

Radiation Therapy of Nasopharyngeal Carcinoma KCCH Experience (1964~1984)

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Total of 154 patients of pathologically proven and previously untreated nasopharyngeal carcinoma who were treated in the Department of Therapeutic Radiology, Korea Cancer Center Hospital during the period from 1964 to 1984 were analyzed. Minimal follow-up period of survivors was 3 years. Thirteen percent of the patients had T₄ primary lesions and 65% had stage IV disease. Total radiation dose to the primary site was 1550~1750 ret in 82 and above 1750 ret in 72 patients. Local control was obtained in 79% of patients. Significant prognostic factors for the survival were tumor dose (above vs. below 1750 ret), age (below vs. above 30 years), stage (AJCC I-III vs. IV), T stage (T₁ vs. T₂₋₄), and N stage (NO vs. N⁺).

Key Words: Nasopharyngeal carcinoma

INTRODUCTION

Carcinoma of the nasopharynx is not an uncommon malignancy and remains most important disease in the management of cancer in Korea. Because of its anatomic location, the primary site is usually not discovered until it is either locally advanced spread or metastasized to the cervical lymph nodes. For the past few decades, radiation therapy has been essential modality of treatment and the results have been steadily improving with the better understanding of the nature of the disease and improvement of radiation therapy machine and technique¹⁻⁶. We analyzed our clinical experiences of past 20 years and tried to find out the optimal treatment method and the prognostic factors which may influence the treatment outcome of the disease.

MATERIALS AND METHODS

We analyzed 154 patients of pathologically proven and previously untreated nasopharyngeal carcinoma who were treated with radiation therapy alone with curative intent in Department of Therapeutic Radiology, Korea Cancer Center Hospital between 1964 and 1984. Minimal follow-up period of survivors was 3 years.

Patients were in the range of the second decade to seventh decade with the mean age of 45 years and male to female ratio was 2.9 : 1. Squamous cell

carcinoma was the most common histologic type (Table 1). All patients were clinically evaluated by head and neck surgeon and radiation therapist at the time of diagnosis and were staged according to the American Joint Committee on Cancer staging system (1983). Seventy-four patients (48%) had T₃ and 20(13%) had T₄ primary diseases. Cervical lymph node metastases were present in 116 patients (75%) (Table 2).

All patients were treated with Co-60 teletherapy units. The nasopharynx, the base of skull and the upper part of neck was irradiated by two lateral parallel opposing portals and the lower neck was

Table 1. Patient Characteristics

		No. of patients	Percent
Sex	male	115	75
	female	39	45
Age (mean)		45 years	
Histology			
squamous cell ca.		92	60
undifferentiated ca.		35	23
lymphoepithelioma		24	15
adenocarcinoma		3	2
Stage	I	7	5
	II	4	3
	III	42	27
	IV	101	65

Table 2. Distribution of T and N Stages

	N0	N1	N2	N4	Total (%)
T1	7	6	3	7	23(15)
T2	4	3	7	23	37(24)
T3	21	12	12	29	74(48)
T4	6	4	2	8	20(13)
Total	38(25)	25(16)	24(16)	67(44)	154

treated with anterior one port. The dose to the primary site was 5000-7500 cGy, delivered in daily fractions of 180~200 cGy, 5 days per week. The posterior and inferior limits of lateral ports were reduced at 4500 cGy in order to exclude the spinal cord. The dose to the lower neck was 4500 cGy at 3 cm depth. Eighty-two patients were treated every other day with a dose of 300 cGy per fraction between 1978 through 1980. The majority of patients were treated with involved fields and only 14 patients (9%) were received elective lower neck irradiation. Tumor response was based on the physical examination, endoscopic and radiologic findings at 1 to 3 month after the end of radiation therapy. Survival time was measured from the start of radiation therapy until death or the patient alive. Survival curves were plotted using life table method.

