Radiation Therapy Results of the Non-Hodgkin's Lymphoma of the Sinonasal Cavity

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From January 1970 through December 1984, 15 patients with sinonasal Non-Hodgkin's lymphoma combined to the head and neck were treated by external irradiation. 13 patients were stage IE and 2 were stage IIE by Ann Arbor Classification. However, when using TNM system, 7 were locally advanced T3, T4 lesions. All patients had follow up from 3.7 to 16 years with the median follow-up of 8.5 years. The overall actuarial 5-year survival rates were 25%, 28% for IE and 0% for IIE. Total tumor dose varied from 40 to 68 Gy. 100% complete response with a total tumor dose of more than 55 Gy and 73% complete response with less than 55 Gy. When the disease was staged using the TNM (AJC) system, the five-year disease free survival for T1 and T2 patients was 50% as compared with 14% for T3 and T4. Failure rate by stage was 33% (2/6) for T1 and T2, 86% (6/7) for T3 and T4, and 100% (2/2) for IIE. The results suggest that

1. Higher CR could be obtained with a total tumor dose of more than 55 Gy.
2. Use of TNM staging system is as important as Ann arbor in management of sinonasal NHL.
3. The addition of combination chemotherapy should be considered for T3, T4 and IIE the sinonasal Non-Hodgkin's lymphoma although the disease is limited to head and neck.

Key Words: Radiotherapy, Sinonasal cavity, Non-Hodgkin's lymphoma (NHL)

INTRODUCTION

Non-Hodgkin's lymphomas (NHL) involving the nasal cavity and/or the paranasal sinuses are very uncommon and they are usually localized to the head and neck area when discovered intially. Gall and Mallory[1] reported only 2 cases of sinonasal NHL from a series of 618 malignant lymphomas and Eichel et al[2] discovered 33 patients with primary nose and sinus lymphoma seen at the Mayo clinic between 1933 and 1962. Sofferman and Cummings[3] reported 22 cases in which lymphoma had occured in the sinuses of patients who had been seen at the Massachusetts Eye and Ear Infirmary, Boston, between 1946 and 1970. The incidence of lymphoma in relation to other malignant tumors of the nasal cavity and paranasal sinuses is also low representing less than 10%[3]. Radiation therapy had been a well established first line treatment modality for stage I and II NHL of the sinonasal cavity. However, 5 year survival rate for this disease has been widely varied from 50-70%[2~5] to 10%[6].

Disease free survival rate by radiotherapy is quite different depending on the degree of extent of the primary disease even though they are in the same I and II according to Ann Arbor staging system. Therefore, some authors insist that TNM staging system is more important idicator to predict the patient's prognosis. Retrospective analysis of radiation response rate, overall survival rate as well as pattern of failure is reported a total of 15 cases of NHL of the sinonasal vavity treated with external irradiation at the Department of Radiation Oncology, Yonsei University College of Medicine, Yonsei Cancer Center between Jan. 1970 and Dec. 1984.

MATERIALS AND METHODS

Between Jan. 1970 and 1984, the radiotherapy records of 15 patients with NHL of the nasal cavity and/or the paranasal sinuses, clinically confined to the head and neck area were reviewed and retropsectively analysed. Twelve patients were male and 3 female with a male-to-female ratio of 4 to 1. The ages of the patients ranged from 17 to 64 years with a median age of 37 years. A review of 125 patients

