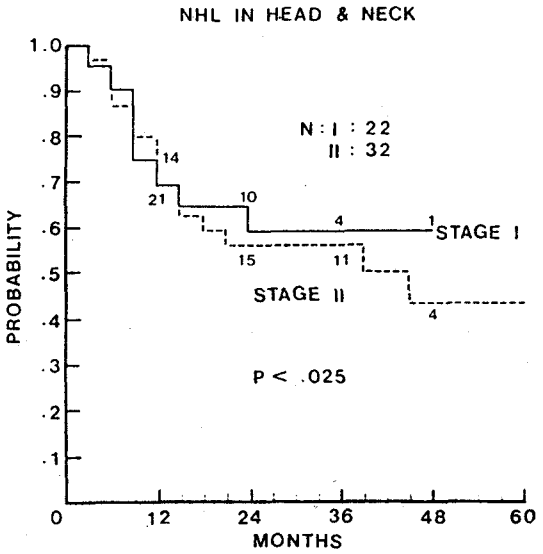

Fig. 3. Actuarial survival by stage

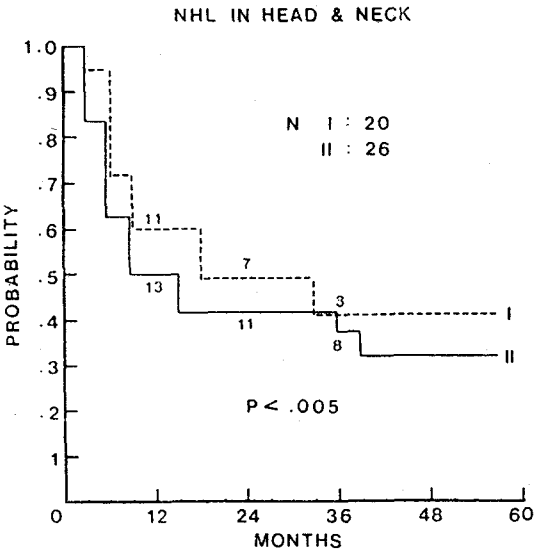

Fig. 4. Disease free survival by stage

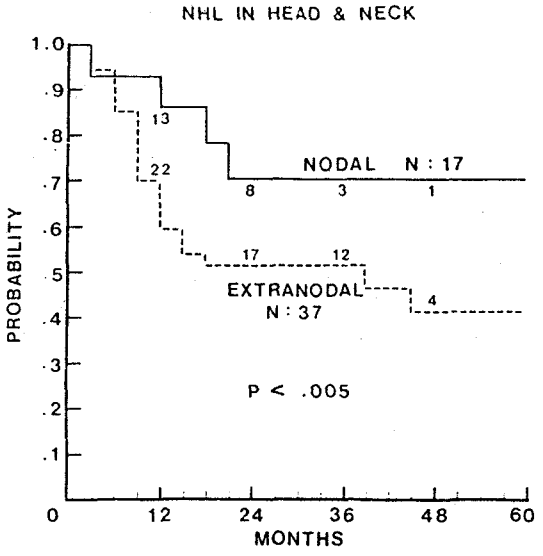

Fig. 5. Actuarial survival by primary site

6 of 24 failures (25%) lived disease free after re-treatment, while 15 of 24 failures (63%) were confirmed to be dead (Table 8).

DISCUSSION

Only 7-37% of the NHL are in the stage I or II at the time of diagnosis and NHL with large original

