Sequential Chemotherapy and Radiation Therapy for Advanced Nasopharyngeal Carcinoma

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Between January 1985 and July 1992, 52 patients with locally advanced nasopharyngeal carcinoma were studied retrospectively for the effectiveness of sequential chemotherapy and radiation therapy. The male to female ratio was 3.3:1 with a median age of 41 years. Forty patients had squamous cell carcinoma and the remaining 12 had undifferentiated carcinoma. Seven patients had stage III disease and the remainder had stage IV disease at time of presentation. All patients were treated two courses of chemotherapy followed by radiation therapy. Chemotherapy consisted of either CVB (cisplatin, vincristine and bleomycin) or CF (cisplatin and 5-FU). Total radiation dose to the primary site ranged from 6000 cGy to 7500 cGy. Neck nodes were given booster treatment to maximum of 7000 cGy, depending on the extent of disease. Local control, overall survival and disease-free survival rates were analyzed. The complete response (CR) rate to chemotherapy was 15% and the partial response (PR) rate was 46% for overall major response rate of 61%. The CR rate was 87% after radiation therapy. Median follow-up time was 51 months. The overall survival and disease-free survival rates at 36 months were 54% and 49%, respectively. Median time to relapse was 15 months. The patterns of initial relapse in CR patients was as follows: locoregional failure only, 12 patients; distant metastasis only, 11; both, 2. Cox's multivariate regression model revealed that nodal status was the single most important independant prognostic factor influencing disease-free survival ($p=0.001$). Comparision of these results with other published reports with radiation therapy alone showed that a high rate of initial response to chemotherapy did not translate into local control or survival. At present time radiation therapy alone remains the standard treatment for locoregional cancer of the nasopharyngeal cancer. More controlled clinical trials must bé completed before acceptance of chemotherapy as a part of treatment of advanced nasopharyngeal carcinoma.

Key Words: Nasopharyngeal carcinoma, Chemontherapy, Radiation therapy

INTRODUCTION

Radiation therapy is the mainstay of treatment for nasopharyngeal carcinoma, primarily due to technical inability to surgical intervention and a high degree of radiosensitivity. Surgery plays a limited role, and is usually reserved for salvage therapy for residual cervical nodal disease. Although the probability of cure for patients with stage I and II nasopharyngeal carcinoma is high, the probability of cure for patients with stage III and IV disease is poor because of a higher rate of locoregional and distant failure. From many studies of patients with advanced nasopharyngeal carcinoma, the 5-year survival rate is approximately 10% to 45% when treated with radiation alone[1~4]. Locoregional failure remains the principal cause of treatment failure and death, unlike other head and neck cancers, distant metastases are a cause of significant morbidity and mortality as well[5,6]. More than 1/3 of the cause of death is represented by distant metastasis, thus providing a justification to determine additional treatments. The integration of chemotherapy into the treatment of nasopharygeal carcinoma is accepted as a theoretical means to improve current results of radiation therapy.

In this retrospective study, we have analyzed the results with sequential chemotherapy and radiation therapy in 52 patients with locally advanced nasopharyngeal carcinoma from January 1985 to July 1992.

PATIENTS AND METHODS

In this study, a total 52 patients with locally

advanced, stage III and IV nasopharyngeal carcinoma treated at the Department of Radiation Oncology, Kyungpook National University Hospital, between January 1985 and July 1992, were reviewed.

All patients had previously untreated, histologically proven carcinoma of nasopharynx and measurable local disease without distant metastasis.

Those patients treated palliatively or those unable to complete the whole course of treatment were excluded.

Patients were staged according to criteria recommended by the American Committee for Cancer Staging and End Results Reporting[7]. Performance status was graded by the Eastern Cooperative Oncology Group (ECOG) scale from 0 to 4. Initial examination included history, clinical examination, endoscopy, complete blood count, extended serum chemistry, chest x-ray, bone scan and CT scan.

TREATMENT

All patients were initially treated with two courses of induction chemotherapy, followed by radiation therapy. Surgery was performed after radiation therapy in patients with localized residual neck disease.

1. Chemotherapy

The chemotherapeutic regimens which were used in this study were either CVB or CF. The 26 patients received CVB; cisplatin (80 mg/m^2) on day 1, vincristine (1.4 mg/m^2) on day 2 and bleomycin 10 mg for day 2 to day 3, and 26 patients received CF; cisplatin (100 mg/m^2) on day 1 and day 3, respectively and 5-FU (100 mg/m^2) infusion for 24 hours on day 2 and day 4, respectively. Cycles were repeated every 3 weeks.

