

## Results in the Treatment of Nasopharyngeal Carcinoma Using Combined Radiotherapy

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Thirty-one patients with previously untreated and locally advanced nasopharyngeal cancer were retrospectively reviewed for comparing the effects of radical radiotherapy alone with that of combining chemotherapy and radiotherapy from 1983 to 1989 at Kangnam St. Mary's hospital. 23/31 were evaluable for recurrence and survival. There were 8 patients for stage III, and 15 patients for stage IV. Eleven patients were treated with radical radiation therapy alone (arm I).

Twelve patients were given 1-3 courses of cisplatin-5FU or cisplatin-bleomycin-vincristine prior to radiation therapy (arm II). The two arms were comparable in patient characteristics. Of 11 radiotherapy patients, complete response was 55% (6/11) and partial response 45% (5/11).

Among 12 patients after induction chemotherapy, complete response was 25% (3/12) and partial response 75% (9/12). After subsequent radiotherapy, complete response was increased to 83% (10/12) and partial response was 17% (2/12). Treatment failure was 36% (local recurrence; 3/11, and regional recurrence; 1/11) in arm I and 33% (local recurrence; 1/12, regional recurrence; 2/12 and distant metastasis; 1/12) in arm II. There was no significant difference in survival between arm I and arm II ( $p > 0.05$ ). The toxicities of treatment were acceptable. More controlled clinical trials must be completed before acceptance of chemotherapy as part of a standard radical treatment for locally advanced nasopharyngeal cancer.

**Key Words:** Nasopharyngeal carcinoma, Induction chemotherapy, Radiotherapy, Response to treatment

### INTRODUCTION

External radiation therapy has been the mainstay of treatment for patients with nasopharyngeal carcinoma. However, despite the administration of high doses of radiation, local control of the primary tumor is not yet satisfactory. With radiation alone many patients, especially those with advanced disease at diagnosis, have shown a high failure rate. When treated with radiotherapy alone, the 5-year survival rate of Stage III and Stage IV patients was 45.8% and 29.2%, respectively<sup>1)</sup>. In addition, because cervical lymph node metastases occur frequently and distant metastases are more common than is the case with other head and neck sites, nasopharyngeal carcinoma is the tumor best suited to be treated with induction chemotherapy. Therefore, in the management of nasopharyngeal carcinoma, systemic chemotherapy has been tried

to improve locoregional control and to prevent or delay the onset of distant metastases, and to prolong survival. We designed a combined treatment protocol consisting of multiple agent chemotherapy in conjunction with radical RT. This article reports the results of different treatment modalities, comparing the effects of RT alone with the effect of induction chemotherapy combined with RT.

### MATERIALS AND METHODS

#### 1. Patients

In this study, 23 of 31 patients with histologically proven nasopharyngeal malignancies treated at the Department of Radiology, Catholic University Medical College, Seoul, Korea, between 1983 and 1989 were reviewed. 8 patients who were treated palliatively or who were unable to complete the whole course of treatment were excluded. No patients were lost to follow-up.

Among 23 patients, 11 patients were treated with radical radiation therapy alone (arm I) and 12 patients were treated with combined induction

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chemotherapy plus radiation therapy (arm II).

In arm I group, the age of the patients ranged from 23 to 67 years (median of 55). The sex ratio was 7:4 with male predominant.

Histologically, there were 9 patients with squamous cell carcinoma, 1 with undifferentiated carcinoma and 1 with adenoid cystic carcinoma. All patients were staged according to the AJC (American Joint Committee) system<sup>29</sup> by review of clinico-radiographic data. There were 3 patients (27%) with stage III and 8 patients (73%) with stage IV disease. Each patient was examined by the departments of Radiation Oncology, Medical Oncology, and Otolaryngology.

In arm II group, the age distribution ranged 35 to 62 (median of 51). There were 10 males and 2 females. The histology was squamous cell carcinoma in 10 patients, undifferentiated carcinoma in 1 patient and unknown pathology in 1 patient. Five patients (42%) were classified as stage III and seven patients (58%) as stage IV by AJC system.