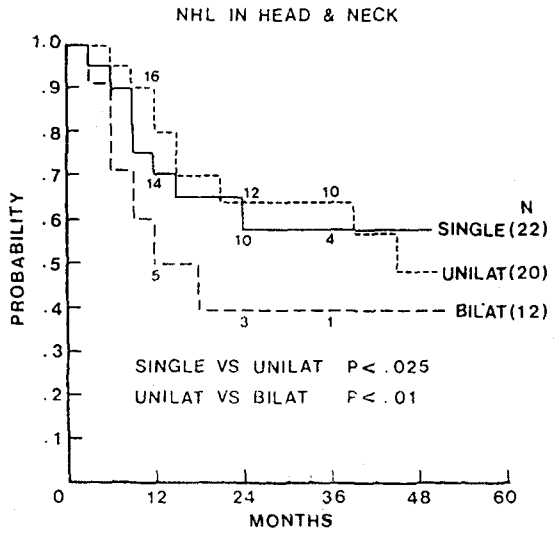

Fig. 6. Survival by uni — and bilateral adenopathy

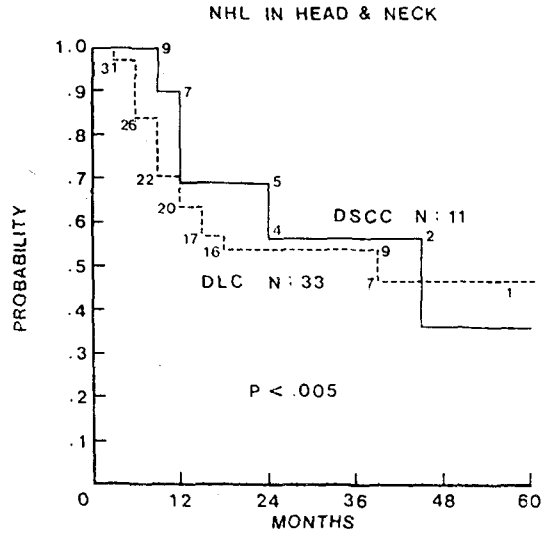

Fig. 8. Actuarial survival: Diffuse large cell vs small cleaved cell.

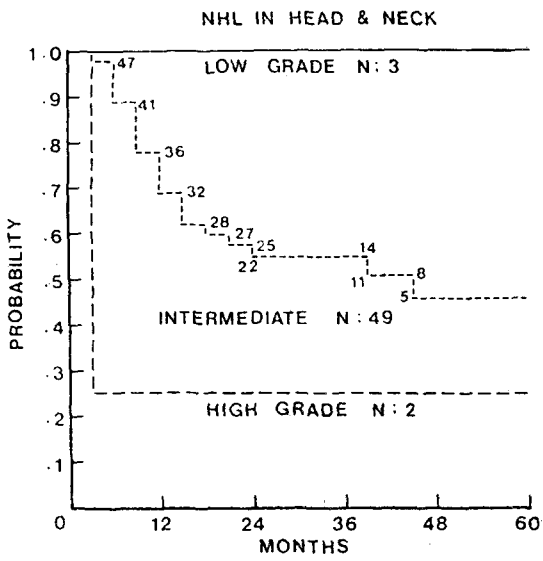

Fig. 7. Actuarial survival by NWF

Table 5. NHL: Sites of Distant Metastasis

Site	No. of Pts. (%)
Abdomen	6 (33)
Inguinal node	5 (28)
Bone marrow	1 (6)
Breast	1 (6)
Brain	1 (6)
Esophagus	1 (6)
Lung	1 (6)
Scalp	1 (6)
Stomach	1 (6)
Total	18 (100)

Table 6. NHL: Time to Relapse (N=24)

Months	No. of Pts.	*Cumulative* Percentage
1	7	29
2	2	38
3	3	50
6	5	71
12	2	79
24	3	92
36	2	100

Median Time to Ralapse: 3.5 month

Table 7. NHL: Tx. for Not Response Group (N=10)

Tx modality	No. of Pts.		Lost & AWD (%)
	NED (%)	Die (%)	
CTx (N=4)	1 (25)	2 (50)	1 (25)
No Tx. (N=6)	2 (33)	4 (67)	
Total	3 (30)	6 (60)	1 (10)

Table 8. NHL: Tx after Relapse (N=24)

Tx. Modality	No. of Pts.			
	NED(%)	Die(%)	AWD(%)	Lost(%)
CTx only (n=13)	5 (38)	6 (46)	1(8)	1 (8)
RTx only (n= 3)	1 (33)	2 (67)	—	—
Ctx+RTx (n= 3)	—	3(100)	—	—
No Tx (n= 5)	—	4 (80)	—	1 (20)
Total	6 (25)	15 (63)	1 (4)	2 (8)