who were diagnosed as having NHL of head and neck treated with irradiation at our institute from 1970 to 1984 showed that the most frequently involved site was Waldeyer's ring representing 43 %, and the nasal cavity and/or paranasal sinuses being 12% (15/125 patients) (Table 2). Using the Rappaport system, histopathologic distributions of 15 patients with sinonasal NHL were; diffuse histiocytic 7, diffuse poorly differentiated lymphocytic 4, lymphoblastic 3, and unclassified 1 patient (Table 1). All patients had limited disease according to Ann Arbor staging system; 13 patients were stage I and 2 patients stage II (Table 1). By location 6 patients with disease involving the maxillary antrum were retrospectively staged according to the TNM (AJC) and 9 patients with disease involving nasal cavity according to the M.D. Anderson Hospital T-staging system. The T-staging for 15 patients with sinonasal disease was as follows; T1-6 patients, T2-2 patients, T3-5 patients, and T4-2 patients. Symptoms were usually related to anatomical involvement of the tumor, such as nasal obstruction and epistaxis; or to invasion of adjacent structures such as soft tissue swelling, facial pain, and headache (Table 3). 14 patients were treated with radiation therapy alone and 1 with postoperative radiation therapy after total maxillectomy as a primary treatment modality. Radiation therpy was administered to the involved field where the disease is in all 15 patients. Using either tele-Cobalt 60 or 10 MV Linear Accelerator. The total tumor dose of 40 to 68 Gy in 4-7 wks was given through anterior with or without two lateral wedged fields (Fig. 1, 2). All 15 patients (100%) were followed as of Aug. 1986. follow-up period ranged from 3.7 years to 16 years with a median follow-up period of 8.5 years. Survival rates were calcurated by the life table of Kaplan-Meier method.

Table 1. Patients Characteristics (N=15)

Age	17 – 64 (Median = 37)	
Sex	M : F = 12 : 3	
Pathology		
	DH	7
	DPDL	4
	Lymphoblastic	3
	Unknown	1
Stage	Ann arbor I	13
	II	2
	TNM* $T_1 - T_2$	8
	$T_3 - T_4$	7
Site	Nasal cavity	9
	Maxillary sinus	6

* AJC in maxillary sinus
M.D. Anderson in nasal cavity
DH : Diffuse histiocytic
DPDL : Diffuse poorly differentiated lymphocytic

RESULTS

1. Survival Rate

Overall actuarial 5-year survival rate for the 15 sinonasal NHL was 25%; 23% for stage IE and 0% for stage IIE. (Fig. 3) The 5-year disease free survival rate for patients with stage T1 and T2 disease was 50% (including 2 patients with Ann Arbor IIE stage) and 14% for T3 and T4 disease (Fig. 4).

2. Initial Relapse after Irradiation

The types of relapse of 15 patients with localized

Table 2. Distribution of Localized Non-Hodgkin's Lymphoma of Head and Neck (1970–1984)

Primary site	No. of cases (%)
Nodal	49 (39.2%)
Extranodal	
Waldeyer's ring	
Tonsil	41 (32.8%)
Nasopharynx	9 (7.2%)
Base of tongue	4 (3.2%)
Nasal cavity and PNS	15 (12.0%)
Oropharynx	2 (1.6%)
Salivary gland	2 (1.6%)
Larynx	1 (0.8%)
Thyroid	1 (0.8%)
Orbit	1 (0.8%)
Total	125 (100.0%)

Table 3. Symptoms of Patients with Non-Hodgkin's Lymphoma of the Nasal Cavity and PNS (N=15)

Symptoms	No. of cases (%)
Nasal obstruction	13 (80%)
Soft tissue swelling	6 (40%)
Nasal and cheek pain	3 (20%)
Epistaxis	1 (7%)
Headache	1 (7%)

sinonasal NHL shown in table 4. There were 2 patients failured in the irradiated field, 2 regional lymph node, and 6 dissemination (Table 5, 6, 7). Of 6 patients with stage T1 and T2 (not including 2 patients with IIE disease), 3 had no evidence of disease, one local recurrence, one systemic dissemination, and one unknown death (Table 5). Of 7 patients with stage T3 and T4, 2 had regional lymph node relapse, one primary recurrence as well as systemic dissemination, 3 systemic dissemination, and one unknown death (Table 6). All 2 patients with stage IIE disease had systemic dissemination after treatment (Table 7). The time of relapse in the 10 patients is presented in Fig. 5. All relapses occurred within 24 months after the treatment.

