

Nasopharyngeal Carcinoma: Correlations with Prognostic Factors and Survival

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One hundred and ten patients with carcinoma of the nasopharynx were treated by radiation therapy in Department of Therapeutic Radiology, Seoul National University Hospital between 1979 and 1985.

Among these, one hundred and five patients were treated with curative intent and 5 patients with palliative aim. Excluding 16 patients who did not receive a full course of radiation therapy, the remaining 89 patients were reviewed for this analysis. Minimum follow-up period of survivors was 36 months.

Forty-three percent of the patients had T4 primary lesions and 72% had stage IV disease. The histology was squamous cell carcinoma in 46% of the patients, undifferentiated carcinoma in 49%, and lymphoepithelioma in 5%.

Total radiation dose to the primary site averaged 6,500 cGY for T1, T2 lesions and 7,500 cGY for T3, T4 lesions. Neck node were given boost treatment to a maximum 7,500 cGY depending on the extent of disease.

Early primary lesion (T1, T2) and neck nodes were successfully controlled in most cases when dose of greater than 6,500cGY was delivered. Forty two patients (47%) had recurred, 16 of whom (38%) recurred at the primary site and 24 (57%) developed distant metastases. Of these, 9 patients received re-irradiation with or without chemotherapy and local control was obtained in 2 patients (22%). Actuarial overall survival and disease-free survival rate was 42% and 38% at 5 years.

T-stage and histologic subtype were not correlated with survival.

However, N-stage was related to survival significantly ($p=0.043$).

Key Words: Nasopharyngeal Carcinoma, Prognostic factors, Survival

INTRODUCTION

In nasopharyngeal carcinoma, the inaccessibility of the nasopharynx, the proximity to the base of skull and cranial nerves, and the widespread lymphatic involvement obviated surgery as part of multimodality treatment. Therefore, nasopharyngeal carcinoma has been treated exclusively by radiation therapy.

For the past decades, radiation therapy has been changed to the sophisticated method, delivering higher dose of radiation therapy^{1,2}, the use of wide radiation field including the elective irradiation of the whole neck^{4,5}.

With the improved technique, survival of the nasopharyngeal carcinoma has shown steadily improved. However, the overall survival of the nasopharyngeal carcinoma ranged from 30% to 57%.

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In nasopharyngeal carcinoma, a high incidence of local failure remains the major cause of death and, unlike other head and neck cancers⁹, hematogenous metastasis in advanced stage continue to be a significant problem, with an overall incidence of 25% in most series^{2,5-8}.

In the current articles^{10,11}, the trial of adjuvant chemotherapy to radiation therapy has become popular to reduce the incidence of relapse rate. But systemic chemotherapy has not yet found an established role in nasopharyngeal carcinoma^{11,12}.

The following retrospective study was undertaken to evaluate the efficacy of external radiation therapy on the survival and local control of nasopharyngeal carcinoma.

MATERIALS AND METHODS

Between February 1979 and May 1985, 110 patients with carcinoma of the nasopharynx were treated in Department of Therapeutic Radiology,

Seoul National University Hospital. Twenty one patients were excluded from this study because five patients presented a distant metastasis at the time of treatment and 16 patients did not complete the full course of radiation therapy. Follow-up range of survivors was 36 to 98 months.

Age of the patients ranged from 16 to 74 years (median 47 years) and male to female ratio was 2.4:1. The histology was undifferentiated carcinoma in 44 patients (49%), squamous cell carcinoma in 41 (46%), and lymphoepithelioma in 4 (5%) (Table 1). Two most frequent initial presenting symptoms were cervical mass (72%) and nasal obstruction (38%) (Table 2).

Mean interval between initial symptoms and diagnosis was 5 months. All patients were clinically evaluated by head and neck surgeon and radiation therapist at the time of diagnosis. CT scan of nasopharynx was performed prior to treatment and every 3-6 months after completion of treatment. All patients were staged according to the American Joint Committee staging system using clinical and radiologic criteria. Twenty-five patients (28.1%) had T3 and 38 (42.7%) had T4 disease. Cervical lymph node metastasis was present in 64 patients (72.0%). Stage I, II (T1-2 No) comprised only 4.5% (Table 3).

All patients were treated with a Co-60 teletherapy unit or 10MV X-ray produced by Clinac-18 linear accelerator. The nasopharynx, the base of skull and the upper part of the neck were irradiated by two lateral, shaped, parallel opposing por-

Table 1. Patient Characteristics (N=89)

Characteristics	No. of pts.	%
Sex		
Male	63	70.8
Female	26	29.2
Age (years)		
range	16-74	
median	47	
Histology		
squamous ca.	41	46.1
undiff. ca.	44	49.4
lymphoepithelioma	4	4.5
Stage		
I	1	1.1
II	3	3.4
III	21	23.6
IV	64	71.9

tals.