The most frequent presenting symptoms were enlarged cervical nodes, epistaxis, nasal obstruction and impairment of hearing. At presentation,

**Table 1. Patient Characteristics**

Variable	Arm I	Arm II
No. of Patients	11	12
Histologic types		
Squamous	9	10
Undifferentiated	1	1
Adenoid cystic	1	—
Type unknown	—	1
Stage III	3	5
IV	8	7
Stage subgroups		
T 1	1	0
T 2	4	6
T 3	3	3
T 4	3	3
N 0	2	2
N 1	2	4
N 2	3	2
N 3	4	4
Sex		
M	7	10
F	4	2
Mean age	50	50
Range of ages	23–67	35–62

42% had cranial nerve palsies in arm II.

Patient characteristics are shown in Table 1.

## 2. Treatment Method

**Arm I:** Eleven patients received external beam radiotherapy on 6 MV linear accelerator. The nasopharynx, the base of the skull and the neck were irradiated by two lateral, shaped, parallel opposing portals. The lower part of the neck was treated through a single anterior portal. The shrinking field technique was employed. The initial field was treated to 40 Gy; the volume was then reduced to the final dose level in the region of the primary tumor. A daily dose of 180 to 200 cGy was delivered five times per week, with a planned total dose to the nasopharynx (6000–7000 cGy) and the lower part

**Table 2. Initial Symptoms**

	Arm I (%)	Arm II (%)
Cervical mass	45	58
Epistaxis	45	33
Hearing impairment	36	58
Nasal obstruction	36	33
Headache	18	25

**Table 3. Response to RT and Combination of IC Plus RT**

	RT	IC + RT
Complete response	6/11 (55%)	3 (25%)—3 10/12 (83%)
Partial response	5/11 (45%)	9 (75%)—2/12 (17%)

\* 1 for stage III, 6 for stage IV

**Table 4. Relapse Rate**

	Arm	
	I	II
Local	3/11 (27%)	1/12 ( 8%)
Regional	1/11 ( 9%)	2/12 (17%)
Distant	—	1/12* ( 8%)

\* lung metastasis

of the neck (5000~6000 cGy).

**Arm II:** Twelve patients were treated with combination chemotherapy containing cisplatin prior to the radiotherapy. In eight patients the cisplatin was combined with 5-fluorouracil as part of a study of which the details have already been published<sup>3)</sup> and in four with bleomycin-vincristine. This chemotherapy was repeated every 3 to 4 weeks, and three cycles in 8 patients, two cycles in two and one cycle in two patients. After a 2-to 4-week interval from the last dose of chemotherapy, radiotherapy was delivered to the nasopharynx and upper neck using two opposite parallel lateral fields including the base to the skull, and to the lower neck and supraclavicular regions with an anterior field. The dose to the primary site ranged from 6000 to 7000 cGy and to the lower neck and supraclavicular regions from 5000 to 6000 cGy by similar method with arm I.

In two arms, the median follow-up is 27 months (range 3 month to 81 month) and no patients were lost to follow-up. We used the T-test for comparing the results.

A complete response (CR) is defined as complete disappearance of all clinical and radiographic evidence of disease for least 1 month. A partial response (PR) is defined as > 50% reduction in size of the primary tumor and palpable cervical lymphadenopathies without progression in any other site.

## RESULTS

On completion of radiation therapy, a reduction in the size of both primary tumor and regional lymph nodes was observed in all patients. In arm I, 11 patients were evaluable for radiation therapy and overall response was 100% including 55% (6/11) complete response and 45% (5/11) partial response. According to the stage, Stage III showed 100% (3/3) overall response with 33% (1/3) complete response and 67% (2/3) partial response. Stage IV showed 100% (8/8) overall response with 63% (5/8) complete response and 37% (3/8) partial response.