2. Radiation Therapy

Radiation therapy was scheduled to begin 2 weeks after the 2nd course of chemotherapy. All patients were irradiated with linear accelerator. Parallel opposed lateral fields were used to encompass the primary tumor, the base of skull and all cervical nodes. A supplemental anterior field was used only for the patients with anterior extension to nasal cavity. One single anterior field to cover the lower neck was used routinely. All patients received 180~200 cGy/day, five times a week using 6 MV x-ray with or without 8~12 MeV electron. 6000~7500 cGy with a median dose of 7100 cGy were delivered to the region of the primary tumor bed and involved neck disease, and 4500~5000 cGy were delivered to clinically uninvolved neck. Small additional fields or intracavitary implant using Co^{60} or Ir^{192} were sometimes used to provide and additional dose of 500 to 1500 cGy to the primary tumor or the residual areas of the disease in the primary tumor and/or neck.

3. Assessment of Response to Treatment and Statistical Evaluation

The response status of the patients was assessed at two points. Within two weeks of completing chemotherapy, all patients were evaluated to determine chemotherapy response and at 4 weeks following radiation therapy another evaluation was undertaken to assess response. Response was evaluated clinically and/or radiologically.

A complete response was defined as complete disappearance of all clinically detectable disease and partial response was defined as a greater than 50% reduction in the production of perpendicular diameters of all measurable disease. No response was difined as a less than 50% reduction in the production of the perpendicular diameters of any measurable disease.

All patients have been followed-up personal contact. Survival was estimated from the initiation of chemotherapy to the date of last follow-up or until patient's death. Time to relapse was defined as the time between initiation of chemotherapy and

Table 1. Patients Characteristics

Characteristics	
No. of Patients	52
Age (in year)	
Median	41
Range	14~73
Sex	
Male	40
Female	12
Performance status (ECOG)	
0	44
1	7
2	1
Pathology	
Squamous	40
Undifferentiated	12
Stage of Disease	
III	7
IV	45

progression of disease documented clinically and/or radiologically. The overall survival, disease-free survival and local control rates for patients were stratified according to tumor variables.

The survival curves were estimated by Kaplan-Meier method[8]. In addition, the Peto-Wilcoxon test and Cox's regression proportional hazards model were used to evaluate the prognostic variables for local control and survival[8]. Statistical significance was defined as $p \leq 0.05$.

RESULTS

1. Patients Characteristics

The patients characteristics are summarized in Table 1. Patient age ranged from 14 years to 73 years with a median age of 41 years. There were 40 men and 12 women, a sex ratio of 3.3:1. Most patients had a performance status of 0 (85%) or 1 (13%) and only 1 patient had a performance status of 2. Forty patients had squamous cell carcinoma and the remaining 12 patients had undifferentiated carcinoma. Seven patients presented with stage III (13%) and the remaining 45 patients (87%) presented with stage IV. The distribution of patients according to T and N is shown in Table 2.

2. Response to Initial Chemotherapy

After the completion of chemotherapy, a CR was achieved with 8 patients (15%) and a PR in 24 patients (46%) for and overall major response rate of 61%. With the chemotherapy regimen associated with CVB was a 58% response rate and 65% with CF (Table 3). The difference was not statistically significant ($p=0.3062$). The response rate to chemotherapy according to age, sex, and tumor variables did not significantly affect the response to chemotherapy.

Forty-eight of the 52 patients received two courses of chemotherapy. Four patients received only one course, three because of SIADH (snydrome of inappropriate ADH production) and another one because of hepatic toxicity following first course of chemotherapy, and it was elected to commence radiation therapy.

Chemotherapy was generally well tolerated by most patients. Toxicities were predominantly nausea and vomiting, mild to moderate mucositis and mild myelosuppression. There wered 3 SIADH and 1 hepatic toxicity, and there was no difference in toxicity according to chemotherapy regimens.