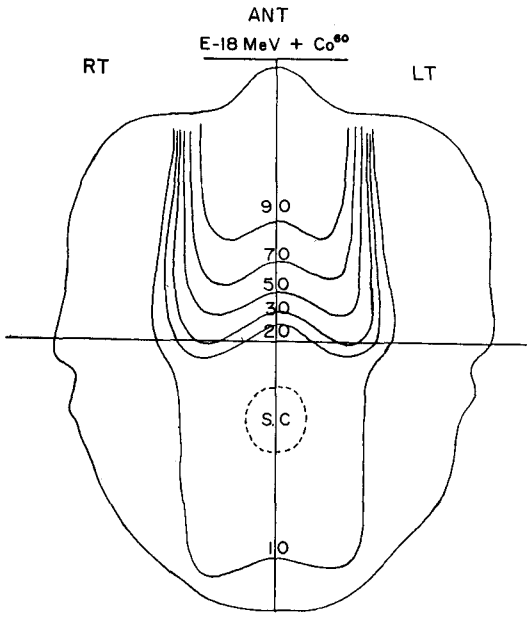

Fig. 1. E-18 MeV : Co-60 = 3 : 2.
Total tumor dose : 4000 – 6000 cGy.

3. Dose-Time Relationship

The relationship between the total tumor dose and the locoregional response is shown in table 8. Good local tumor control was obtained with a total dose ranging from 40 to 70 Gy. All patients had complete response (100%, 4/4) with a dose of more than 55 Gy but 73% had complete response with a dose of less than 55 Gy.

4. Treatment after Relapse

Of 10 patients with disease relpse after irradiation, one received chemotherapy, one chemoradiotherapy, and one radiotherapy for salvage

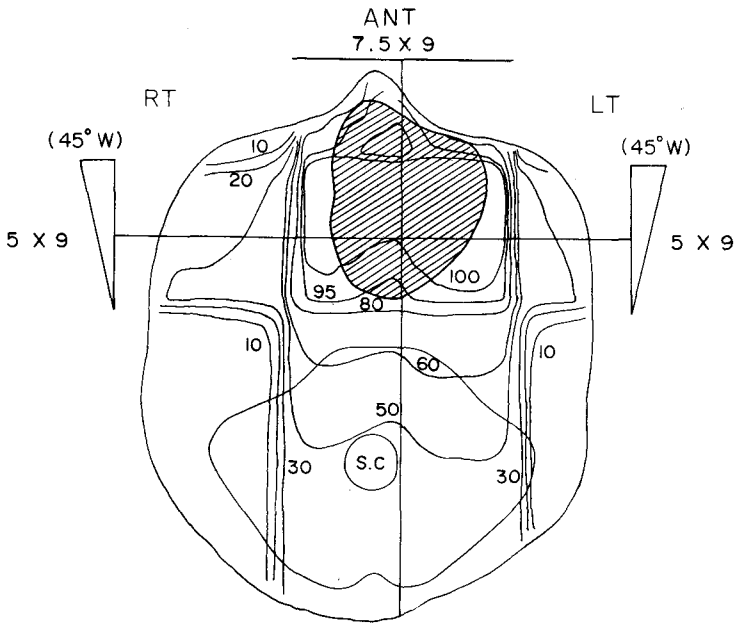

Fig. 2. Isodose curve using 3 portal combination with wedge filter.
ANT : RT : LT = 6 : 1 : 1

treatment. however, none of relapsed patients was salvaged.

DISCUSSION

About one fourth of all NHL reported to be extranodal origin. Malignant lymphomas usually originate in cervical lymph nodes or Waldeyer's ring in the head and neck area. Lymphomas of the nasal cavity and paranasal sinuses are rare tumor[1~3]. In our study sinonasal NHL comprised 12 % of all localized NHL of head and neck origin (Table 2). The incidence of lymphoma in relation to other malignant tumors of the sinonasal cavity is low representing less than 10%[3]. It was 7% in our study (Table 9).