In arm II, after induction chemotherapy, overall response was 100% (12/12) including 25% (3/12) complete response and 75% (9/12) partial response. There were 3 (60%) complete responses and 2 (40%) partial responses for Stage III, and no complete responses and 7 (100%) partial responses for Stage IV to chemotherapy. At the completion of radiation program, complete response was 83% (10/12) and partial response 17% (2/12). According

to the Stage, complete responses were 80% (4/5) for Stage III and 86% (6/7) for Stage III, and partial responses 20% (1/5) for Stage III and 14% (1/7) for Stage IV. Among the partial responders to pre-radiation chemotherapy, 1 patient showed complete response in Stage III and 6 patients in Stage IV to subsequent radiotherapy.

The total number of patients experiencing relapses was 4 (36%) for arm I, and 4 (33%) for arm II. In arm I, 27% (3/11) of local recurrence and 9% (1/11) of regional recurrence occurred within 11 months as compared with 8% (1/12) of local recurrence, 17% (2/12) of regional recurrence and 8% (1/12) distant metastasis within 36 months in arm II. In arm II, no patient later developed lung metastasis which responded to further drug treatment and he remained alive and well more than 30 months later.

There was no statistically significant difference in survival between arm I and arm II ( $M \pm SD = 28.55 \pm 17.15$  and  $M \pm SD = 28.58 \pm 25.39$ ,  $p > 0.05$ ). There were no statistically significant differences among patients in the two arms in terms of histologic types, T, N, or grouped TNM stages, sex or age distributions.

The small numbers of cases does not allow a more sensitive analysis of the effect of arm I and arm II.

Apparently, the main effect of chemotherapy is reduction of primary and cervical recurrences, rather than reduction of distant relapses. The acute toxicities were tolerable and all were able to receive radiation therapy or chemotherapy.

## DISCUSSION

The main failure of treatment of the patients with nasopharyngeal carcinoma was distant spreading of the disease, even in early staged patients with high local control rates.

The treatment of choice was shifted from radiation alone to combined regimens with drugs<sup>4)</sup>.

The potential efficacy of induction chemotherapy has been advocated since the late 1970s, and clinical trials reported especially in locally advanced carcinoma of the head and neck<sup>3,5)</sup>.

Although several studies of induction chemotherapy have unfortunately not shown any survival benefit compared to conventional local therapy, it is well established that patients who achieved a complete response to chemotherapy showed an overall improvement in survival<sup>6)</sup>. In contrast with that, although induction chemotherapy appeared

effective on the basis of the response rates, it did not result in prolonging the survival time of a group of patients in randomized studies.

Many investigators have observed that responders to chemotherapy can be predicted to further response to subsequent radiotherapy and that sequential chemotherapy and radiotherapy can achieve high response rate<sup>7</sup>. Ensley et al<sup>8</sup> studies 57 untreated patients who underwent radiotherapy immediately after cisplatin combination chemotherapy.

Forty-one of the 42 responders (98%) subsequently responded to radiotherapy compared to 1 of the 18 nonresponders. This suggested that there was better results for subsequent local treatment (surgery or radiotherapy) in responders than in non-responders to induction chemotherapy.

Hill et al<sup>9</sup> have suggested that site of the primary disease in patients with Head and Neck cancer impacts the response to induction chemotherapy and survival, and Everett et al<sup>10</sup> showed excellent survival for patients with nasopharyngeal cancer.

Tannock et al<sup>11</sup> found no evidence of improved survival for the use of chemotherapy containing cisplatin from a retrospective review. In their study the response rate to chemotherapy was 74%, but overall survival at 3 years for both the 52 patients who received chemotherapy and radiotherapy (50~60 cGy in 20~30 fractions) and 140 historical controls who were treated by radiotherapy alone, was between 50 and 60%. Huang et al<sup>12</sup> reported a 5 year survival of 70.6% for over 900 patients treated by a variety of chemotherapy regimens, some of which included cisplatin. This represented an improvement compared to previous studies in which radiotherapy alone was used and the authors concluded that the results could be attributed to small doses of adjuvant chemotherapy. We are able to confirm that nasopharyngeal carcinoma is responsive to chemotherapy containing cisplatin, but that it remains unclear to what extent, if any, the overall survival is affected.