The dose to the primary site was 6,500-7,000 cGy for T1, T2 lesions and 7,000-7,500 cGy for T3, T4 lesions, delivered in daily fractions of 180 to 200 cGy, treating 5 days per week. The posterior and inferior limits of the lateral ports were reduced when a dose of 4,500 cGy was reached in order to exclude the spinal cord. The dose to the lower neck was 4,500 cGy using tangential Co-60 field with midline shielding and the palpable nodes were given boost treatment with 9-12 MeV electron beam.

All patients continued to be examined by endoscopy and physical examination every 2 months during the first 2 years and at 4-6 month interval thereafter. Survival was calculated from the start of radiation therapy to the date of death or the most recent follow-up date if the patient alive. The survival curves were plotted using life table method.

RESULTS

Survival

The 5 year actuarial survival for all 89 patients was 41.8% (Fig. 1). Lymphoepithelioma appears to

Table 2. Frequency of Clinical Presenting Symptoms

Symptoms	Initial Sx.	Sx. at Dx.
	No. of pts. (%)	No. of pts. (%)
Cervical mass	36 (40.5)	64 (72.0)
Nasal obstruction	30 (33.7)	34 (38.2)
Ear fullness	15 (16.9)	17 (19.1)
Epistaxis	11 (12.4)	14 (15.7)
Hearing difficulty	9 (10.1)	16 (17.9)
Pain	8 (8.9)	14 (15.7)
Cranial N. involvement	5 (5.6)	27 (30.3)
Otorrhea	2 (2.2)	2 (2.2)

Table 3. T and N Status of Disease at Presentation

	T				Total No. of pts (%)
	N0	N1	N2	N3	
T1	1	1	3	1	6 (6.7)
T2	3	4	5	8	20 (22.5)
T3	9	7	4	5	25 (28.1)
T4	12	3	8	15	38 (42.7)
Total	25 (28.1)	15 (16.8)	20 (22.5)	29 (32.6)	89 (100)

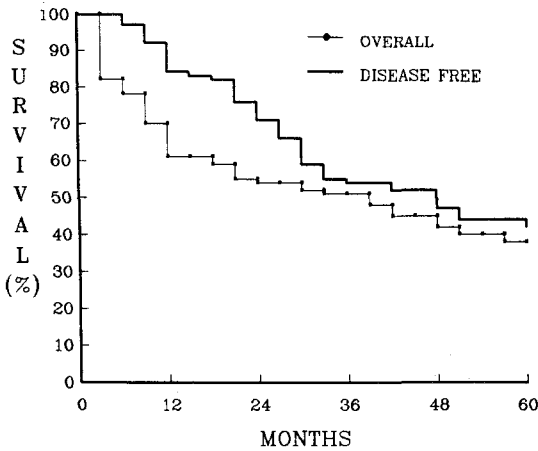


Fig. 1. Overall and disease-free survival (N=89).

have the best prognosis. The 5 year survival rate for lymphoepithelioma was 66.7% as compared to undifferentiated carcinoma with 42.3% and squamous cell carcinoma with 25.3%. But there was not statistically significant ($p=0.762$). The 5 year survival rates for T1, T2, T3 and T4 lesions were 50%, 35%, 54% and 33%, respectively and the disease free survival rate were 50%, 40%, 43% and 31%, respectively (Fig. 2). No correlation between T-stage and survival was found ($p=0.34$). The N-stage was related to survival. Those patients with N0 had a 5 year survival of 65% as compared to those with N1, N2, and N3, being 44%, 40% and 21%, respectively ($p=0.043$) (Fig. 3). Bilateral cervical lymph node metastasis was related to poorer prognosis and this was related to higher incidence of distant metastasis. The best survival

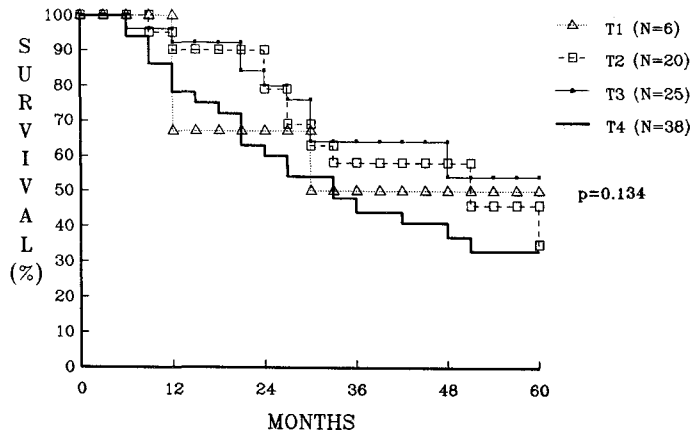


Fig. 2. Survival by T-stage.