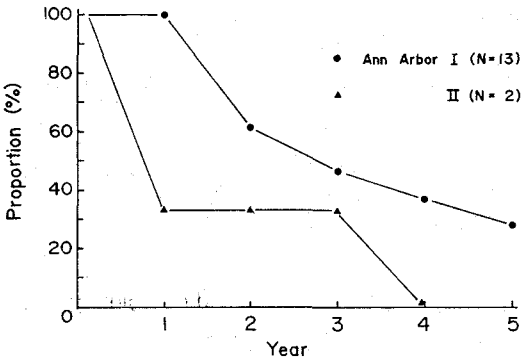

Fig. 3. Actuarial survival rate of stage I vs II.

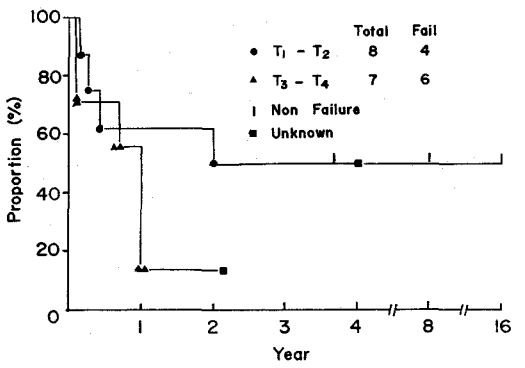

Fig. 4. Disease free survival rate of T_1–T_2 vs T_3–T_4.

Table 4. Initial Treatment Failure Pattern According to the Stage

Stage	No. of cases	Failure site			
		Primary site	Node	Dissemination	Unknown
Ann arbor					
I	13	2	2	4	2
II	2			2	
TNM					
$T_1 - T_2$	8 (2)	1		3 (2)	1
$T_3 - T_4$	7	1	2	3	1

( ) Ann arbor II

Table 5. *Patients of* $T_1 - T_2$ *Non-Hodgkin's Lymphoma of Nasal Cavity and Paranasal Sinus without Node (N=6)*

Case	Age/Sex	Primary site	Pathology	RT dose (cGy)	Initial faliure	Present status	
1	17/M	Maxillary	DH	6080	No	16 years	NED
2*	60/M	Nasal	DPDL	4600	No	9 years	Died
3	37/M	Nasal	DH	4400	Unknown	4 years 1 mo	Died
4	47/F	Nasal	DH	5000	No	3 years 8 mo	NED
5	43/M	Nasal	DPDL	5000	Primary	3 years	DWD
6	64/M	Nasal	DH	4000	Dissemination	2 years	DWD

* Secondary malignancy developed, DH : Diffuse histiocytic, DPDL : Diffuse poorly differentiated lymphocytic
NED : No evidence of disease, DWD : Died with disease

Table 6. Patients of $T_3 - T_4$ Non-Hodgkin's Lymphoma of Nasal Cavity and Paranasal Sinus without Node (N=7)

Case	Age/Sex	Primary site	Pathology	RT dose (cGy)	Initial failure	Present status
1	32/M	Maxillary	DPDL	5000	Dissemination	1 year 6 mo DWD
2	40/M	Maxillary	Unknown	5600	Dissemination	1 year 8 mo DWD
3*	37/F	Maxillary	DPDL	4000	Unknown	2 years 1 mo Died
4**	18/M	Maxillary	DH	5200	Neck node	4 years 10 mo DWD
5	34/M	Nasal	Lymphoblastic	4000	Neck node	1 year 2 mo DWD
6	30/M	Nasal	DH	6800	Dissemination	2 years DWD
7***	46/M	Nasal	Lymphoblastic	6000	Primary and scalp	5 years 8 mo DWD

* Total maxillectomy, ** Salvage chemotherapy, *** Salvage chemotherapy and radiotherapy
DH : Diffuse histiocytic, DPDL : Diffuse poorly differentiated lymphocytic, DWD : Died with disease