In spite of a general recognition that nasopharyngeal carcinoma is relatively sensitive to chemotherapy, there is not yet a general agreement of the optimal timing of chemotherapy with respect to radiotherapy. Teo et al<sup>13</sup>, in an attempt to obtain a tumor-debulking effect, treated nasopharyngeal carcinoma with chemotherapy followed by radiotherapy. They observed no significant improvement in survival, and distant relapse even occurred a significantly shorter time after diagnosis than for those treated by radiotherapy alone. It was as-

sumed for earlier distant relapses, resulting in no change of survival. Khoury et al<sup>14</sup>, on the other hand, reported the actuarial 3-year survival of 86% for patients treated by combination chemotherapy containing cisplatin before radiotherapy compared with that of 35% for those treated by radiotherapy alone.

Administering pre-RT chemotherapy is, in fact, postponing the more effective main treatment by a treatment that is less effective. This may give the chemoresistant tumor a chance to metastasize, thus jeopardizing survival. Furthermore, the chemotherapy might accelerate the growth of the subclinical resistant metastases. Either hypothesis gains further support from the shortened time-intervals between diagnosis and the clinical manifestation of distant metastases for the adjunctive chemotherapy arm as compared to the radiotherapy alone arm. This may explain the drop in actuarial and disease-free survival during the first year for the chemotherapy treated arm as compared to the radiotherapy alone arm.

This study did not confirmed arm positive activity of induction chemotherapy for untreated, locally advanced nasopharyngeal carcinoma. We were unable to show any significant difference in survival in our cases according to treatment modalities.

For advanced nasopharyngeal carcinoma, further clinical trials to confirm the role of induction chemotherapy to RT are needed.

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＝ 국문초록 ＝

### 비인강 종양에 있어서 방사선 치료와 유도화학 요법

가톨릭의과대학 방사선과학교실, 내과학교실\*, 이비인후과학교실\*\*

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1983년에서 1989년까지 가톨릭의대 부속 성모병원 방사선치료실에서 비인강종양으로 확진되어 치료를 시행한 환자 31명중 치료가 불완전했던 환자 8명을 제외한 23명의 치료성적으로 후향조사 하였다.

이들 중 11명의 환자에 있어서는 방사선 단독요법을 시행하였으며, 12명의 환자에서는 cisplatin+5-fluorouracil 혹은 cisplatin-bleomycin-vincristine을 이용하여 1회 내지 3회에 걸친 유도 화학요법후 방사선치료를 시행하였다.

방사선 단독요법으로 치료된 11명의 환자에서 완전 관해율은 55%(6/11), 부분관해율은 45%(5/11)였다. 유도화학요법을 시행한 12명의 환자중 약물 치료후 완전관해율은 25%(3/12)였으며, 부분관해율은 75%(9/12)였고, 연속적으로 시행된 방사선 치료후에는 완전 관해율이 83%(10/12)로 증가되었으며, 부분 관해율은 17%(2/12)였다.

유도 항암요법에 부분관해를 보였던 환자중 stage III 환자 1명과 stage IV 환자 6명이 추가 방사선 치료후 완전 관해를 보였다.

방사선 단독요법군에서는 4명에 국소재발이 발생했으며, 약물요법과 방사선치료를 병행했던 군에서는 국소재발 3명과 폐로의 원격전이가 1명에서 발생되었다.

방사선단독으로 치료한 환자군과 유도화학요법과 방사선 치료를 병행한 환자군에서의 생존율의 차이가 통계적으로 유의하지 않았다. ( $M \pm SD = 28.55 \pm 17.15$  and  $M \pm SD = 28.588 \pm 25.39$ ,  $p > 0.05$ )

치료환자군의 수가 적은 이유로 통계분석 결과 큰 의의를 발견할 수 없었다.