* NED : No Evidence of Disease
AWD : Alive with Disease

tumor size or with involvement of non-contiguous organs have similar natural history to that of advanced NHL over stage III.[16-19]

Extranodal involvement at the time of presentation in NHL is reported to be 25%.[7,20] 66-100% of NHL with extranodal origin are diffuse type and 85% of them are either diffuse large cell type or diffuse small cleaved cell type. NHL progress so rapidly that only a few of them are locally confined at the time of diagnosis, and recurrence rate after the therapy is reported to be 44-51%. Once they recur, they are hard to cure and 75% of the patients die within 15 months after recurrence.[6-9,20-22]

In our study 81% showed complete remission and 19% showed partial remission after the radiotherapy. Of the 10 patients with partial remission, 7 patients had lesions in Waldeyer's ring, 2 patients in nasal cavity, and 1 patient in non-contiguous lymph nodes, i.e., right cervical and epitrochlear nodes. This result is consistent with the study of Brugere et al who claimed that Waldeyer's ring, nasal cavity, and paranasal sinus lesions have less complete remissions after the radiotherapy.[8] Of the 10 patients with partial remission, 9 cases were diffuse large cell type and 1 patient had diffuse small cleaved cell type. Remission rate in diffuse large cell type is lower than diffuse small cleaved cell type even though the former received additional 500-1,000 rad more than the latter bringing up the total dose to 6,000 rad to some patients with diffuse large cell type. But it should be interpreted cautiously since residual mass could not be differentiated from the fibrous scar tissue on palpation.

Failure rate in our study was 55% (24/44 patients) which is a little bit higher than: 44% of Fuks et al,[6] 43% of Mill et al, and 51% of Brugere et al.[8] 15 out of 24 failures were diffuse large cell type, 5 were diffuse small cleaved cell type, 3 were follicular large cell type, and 1 was small lymphocytic type, which means the diffuse and the large cell types have higher failure rate.

Analysis of the failed patients by the sites of origin is as follows; 2 patients (25%) had regional recurrence, 3 patients (37.5%) with distant metastasis, and 3 patients (37.5%) with simultaneous regional recurrence and distant metastasis. Higher proportion of distant metastasis was noted in NHL of extranodal origin as 5 patients (31.5%), 10 patients (63%), and 1 patient (5.5%) respectively.

According to Mill et al, failure rate within the radiation field was 21%, regionalfailure rate outside of the radiation field was 16%, while distant metastasis rate was 63%.[7] Brugere et al noted that the failure rate within the radiation field was 27%, failure in the lymph node was 15%, and extranodal failure was 58%.[8] Therefore the results of these two studies were similar to ours.

79% relapsed within one year and the median time of relapse was 3.5 months for all type. The diffuse large cell type relapsed earlier than other subtypes with the median interval of 3 months. 76% relapsed within 1 year according to Brugere et al,[8] while 65% within 1 year by Jones et al[23] which is similar to the results of our study.

The 2 year survival rate and 2 year disease free survival rate in our study were 57% and 45% respectively. It is difficult to compare directly with the results of other studies in which 5 year survival rates were reported in 38-68%.[7,8,10,24]

2 year survival rates by stage were 59% in stage I and 56% in stage II. Stage I had statistically significant higher survival rate than stage II ($p<0.025$).

2 year disease free survival rates were 49% in stage I and 42% in stage II. Stage I had higher 2 year disease free survival rate than stage II ($p<0.005$). According to Oh et al,[25] there was no difference in survival rate by stages, but stage I had higher survival rates than stage II in the study of Mill et al[7] and Brugere et al.[8]

2 year survival rates by the site of origin were 71% in lymph node origin and 52% in extranodal origin. Therefore survival rate was higher in lymph node origin in our study, while there was no difference in survival rates between them according

to Musshoff et al.[20] Fuller et al reported higher survival rate in the extraodal origin than in the lymph node origin.[9]

There was no statistically significant difference in survival between high and low grade by New Working Formulation probably due to the small sample size. In the intermediate grade, however 2 year survival rate and median survival period were 55.4% and 3.3 years respectively. This is similar to the results of Krueger et al who had 3.5 years in median survival period.[26]

10 of the total 54 patients had fever, night sweat, and weight loss (B symptoms). 7 of these 10 cases with B symptoms showed complete remission while the other 3 patients relapsed. All of these three failures had distant metastasis, therefore B symptoms may suggest the possibility of bone marrow infiltration or distant metastasis which was not found at the time of initial dignosis.