RESULTS

1. Survival

Survival was analyzed according to various factors; sex, age, histology, T stage, nodal presentation, stage, and tumor dose. To begin with, we performed survival analysis according to tumor dose (ret) calculated by Ellis' formula and analyzed distribution of patients by tumor dose within the various factors to rule out the possible influence of tumor dose to survival of each factor. Within the factors compared, patient distribution by tumor dose was relatively even (Table 3). Five-year survival rate was 25.2% in male and 32.9% in female, but it was not statistically significant. Younger age group below 30 year-old (24 patients) had a better survival rate (44.5%) compared with the older group (15.7%) with a statistical significance ($p < .05$) (Fig. 1). Histologic type did not influence the survival except one type, adenocarcinoma, being 0% of 5-year survival rate compared with other types, being 23.4%, 27.2% and 23.8% for

Table 3. TN Stage Distribution by Tumor Dose

	<1750ret	> 1750ret
T1	8	15
T2	24	13
T3	41	33
T4	9	11
N0	23	15
N+	59	47

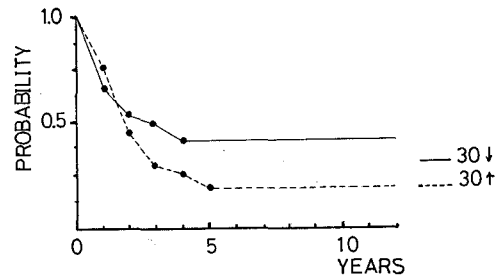


Fig. 1. Actuarial survival by age.

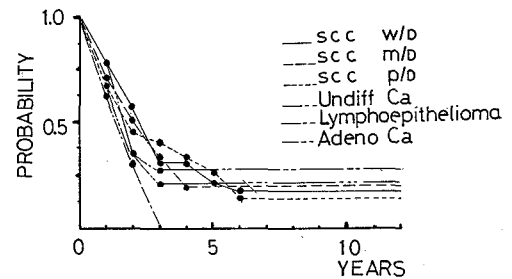


Fig. 2. Actuarial survival by histology.

squamous cell carcinoma, undifferentiated carcinoma and lymphoepithelioma, respectively (Fig. 2). Survival rates at 5 year according to T stage were 50.8%, 23.8%, 19.9% and 21.4% for T₁, T₂, T₃ and T₄ disease, respectively, and T₁ showed better survival with statistical significance compared with more advanced primary disease (T₂~T₄) ($p < .05$) (Fig. 3). Presence or absence of lymph node metastases showed a significant survival difference, being 23.6% vs. 36.8% ($p < .05$) (Fig. 4). As a matter of course, survival difference was observed according to stage, being 43.2% and 16.6% for stage I-III and stage IV, respectively ($p < .05$) (Fig. 5). We divided patients into two groups received doses above or below 1750 ret (equivalent to 6000 cGy/30 fractions/42 calendar days), which was

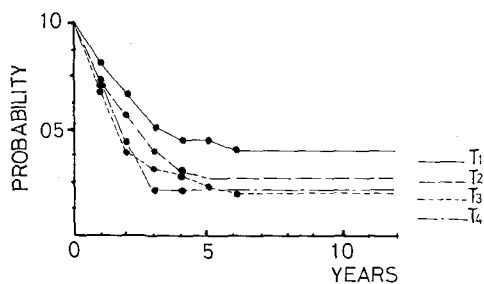


Fig. 3. Actuarial survival by T-stage.

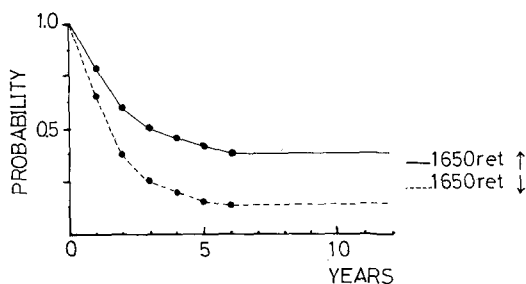


Fig. 6. Actuarial survival by tumor doses (NSD).

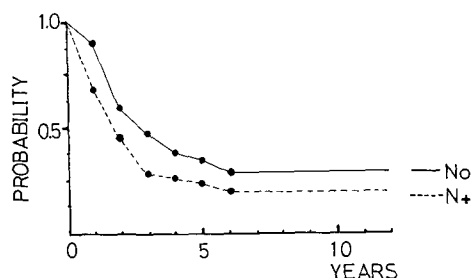


Fig. 4. Actuarial survival by Nodal status.