Table 7. Patients of Ann Arbor Stage II Non-Hodgkin's Lymphoma of Nasal Cavity and Paranasal Sinus (N=2)

Case	Age/Sex	Primary site	Node	Pathology	RT dose (cGy)	Initial failure	Present status
1	38/M	Maxillary	Subdigastric	DH	5400	Dissemination	3 years 2 mo DWD
2	25/F	Nasal	Submaxillary lower neck	Lymphoblastic	5000	Dissemination	3 mo DWD

DH : Diffuse histiocytic, DWD : Died with disease

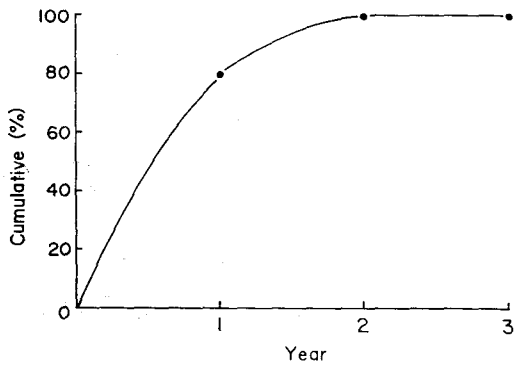

Fig. 5. Cumulative distribution of relapse.

Table 8. Response Rate of Tumor According to Radiation Dose

Dose (cGy)	No. of cases	CR	PR
4000 – 5500	11	8	3
5500 – 7000	4	4	0
Total	15	12	3

The clinical appearance of sinonasal lymphoma may be easily confused with that of an infections, granulomatous, or nonlymphomatous neoplastic processes[7,11]. The physician must be alert to the possibility of lymphoma when persistent symptomatology is refractory to congestant and antibiotic treatment. The clinical manifestation of our 15 NHL of sinonasal cavity were similar to those of other reports[3,7,11] (Table 3).

66-100% of NHL with extranodal origin were diffuse type pathologically and majority were hitiocytic lymphoma[3,6]. The most of reported NHL of sinonasal cavity were diffuse histiocytic lymphoma in Rappaport classification[3,11~13]. Similarly, majority of our cases were diffuse type (Table 1).

The comparison of lymphoma to carcinoma of the nasal cavity and paranasal sinuses also reveals a striking resemblance in the pattern of spread for local disease[3,5,15]. Most of patients with sinonasal lymphoma present with stage I-II disease[7,12]. All our cases were stage I or II disease.

Local irradiation of early extranodal NHL appears to be effective. Some authors[3,5] suggested that sinonasal lymphoma is a potentially radiocurable malignant neoplasm with a survival rate of 50% to 70%. But others[6] reported that dispite good local control with radiotherapy, lymphoma of the paranasal sinuses was associated with a very poor prognosis (5 year survival rate

Table 9. Histopathological Distribution of Malignancies of Nasal Cavity and Paranasal Sinuses

Cell type	No. of cases (%)
Epidermoid	146 (71%)
Undifferentiated	19 (9%)
NHL	15 (7%)
Adenoid cystic	9 (4%)
Neuroblastoma	7 (3%)
Adenocarcinoma	2 (1%)
Mucoepidermoid	2 (1%)
Others	8 (7%)
Total	208 (100%)

(1970 – 1984)

Table 10. Five Year Survival Rate of Non-Hodgkin's Lymphoma of the Nasal Cavity and PNS