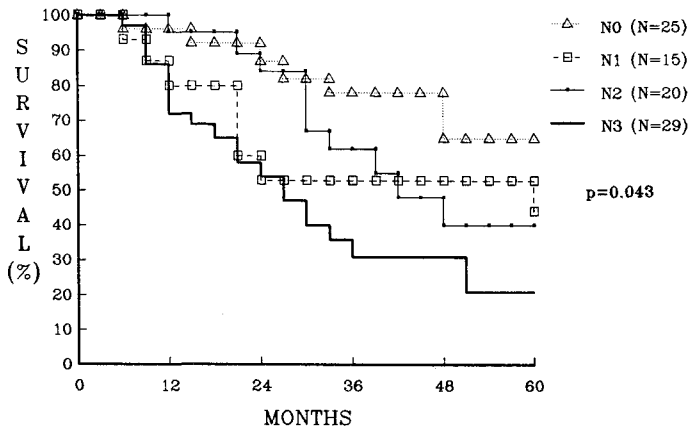


Fig. 3. Survival by N-stage.

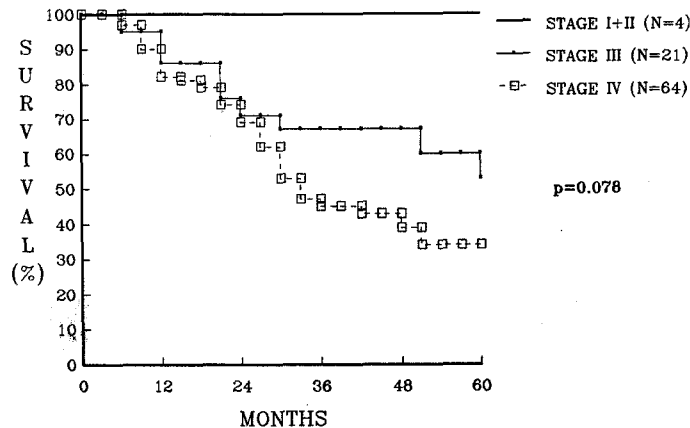


Fig. 4. Survival by stage.

rates were observed in T1N0 and T2N0, being 100%. The 5 year survival rates for stage III and stage IV were 53% and 34.3% (Fig. 4).

Relapses

Of 42 patients (47%) who had relapsed, 17 patients (40.1%) were failures at the primary site with or without cervical lymph node metastases and/or distant metastases. Regional recurrence alone and distant metastases alone were 2.4% and 57.1%, respectively (Table 4).

Fifty percent of primary relapse and 85% of distant metastasis occurred within 2 years of follow-up. The median survival after relapses was 14 months, ranging from 2 months to 76 months. Local recurrence rates by T-stage were 15%, 23%, 29% for T2, T3 and T4, respectively. None of the T1 lesions recurred at the primary site. The common site of distant metastasis were bone, lung and liver with a decreasing order of frequency. The distant metastasis rate for No, N1, N2 and N3 were 8.0%, 33.3%, 35.0% and 41.4%, respectively. The distant metastasis rate for N3b was 45.8%. However, distant metastasis rate was not correlated with T stage; for T1, T2, T3 and T4 being 33.3%, 30%, 32% and 26.3% respectively. A higher incidence of distant metastases were observed in undifferentiated carcinomas (34%) in comparison with squamous cell carcinoma (27%).

Local Disease Control

The response of the primary lesion and the cervical lymph node metastasis with radiation therapy were assessed at 1 to 3 month follow-up after the completion of treatment.

Table 4. Local Control of the Primary Sites

Stage	No. controlled/ No. treated	%
T1	6/ 6	100
T2	20/20	100
T3	22/25	88.0
T4	28/28	73.7
Total	76/89	85.4

Table 5. Control of Neck Node Disease

Stage	No. controlled/ No. treated	%
N1	15/15	100
N2	18/20	90
N3	24/29	82.8
Total	57/64	89.1

The overall control rate for T lesions was 85.4%. Local control rate for T1, T2, T3 and T4 lesions were 100%, 100%, 88.5% and 73.0%, respectively. (Table 4). 6500-7000 cGy was thought to be sufficient dose to control the early lesions such as T1 and T2.