Table 2. Patient Distribution by Tumor and Nodal Status

Nodal Status	Tumor Status				Total
	T1	T2	T3	T4	
N0	0	0	6	1	7
N1	0	2	0	1	3
N2A	2	0	0	2	4
N2B	3	5	6	3	17
N2C	3	4	5	3	15
N3	1	2	2	1	6
Total	9	13	19	11	52

Table 3. Response to Chemotherapy According to Regimens

	CR	PR	NR	p-value
CVB	2	13	11	p=0.3062
CF	6	11	19	

3. Response to Radiation Therapy

The response to radiation therapy was assessed at 4 weeks after the completion of treatment. Overall, 45 patients (87%) achieved a CR after radiation therapy. The PR rate was 13% yielding a total response rate of 100%. Age, sex, nodal status, tumor status, pathology or response to chemotherapy did not significantly affect the response to radiation therapy. Radiation therapy was well tolerated with no increase in rate or severity of acute reactions.

Salvage treatment with curative intent was attempted in 9 of 12 patients who relapsed in local and/or regional area by additional radiation therapy, surgery and/or chemotherapy, and 3 patients were salvaged. Two pateints who treated with additional radiation therapy alone are still alive and clinically disease-free at 76 months and 40 months, respectively. Another one patient treated with surgery, radiation and chemotherapy is still alive and disease-free at 56 months after treatment.

4. Survival and Failure Analysis

Minimum follow-up was 14 months at time of review and maximum 112 months, with a median of

Table 4. Patterns of Initial Failure in Patients with Persistent or Recurrent Disease (N=52)

	No. of Patients
Persistent Disease	7(13%)
Locoregional Failure only	12(23%)
Distant Failure only	11(21%)
Distant Failure+ Locoregional Failure	2(4%)

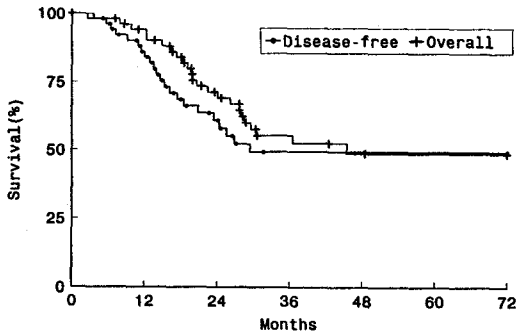

Fig. 1. Overall survival & disease-free survival.

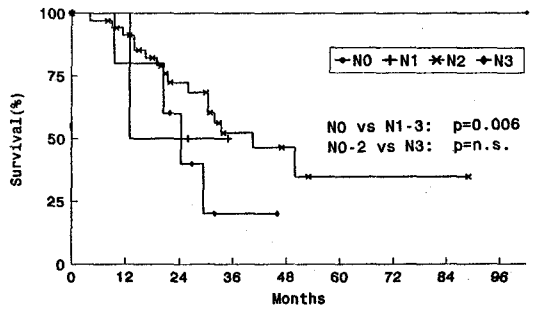

Fig. 2. Overall survival by nodal status.

Table 5. Prognostic Factors Predicting Disease-Free Survival or Overall Survial: Multivariate Analysis

Factor	Disease-Free Survival (P value)	Overall Survival (P value)
Age (42 patients<50) ν 10 patients≥50)	N.S.	0.02
Sex (40 male ν 12 femle)	N.S.	N.S.
Tumor Stage	N.S.	N.S.
Nodal Stage	0.001	0.006
Nodal Location	N.S.	N.S.
Pathology (40 squamous ν 12 undifferentiated)	N.S.	N.S.
Response to Chemotherapy (32 responders ν 20 nonrespondrs)	N.S.	N.S.
Response to Radiotherapy (45 CR ν 7 PR)	--	0.001

CR: complete respose, PR: partial response

51 months. No patient was lost to follow-up.

The overall and disease-free survival rates are shown in Fig. 1. The overall survival and disease-free survival rates were 70% and 61% at 24 months and 54% and 49% at 36 months, respectively. Median survival was 47 months.

Upto August 1993, 22 patients are alive and free of disease, 6 are alive with recurrent or progression of persistent disease, and 24 had died. The death was caused by recurrent disease or progression of persistent disease in 23 patients and by other cause in 1 patient. Relapse was first noticed at locoregional site in 12 patients, and distant site in 11, whereas 2 patients relapsed at both locoregional and distant site. Sites of distant metastasis were bone (6 patients), lung (4 patients), liver (1 patient), axilla (1 patient) and brain (1 patient). Time to relapse ranged from 5 months to 34 months, with a median time of 15 months.