Institute	No. of cases	Survival rate (%)
M.D. Anderson (1947 – 1983)	38	56
Stanford (1963 – 1982)	20	12
M.G.H. (1950 – 1984)	29	59
Y.C.C. (1970 – 1984)	15	25

presented 12%). Five year survial rate was relatively poor in our study as compared with that of other institute (Table 10). The radiotherapy approach is divided into two ways, one is the irradiation of only involved field and the other is to treat the primary and prophylactic irradiation to neck nodes. In some reports[3,5,14], prophylactic irradiation of the neck seems to have no place in the treatment of stage I patients with sinonasal lymphoma. Jacobs et al[6] reported that some failures of sinus lymphoma were intracranial relapses, so that they recommended early CNS prophylaxis. Of 13 patients who was not treated with prophylactic irradiation of neck node, 2 patients with stage T3 and T4 had neck node relpase in our study. So prophylactic irradiation of neck node is considered to locally advanced sinonasal NHL. According to Silver et al[15] and Wang[5] recommended RT dose is about 50 Gy in five weeks. In our study the local tumor control was good at doses ranging from 40 to 70 Gy, but 100% complete response was obtained with a dose of more than 55 Gy.

20 to 67 percent of reported patients with localized disease have had a relapse after irradiation[3,4,8,14]. There is a wide range of relapse rates reported for sinonasal lymphoma and most patients who relapsed had distant spread of the disease[2,5,6]. Of 10 failured cases, 6 cases had dissemination, 2 failure of regional lymph node, and 2 in-field failure. In head and neck NHL, 92% of failured patients relapsed within 2 years according to Kim et al[16], similarly all failured patients relasped within 2 years in our study. Mill et al[8] reported that local extension to adjacent extranodal sites did not necessarily impart a poor prognosis in sinonasal NHL. In other hand, Robbins et al[7] suggested that radiotherapy alone was insufficient treatment for advanced local disease and the presence of neck nodes in patients with lymphoma of the nasal cavity and paranasal sinuses likely represents more advanced disease with a high proportion having widespread dissemination. So Robbins et al[7] supported the usefulness of the TNM system to supplement the Ann Arbor method of staging head and neck extranodal lymphomas. In our study, all 2 patients with stage II had dissemination; 4 patients of locally advanced disease (T3 and T4) had dissemination (4/7); but 4 patients of locally early disease (T1 and T2) cured by radiotherapy (4/6) (Table 5, 6, 7). Mikata et al[14] suggested that the histology may be the single most important predicting factor for relapse in patients with sinonasal lymphoma. Others[7] reported that histopathology did not significantly relate to results, since most patients had diffuse large cell lymphoma.

In summary, although total number of patients in this study was too small to elicit meaningful conclusion, we suggest followings for management of sinonasal NHL;

1. Most patients with small local disease (T1 and T2) can be treated with radiotherapy alone and recommended RT dose is 55 Gy or more.
2. Radiotherapy alone was insufficient treatment for advanced local disease.
3. TNM system to supplement the Ann Arbor method of staging is useful.
4. Chemotherapy should be considered in the management of patients with stage II, T3 and T4 disease.

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= 국문초록 =

비강 및 부비동 Non-Hodgkin's Lymphoma의 방사선 치료

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류 삼 열

1970년부터 1980년까지 연세대학교 치료방사선과에서 방사선치료 받은 비강 및 부비동에 발생한 NHL 환자 15예를 대상으로 후향성 분석을 하여 다음과 같은 결과를 얻었다.

1. 병기분포는 13예가 IE 2예가 IIE였고 TNM병기에 따르면 7예가 국소병변이 진행된 T_3, T_4 환자였다.

2. Overall 5년 생존율을 25%, IE는 28%, IIE는 0%였다.

3. 병기별 치료실패율은 T_1, T_2는 33% (2/6), T_3, T_4는 86% (6/7), IIE에서는 100% (2/2)였다.

4. 방사선 조사량이 55 Gy 이상인 경우 100%의 완전 관해율을 보였으며 55 Gy이하인 경우 73%의 완전 관해율을 보였다.

5. 비강 및 부비동의 NHL의 Ann Arbor 병기 분류와 함께 TNM 병기도 예후에 중요한 요인이 될 것 같다.

6. 국소병변이 진행된 병기 T_3, T_4와 IIE 환자에서는 화학요법제의 병용치료가 필요할 것 같다.