The overall control rate of regional lymph node was 89.1%. The size of lymph node influenced the control rate. Lymph node smaller than 3 cm can be controlled easily by radiation therapy, but lymph node larger than 3 cm showed a lower control rate (Table 5).

The best survival was found only in patients

who obtained a complete clearance of disease after radiation therapy. The 5 year survival in complete responders was 48% compared with 10% in partial responders and no responders.

Thus, the status of complete response of loco-regional disease after completion of radiation therapy is of paramount important in predicting survival and chance of remaining relapse-free.

Retreatment of Recurrence

Of 18 patients who had local and/or regional recurrences, six patients were retreated with radiation therapy, 3 patients with radiation therapy plus chemotherapy, one patient with chemotherapy alone and the remaining 8 patients were followed without treatment (Table 7).

Radiation portal was kept as small as possible encompassing the known disease with a minimal

margin. Generally it was 6 cm x 6 cm. Parallel opposed lateral fields or anterior-bilateral 3 fields were employed delivering 2,000-4,000 cGy, 200 cGy per day, five days per week using 10MV X-ray.

The chemotherapeutic regimen consisted of bleomycin, vincristine, mitomycin-C and cisplatin

Table 6. Pattern of Failures (N = 42)

Sites	No. of pts. (%)
Local recurrence only	10 (23.8)
Locoregional recurrence	5 (11.9)
Regional recurrence only	1 (2.4)
Locoregional recurrence and distant metastasis	2 (4.7)
Distant meatstasis only	24 (57.1)

Table 7. Prognostic Factors

Factor	P value	5-year survival rates (%)			
		T1	T2	T3	T4
T-stage	0.134	50.0	34.8	53.8	33.2
N-stage	0.043	N0 65.3	N1 44.4	N2 40.3	N3 20.8
Stage	0.078	I,II 100.0	III 53.0	IV 34.3	
Histology	0.762	Squamous ca. 35.3	Undiff. ca. 42.8	Lymphoepithelioma 66.7	

Table 8. Local Control and Survival According to Treatment Modality for the First Recurrence

	No. of pts.	Local control (%)	Follow-up	
			Mos. from recur.	
External RT alone	6	1/ 6 (16.7%)	15	Dead
			51	Dead#
			6+	AWD*
			14+	AWD
			3	Dead
RT + Chemotherapy	3	1/ 2 (33.3%)	17	Dead
			32	Dead
			76+	NED**
Chemotherapy alone	1	0/ 1 (0)	23	Dead
			14	Dead
Total	10	2/10 (20%)		

died of stomach cancer with controlled nasopharyngeal lesion

* AWD = alive with disease

** NED = no evidence of disease

(BOMP), or 5-FU and cisplatin (FP) and administered until tumor progress was evident.

Of six patients who received radiation therapy alone, one patient was followed without disease 51 months after retreatment but died of secondary stomach cancer. Two patients are still alive with no evidence of disease at 6 months and 14 months of follow-up. The remaining 3 patients died 3, 15, and 17 months after retreatment.

Among 3 patients who received radiation and chemotherapy, one patient is still alive 6 years after retreatment. However he had brain necrosis at 56 months after retreatment, which was managed by surgical intervention. The other patients died at 23 months and 32 months of follow-up. All patients who received no further treatments died within 11 months after recurrence.

DISCUSSION

Nasopharyngeal carcinoma is relatively uncommon, representing fewer than 1% of malignancies in Caucasian populations^{13,14}, however the incidence of disease in Southern China is extremely high^{14,15}. Recent epidemiologic and experimental data^{14,15,16,17} suggest that three factors are involved—the Epstein-Barr virus, a genetically determined HLA antigens¹⁸ and environmental factors¹⁹ which may vary from one population group to another. Another interesting factor is the association with elevated titers of antibody to Epstein-Barr virus²⁰. Recently this association has been refined to the point that elevated titers of the highly specific EA-IgG antibody has screening value in high risk populations²¹. In view of its anatomic location, diagnosis of Nasopharyngeal carcinoma is rarely made early and it is quite common for patients to present with disease outside the nasopharynx. Because of the surgical unresectability, treatment has been limited only to radiation therapy. Occasionally, neck dissection may be indicated for persistent lymphadenopathy, if the primary tumor is controlled, and distant metastases are absent. Approximately 80% to 90% of patients develop lymphadenopathy and it is present in about 60% at the time of diagnosis⁵.

Cervical lymph node metastases at presentation was in 64/89 patients (72%). Of those, 28/89 (33%) had bilateral cervical lymph node metastases. Fully one quarter of patients will have the base of skull involvement on presentation, half of them with cranial nerve involvement²². In recent series^{23,24}, 15%-26% of nasopharyngeal car-

cinoma has cranial nerve involvement.