Patterns of initial failure are indicated in Tabel 4. Multivariate analysis was used to find out factors that might predict for overall survival (Table 5). Age, nodal status and response to radiation therapy were found to be important prognostic factors. Patients less than or equal to 50 years had a better survival than over 50 years (62% vs 45%, p=0.02). The 3 year overall survival for N0, N1, N2 and N3 were 100%, 50%, 52% and 20%, respectively. Those patients with N0 had a better survival than those patients with N1, N2 and N3 (p=0.006, Fig. 2). Patients with CR to radiation therapy had a better survival than patients with PR to radiation therapy (p=0.001, Fig. 3). Sex, tumor stage, nodal location, pathology and response to chemotherapy did not affect overall survival in statistically significant manner. The same procedure was undertaken to find out factors which predict for disease-free survival (Table 5). Only nodal status was of significant prognostic value (p=0.001, Fig. 4). Comparisons of disease-free survival according to nodal status were performed by Peto-Wilcoxon test. The differences among nodal group (N0 vs N1-3, N0-1 vs N2-3 and N0-2 vs N3) were statistically significant. P-values were 0.04, 0.02 and 0.03, respectively. Other variables did not significantly affect disease-free survival.

DISCUSSION

Nasopharyngeal carcinoma is not uncommon in Korea, accounting 0.6% of all malignancies, and it is the third most common cancer among all head and neck cancers following the cancer of the larynx and paranasal sinus[9]. The incidence of nasopharyngeal carcinoma is relatively high in south China and in individuals born in south China regardless of their relocation to the other countries, thus suggesting a genetic predisposition to this disease[1,10].

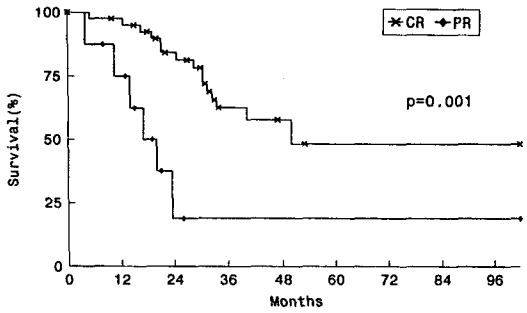

Fig. 3. Overall survival by response to radiation therapy.

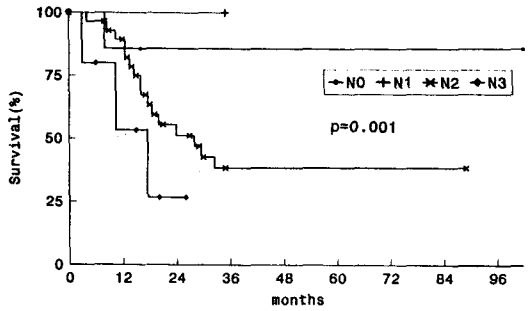

Fig. 4. Disease-free survival by nodal status.

Incidence rates decrease for American-born, second-generation Chinese, implicating unknown environmental factors in the pathogenesis of this disease. This is associated with elevations in Epstein-Barr antiviral titers and alterations in the HLA gene system[11,12]. The role of these immunological and genetic factors in the pathogenesis and recurrence of the nasopharyngeal carcinoma are subject of active investigation[11,12].

Distinguishing clinical features among head and neck cancers are presented by a high frequency of regional metastasis at disease presentation, good immediate control with radiation therapy, and poor long-term results. Primary treatment of nasopharyngeal carcinoma needs to be optimized to improve the total cure rate. Although early response to radiation therapy have been improved with modern radiation sources and techniques, a therapeutic plateau to have been reached[6,13]. Furthermore, systemic dissemination represents a frequent cause of failure in patients receiving adequate local treatment[5,6,15]. It has been suggested from many studies that the rate of distant metastasis with incidence of 20% to 40% is higher in patients with nasopharngeal carcinoma than in patents with other primaries of the head and neck region[5]. Metastatic sites are probably seeded before the initiation of radiation therapy[5,15]. For these reasons there is potential for chemotherapy to improve survival in patients with nasopharyngeal carcinoma through eradication of micrometastasis and increase in the rate of locoregional control.

Several chemotherapeutic regimens have been used and CR rates ranging from 10% to as higher as 87% have been reported[5,15~17]. In our study the CR rate after chemotherapy was 15% which are comparable to those reported by others[5,16]. However, other reports were higher than that reported by here[15,17]. Possible explanation for this discrepancy include difference in chemotherapy regimens used or difference in extent of disease in treated patients. The CR rate after radiation therapy was 87% and this CR rate is similar to rates reported by other authors using radiation therapy alone[2,3,5,13,19].