In our study no explorative laparotomy was done for staging, while Toonkel et al emphasized the necessity of explorative lapartomy by obtaining 85% 5-year survival rate for stage I and II determined by thorough work up including explorative laparotomy. On the other hand, Chabner et al reported that appropriate staging does not necessarily require explorative laporatomy.[18]

Unlike Hodgkin's disease, NHL has a tendency to be in an advanced stage at the time of initial diagnosis. As there is no difference in the prognosis betweens the stages III and IV, and the metastatic pattern is unpredictable, the advantage of explorative laparotomy is not emphasized.

Ann Arbor staging classification which was originally designed for Hodgkin's disease is also currently used for NHL. But it might not be ideal to be applied directly to NHL which has higher frequency of extranodal presentation and distant metastasis. Staging for NHL should be reconsidered in the light of the report of Toonkel et al. that large and multiple primary lesions had relatively low regional response rate.[27]

Marfardini reported that 5-year survival rates for the stages I and II NHL treated with radiotherapy alone and combination of radiotherapy and systemic che-motherapy were 55.8% and 82.8% respectively ($p=0.03$), and 5-year disease free survival rates for them were 46.3% and 72.1% respectively ($p<0.005$).[28] Fraser et al reported that 75% of relapsed patients died within 1 months. Therefore the systemic chemotherapy is encouraged in addition to the regional radiotherapy when the patients have diffuse cell type of NHL with the large original lesion, the multiple area of invasion, and the extranodal origin. Further prospective randomized studies should be required.

CONCLUSION

54 cases of NHL in the head and neck region treated with radical radiotherapy during the period of Feb. 1979 to Sept. 1982, were analyzed and the following results were obtained:

1. Complete remission rate of primary lesion was 81% and partial remission rate was 19%.
2. 2-year survival rate and 2-year disease free survival rate were 57% and 45% respectively, and there were statistically significant differences in survival rates with response to stages, sites of origin, bilaterality of lymph node enlargement, and histological subtypes.
3. The overall failure rate was 54.5% (24/44 patients); regional recurrence rate was 29%, distant metastasis rate was 54%, and simultaneous regional recurrence and distant metastasis rate was 17%, and 92% of overall recurrence relapsed within 2 years.
4. When the size of the primary lesion was over 6 cm in diameter or multiple conglomerated, the site of origin was extranodal, and the subtype was diffuse cell type or large cell type, there was a relatively high rate of distant metastasis. Therefore systemic anticancer chemotherapy should be considered in these subgroups after regional radiotherapy.

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=국문초록=

두경부에 국한된 Non-Hodgkin's Lymphoma의 방사선치료 성적

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1979년 2월부터 1982년 9월까지 서울대학교병원 치료방사선과에서 두경부에 국한된 Non-Hodgkin's Lymphoma 환자중 근치적 방사선치료를 받은 54예를 대상으로 다음과 같은 결론을 얻었다.

1. 원발병소의 관해율은 완전관해가 81%, 부분관해가 19%이었다.

2. 2년 생존율 및 무병 생존율은 각각 57%, 45%이었으며 병기별, 발생부위별, 임파절 종대의 양측성 여부, 조직아형에 따라 생존율에 통계학적으로 유의한 차이가 있었다.

3. 재발율은 54.5%(24예/44예)로 국소재발이 29%, 원격전이가 54%, 원격전이와 국소재발이 공존했던 경우가 17%로 92%가 2년이내에 재발하였다.

4. 원발병소의 크기가 6 cm 이상이거나 다발성인 경우, 원발병소가 임파절외 장기 또는 조직아형이 미만성이거나 대세포형인 경우 원격전이율이 높아 국소방사선치료후 전신적 항암요법의 추가치료가 고려되어야 한다.

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