Some series^{7,23,24,25} reported that cranial nerve and base of skull bone involvement has influenced tumor control and survival. Cranial nerve involvement was present in 27/89 patients (27%). The fifth cranial nerve was most frequently impaired, followed by the sixth cranial nerve. Survival rates for cranial nerve involvement was 36% at 5 years compared with 43% for bone involvement. Cranial nerve and base of skull bone involvement was not significantly associated with decreased survival. ($P=0.359$) No correlation between T-stage and survival was observed. 5 year survival for T1 was 50% while average survival for T2 through T4 was 33% to 35%. This findings reflect the poor correlation between T-stage and the incidence of cervical lymph node metastases. 83% of T1 lesions had cervical lymph node metastases at presentation. Although T-stage was not related to survival, N-stage did influence survival rate. Survival decreased as cervical lymph node metastases progressed from upper to lower cervical lymph nodes²³. N3 lesions had a distant failure rate of 41.4% compared with 8% for N0 lesions. Many of the patients with lymph node metastases of the lower thirds of neck or with bilateral cervical lymph node metastases may have subclinical extension to the mediastinum or distant metastases which is not detectable by current diagnostic methods. Survival rates in these patients was 20.8% compared with 65.3% for N0 patients. Nodal control in itself was not a major factor problem as even large neck nodes, tended to respond well to radiation therapy. Local control rates for N3 lesions, was 83% and even for N3 lesions only 5/29 patients (17%) showed an isolated lymph node recurrence. 5 year survival for stage I, II was 100% while survival for stage III and IV was 53% and 34.3%, respectively. No correlation between the various histologic types and survival was observed. Five year survival for lymphoepithelioma, undifferentiated carcinoma was 35.3%, 42.8% and 66.7%, respectively ($P=0.762$). Some series^{5,6,26} report a better prognosis for lymphoepitheliomas and undifferentiated carcinomas than for the squamous cell carcinoma but this is by no means uniformly accepted. Not infrequently, in contrast to other head and neck cancers, locally recurrent carcinoma of the nasopharynx could be salvaged by aggressive retreatment^{27,28}. Several techniques has been used, including brachytherapy, the use of a mould or external irradiation or both modalities.

Ten patients with locally recurrent carcinomas

retreated with external irradiation, two patients (20 %) survived more than 4 years with no evidence of disease. However, complications in these patients were inevitable, consisting of temporal lobe necrosis, hypopituitarism and trismus. Previous experience with chemotherapy in treatment of nasopharyngeal carcinomas is scant, with reports generally being parts of larger head and neck studies of squamous cell carcinoma. Several non-randomized studies^{11,29)} reported that the addition of a short course of chemotherapy with radiation therapy in nasopharyngeal carcinomas improved survival rates. Several studies of platinum-containing regimens have shown initial promising results, yet, no long-term results exist^{11,30~34)}. Effort to improve the treatment results must be directed towards better primary tumor control which mean the use of intracavitary therapy as part of planned initial treatment. Concomitant use of a radiosensitising agents such as 5-FU and/or cis-platinum might be benefit but still need to be investigated in randomized trials

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= 국문초록 =

비인강암의 예후인자가 생존율에 미치는 영향

서울대학교 의과대학 치료방사선과학교실

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김 종 선

1979년부터 1985년까지 서울대학교병원 치료방사선과에서 비인강암으로 확진되어 방사선치료를 시행한 총 환자는 110명이었다. 이중 진단시 원격전이된 5명과, 근치 방사선량을 받지 못한 16명을 제외한 89명의 치료성적을 분석하였다.

생존 환자의 최소 추적기간은 36개월이었다. 전체 환자의 43%가 T4 병변, 72%가 제 4 병기이었으며, 편평상피암이 40%, 미분화암이 47%이었고 임파상피암은 5%이었다. T1, T2의 초기병변과 경부 임피절 전이는 6,500 cGY의 선량으로 대부분이 근치되었다. 추적기간중 재발된 환자는 42명 (47%)으로, 이중 16명 (38%)은 국소재발, 24명 (57%)은 원격전이를 일으켰다. 국소재발된 예중 9명에게 재치료를 시행하여 이중 2명에서 장기 생존이 관찰되고 있다. 전체 환자의 5년 생존율 42%, 무병생존율은 38%이었다.

T-병기와 조직학적 아형은 생존율에 무관하나, N-병기는 생존율에 유의한 상관관계가 있음이 증명되었다.