Twenty-five patients with CR after treatment relapsed in locoregional and/or distant sites. These observations are similar to previously reported in patients treated with radiation therapy alone[5,13,19,20]. In this study, the overall survival and disease-free survival rates at 36 months were 54% and 49%, respectively. Although local control was high, there were no long-term benefits. These results were comparable to those reported in the literatures patients treated by radiation therapy alone[1~5]. Tannock et al[5], using sequential chemotherapy (methotrexate, bleomycin and cisplatin) and radiation therapy, did not find any improved survival from the use of chemotherapy. They treated 51 patients with locoregional disease with chemotherapy and radiation therapy. Although the response rate was high, overall survival and disease-free survival were not different from those achieved by radiation therapy alone with similar stage and age distribution. Zhang et al treated 696 patients with nasopharyngeal carcinoma of all stage with several chemotherapeutic agents, either as single agent or combination chemotherapeutic agents, either as single agent or combination chemotherapy. They reported that disease-free survival and overall survival were almost identical to those for 604 patients of historical controls treated with radiation alone[15].

However, Huang et al[21] treated more than 900 patients with a variety of chemotherapy regimens and radiation therapy. After combination chemotherapy and radiation therapy, they showed that overall survival was improved and the recurrence rate declined. The authors concluded that this

difference could be attributed to the addition of chemotherapy and planning techniques using computed tomography in order to achieve better tumor delineation. The present study as well as above mentioned studies using historical controls suggest that the role of chemotherapy for nasopharyngeal carcinoma remains controversial and the importance of timing of chemotherapy with respect to radiation therapy is unclear. Only by prospective, randomized and controlled trials it is possible to evaluate the value of chemotherapy in the treatment of nasopharyngeal carcinoma.

In conclusion, despite the high rate of tumor response to initial chemotherapy, the local control and survival were similar to other published reports with radiation alone. Chemotherapy did not appear to convey local control and survival benefit to patients when used before radiation therapy. More controlled clinical trial must be completed before acceptance of chemotherapy as part of standard treatment for advanced nasopharyngeal carcinoma. At this time, the use of chemotherapy in the treatment of nasopharyngeal carcinoma remains an investigational tool of considerable promise.

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═국문초록═

진행된 비인강암의 화학요법 및 방사선 치료

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1985년 1월부터 1992년 7월까지 경북대학교병원 치료방사선과에서 화학요법후 방사선치료를 받은 국소진행된 비인강암 환자 52명을 대상으로 화학요법의 효과를 판정하기 위하여 후향적 조사를 실시하였다.

남녀성비는 3.3:1이었고 중앙연령은 41세였다. 병리조직학소견은 40예에서 편평세포암이었고, 나머지 12예에서는 미분화세포암이었다. AJC병기에 따른 분류는 III기가 7예였고, 나머지 45예는 IV기였다. 모든환자는 2회의 화학요법후 방사선치료를 받았으며 사용된 화학요법 제재는 CVB (cyclophosphamide+vincristine+bleomycin)이나 CF (cicplantin+5-FU)였다. 방사선조사량은 원발병소에 6000~7500 cGy, 임파절은 병의 정도에 따라 최대 7000 cGy까지 조사하였다. 국소관해율, 생존율 및 무병생존율을 분석하였다.

화학요법에 대한 완전관해율은 15%, 부분관해율은 46%였으며 방사선치료후 완전관해율은 87%였다. 중앙추적기간은 51개월 이었으며 3년 생존율 및 무병생존율은 각각 54%와 49%였다. 중앙재발기간은 15개월이었으며 완전관해 후 재발의 양상은 국소재발단독이 12예, 원격전이단독이 11예, 국소재발 및 원격전이가 2예였다.

Cox's multivariate regression model에 따르면 임파절전이 유무가 무병생존율에 영향을 미치는 가장 중요한 예후인자이었다(p=0.001). 다른 보고에서의 방사선 단독치료의 결과와 비교하여 볼때 화학요법에 대한 종양의 반응율은 높으나 화학 요법 및 방사선치료가 국소관해율 및 생존율의 향상으로는 연결되지는 않았다.

결론적으로 진행된 비인강암에서의 화학요법은 좀더많은 비교대조군 연구(controlled clinical trial)를 통해서만 역할을 이야기할 수 있을 것으로 사료된다.