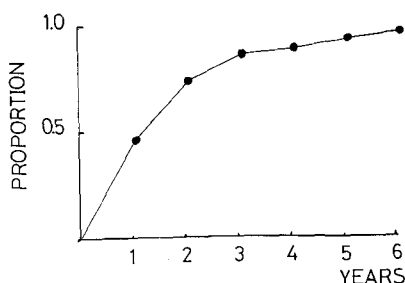


Fig. 7. Cumulative treatment failure.

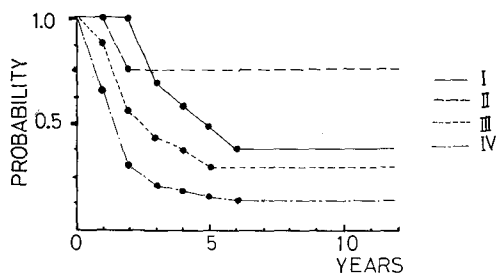


Fig. 5. Actuarial survival by stage.

Table 4. 5-year Actuarial Survival by Tumor Dose

	<1750ret	> 1750ret
T1	50.0%	51.1%
T2	14.0%	43.6%
T3	4.8%	27.5%
T4	0	33.0%
N0	28.7%	54.7%
N+	3.7%	33.2%

considered as a minimum dose to control the disease. A significant difference was observed between the two groups ($p < .001$) (Fig. 6). Although

Table 5. Significant Prognostic Factors

Tumor dose (above vs. below 1750 ret)	$p < .001$
Age (below vs. above 30 years)	$p < .05$
T stage (T1 vs. T2-4)	$p < .05$
N stage (N0 vs. N+)	$p < .05$
Stage (I-III vs. IV)	$p < .05$

it was not observed in T₁ disease, the difference increased as the primary disease status advanced and in the presence of lymph node metastases (Table 4,5).

2. Local Disease Control

Local control was obtained in 122 patients totally and overall local control rate was 79.2%. Also, the difference of local control rate was observed (74% vs. 85%) with the dose increment (below or above 1750 ret).

3. Recurrence

During follow-up 73 patients got recurrences; local recurrences alone in 56 patients, distant metastases alone in 12, combined local and distant recurrences in 5. Forty-six percent of local recurrence was observed during the first year of follow-

Table 6. Failure Pattern by Tumor Dose

	<1750ret	> 1750ret	Total
Local recurrence only	30	26	56
Distant metastasis only	8	4	12
Combined	4	1	5
Total	42/61 (68%)	31/61 (51%)	73/122 (60%)

up and 75% of distant metastasis was observed during the second year. Totally 75% of recurrence was observed during the second year of follow-up (Fig. 7). The most common distant metastatic site was bone (12 patients), followed by lung and liver. The higher failure rate was observed in the lower dose group (68% vs. 51%) (Table 6).

DISCUSSION

Nasopharyngeal carcinoma is an uncommon malignancy in the western world, but it remains one of the leading problems of cancer management in southeast Asia⁷⁻¹⁰. Nasopharyngeal carcinoma generally occurs during the fifth decade and male is predominant^{8,11,12}. The histopathological classification has been controversial. Since the first description by Schmincke, lymphoepithelioma (so-called schmincke tumor) has been considered a pathological and clinical enigma¹³⁻¹⁵. Percentage of lymphoepithelioma had been reported to be 20~25%¹⁶. Because of this proximity to the base of the skull and the high concentration of lymphatic supply in the nasopharynx, nasopharyngeal carcinoma tend to spread quickly to regional lymph nodes¹². Cranial nerve involvement has been reported in 20~30% of patients at diagnosis^{5,17,18} and a high rate (70~80%) of cervical lymphadenopathy is well established^{4-6,19,20}. Patient in our study agree well with those of other series in epidemiologic and clinical features.

The majority therapeutic challenge in the treatment of nasopharyngeal carcinoma has been the control of local disease^{3,5,17,20-22}. Some of the factors responsible for local failure have recently been reviewed^{18,20}: inadequate tumor localization, inadequate radiation field size, and poor daily replication of field placement and beam alignment. In addition, several authors have emphasized that an inadequate dose of irradiation results in a higher local failure^{16,17,20} although the optimal dose remains

somewhat controversial. With the higher total doses of radiation, and enlarging radiation fields, as well as improvement in technical accuracy and dose delivery to the tumor, local tumor control has steadily improved without the significant increment of severe or mild complications. As shown in our study, it is suggested that T₁ and T₂ lesions receive 6000~6500 cGy, where as T₃ and T₄ lesions require higher doses: Minimum doses of 7000 cGy, as is consistent with the results of others^{5,6,17,20,23}. Owing to the high incidence of overt and occult cervical lymph node metastases, it had been suggested that the management must be directed to both the primary site and neck even in patients without palpable nodal disease^{2,16,24,25}. Merely enlarging radiation fields or increasing radiation doses may not improve curability in some populations. And as it is difficult to irradiate more than 7000 cGy to the nasopharynx with external beam alone, considering the late sequelae of intensive irradiation, brachytherapy in combination with external irradiation has been used with increasing local control^{6,22,26}. We have been doing brachytherapy using iridium-192 as a boost or re-treatment for local recurrence with a good result since october 1986 (unpublished). There are a number of factors which may influence the treatment results: Stage of the disease, histopathology, age, sex, race, symptom duration, pain, anti-Epstein-Barr virus (EBV) antibody titers and the immune status of the patient. However, general agreement on the staging system, histopathological classification and the importance of age, sex, race, symptom duration and pain is lacking and prognostic value of serum IgA level remains unestablished^{19,27,28}. Among the various prognostic factors the extent of disease on presentation is most important in determining the outcome of treatment. As barely in most series^{6,21,23,27,29}, cervical lymph node involvement was the single most important prognostic factor. Some reported that the level of cervical lymph node may be more important. However, the separation of the neck into three distinct levels may be arbitrary and not always distinct in some patients. Prognostic correlation between the different histological types has been variable. Lymphoepithelioma have been reported to be more radiosensitive and associated with better prognoses than squamous cell carcinoma in some series^{3,4,6,30,31}; others have no significant prognostic difference between the different histopathological types^{13,5,16,28}. In our study no correlation was observed. This inconsistency in the clinicopathological correlation among the different

reported series is, at least in part, because of the lack of uniformity in the criteria of histopathological classification.

Cervical lymph node metastases occur frequently and distant metastases are more common than disease with other head and neck sites, so nasopharyngeal carcinoma may be a tumor which is particularly well suited to assess the possible effects of adjuvant chemotherapy³²⁻⁴⁰. A number of reports suggest that responses to chemotherapy are higher for nasopharyngeal carcinoma than for arising in other head and neck sites, but the effects on survival are uncertain yet^{34,41-43}. The value of chemotherapy can only be determined by prospective randomized controlled trials.

Locally recurrent carcinoma of the nasopharynx is a great radiotherapeutic challenge to the radiotherapist. The tumor may recur after a long period of freedom from disease^{2,44}. There was some reports of re-irradiation⁴⁴⁻⁴⁸. A high dose is necessary to obtain local control and improve survival, and 20-30% of patients are expected to have necrosis after re-irradiation. Some proportion of patients with recurrent nasopharyngeal carcinoma can be salvaged by interstitial irradiation with acceptable morbidity.

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== 국문초록 ==

비인강암의 방사선 치료

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1964년부터 1984년까지 원자력병원 치료방사선과에서 비인강암으로 근치적 목적의 방사선치료를 받은 154명의 환자에 대한 임상적 특성과 치료결과를 분석하였다. 생존자의 최소추적기간은 3년이였다. 환자의 13%가 T₄의 원발병소를 가졌고, 65%가 AJCC 병기 제 4기였다. 병소부위의 총방사선량은 82명에서 1550~1750 ret였고, 72명에서 1750 ret이상이었다. 국소적 완전관해율은 79%이였다. 유의한 예후인자로는 방사선량(1750 ret이상 또는 이하), 나이(30세이하 또는 이상), 병기(AJCC 제1~3기 또는 제 4기), 원발병소정도(T₁ 또는 T₂~T₄병기), 경부임파절유무(NO 또는 N⁺)이였다.