

Analysis of Treatment Result of Nasopharyngeal Cancer

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From 1984 to 1988, forty two patients with nasopharyngeal cancer were treated at the Department of Radiation Oncology in Kyungpook National University Hospital. Thirteen patients refused treatment and the median survival time was 7.8 months. Twenty nine patients received a full course of radiation at least 70 Gy to the primary site and 60 Gy to the nodal sites. These patients were all belonged to stage III or IV. The local control rate was 75% in squamous cell carcinomas, and all the patients with lymphoepithelioma showed a complete response. Overall locoregional failure was 27.6%. Distant metastasis was the predominant pattern of failures; 4/6 in lymphoepithelioma, 4/10 in squamous cell carcinoma. The Three-year-survival rate for squamous cell carcinoma was 40.5%, and for lymphoepithelioma 25.9%, respectively.

This may be due to the more frequent distant metastases in lymphoepithelioma and ineffective chemotherapy. No survival correlation was found with the level of neck node involvement. Though adjuvant chemotherapy was found to be of no benefit in overall survival, more prudent and aggressive chemotherapy would be necessary.

Key Words: Nasopharyngeal cancer, Radiotherapy

INTRODUCTION

Malignant neoplasm of the nasopharynx is relatively uncommon in Korea, whereas in China, though geographically not distant it is one of the common neoplasms. Owing to inaccessibility to surgical intervention, the primary treatment of this tumor is radiation therapy. Over recent decades, changes in the techniques of radiation delivery have yielded better locoregional control and better survival in this neoplasm. But the prognosis for patients with nasopharyngeal cancers remains rather grave, with overall 5-year survival rates ranging from 30% to 60%¹⁻⁷. Local and regional recurrences still remain the major cause of death and, unlike other head and neck tumors, distant metastasis is also a cause of significant morbidity and mortality as well^{2,4,6}.

In the current paper, we report on our clinical experience with nasopharyngeal cancers and focus our attention on the local control rate, survival rate, and the rate of locoregional recurrence and distant metastasis in patients with squamous cell carcinoma and lymphoepithelioma of the nasopharynx.

MATERIALS AND METHOD

During the years 1984~1988, the number of total

registered nasopharyngeal tumors was 65. Of these, benign tumors, lymphomas, adenoid cystic carcinoma, and lethal midline granulomas were excluded from this study. Forty-four patients were assessed and treated for squamous cell carcinoma and lymphoepithelioma of the nasopharynx at the Department of Radiation Oncology and Otolaryngology of Kyungpook National University Hospital. Two patients were excluded because their survivals could not be confirmed. Of the 42 patients analyzed, 13 patients refused treatment and only median survival time was calculated, 29 patients received a complete course of radiation therapy and these patients were all belonged to stage III or IV.

Each case was jointly evaluated by an otolaryngologist and a radiation oncologist before treatment was instituted. After therapy was completed, patients were followed monthly for the first year and then increasing time intervals until a five-year-survival were reached, when visits became annual. The treatment and follow-up of each patient was retrospectively studied in detail and a computer analysis performed.

All patients had histological proof of either squamous cell carcinoma or lymphoepithelioma of nasopharyngeal primary. For the purpose of pathological differentiation, a pathologist thoroughly reviewed all the biopsy slides. Lymphoepithelioma

was evaluated separately based on the reports of a better prognosis and different treatment methods with this diagnosis^{1,8)}.

A combination of radiologic investigations was performed on admission or according to pathological diagnosis. Chest x-ray and CT scans were done on all patients, and bone or liver scans were done according to the presenting symptoms.

Staging classification was done on the basis of the American Joint Committee for Cancer Staging System. The node stage was again classified according to the levels of the neck, which modified the original Ho's classification^{9,10)}. The neck was divided into three levels. The middle neck was determined by the two imaginary lines formed by the hyoid bone and by the inferior border of the easily palpable thyroid cartilage. The upper and lower level of the neck were adopted by the superior and inferior part to the cartilages in the neck, respectively. The adopted method of neck levels was diagrammed in Fig. 1.

Radiation has been and still is the primary treatment for nasopharyngeal cancer in our hospital. The total dose to the primary site and both sides of the neck was at least 60 Gy in 30 fractions over 6~7 weeks. The primary nasopharyngeal site was boost treated with 10 Gy in 5 fractions a week. The lower neck nodes were given 50 Gy with the same pattern of fractions in 5 weeks. The Posterior neck was treated with 6~9 mev electron beam after the spinal cord was shielded when 45 Gy was reached.

Induction chemotherapy was administered with the regimen of CVB or CF, usually 2 cycles prior to radiation therapy. Surgical treatment was limited to radical neck dissection for recurrent neck disease

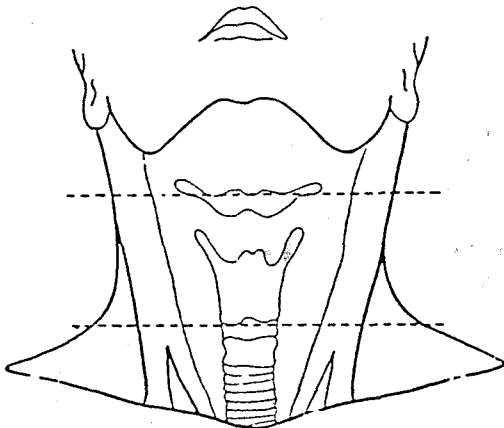


Fig. 1. Levels of the neck adopted in the present study.

or resistant residual neck nodes.

Persistent or recurrent tumors were treated with a boost radiation dose with 20 Gy, either with field shrinkage technique or with intracavitary cobalt-60 brachytherapy and/or neck dissection and chemotherapy.

RESULTS

Sixty percent of the patients were in their fifties and sixties when the nasopharyngeal cancer was diagnosed. The Male to female ratio was 3:1. Twenty-six patients initially presented with a neck mass, the most common presenting symptom. Common presenting symptoms were demonstrated in Table 1. Of the symptoms of cranial nerve involvement, abducent nerve palsy and trigeminal nerve irritation sign were the most frequently associated with the tumor. Vagus nerve palsy leading to hoarseness was also noted in four patients. Initial sites of diseases were shown in Table 2. Most of the tumors appeared in the superolateral and posterior walls of the nasopharynx.

Pathologic type consisted of squamous cell

Table 1. Symptoms

Neck mass	25
Ear problem	16
Nasal problem	10
Paresthesia	7
Diplopia	8
Pain	5
Headache	5
Voice change	4
Nasal bleeding	1

Table 2. Site of Disease

Superior wall	17
Posterior wall	26
Lateral wall	35
Nasal cavity	7
Oropharynx	7
Cavernous sinus	4
Base of skull	3
Sphenoid sinus	1
Ethmoid sinus	1
Tonsil	1
Hypopharynx	1

Table 3. Clinical Stage According to AJC

	Tx	T1	T2	T3	T4	Total
N0		1		3	4	8
N1					2	2
N2a		1		2	1	4
N2b		3	4	4	3	14
N2c	1		3	6	3	13
N3		1	2			3
Total	1	6	9	15	13	44

Table 4. Response Rate

Response	SCC (%)	LE (%)	Total (%)
CR	15 (75)	9 (100)	24 (83)
PR	5 (25)	0 (0)	5 (17)
Total	20	9	29

CR : Complete response

PR : Partial response

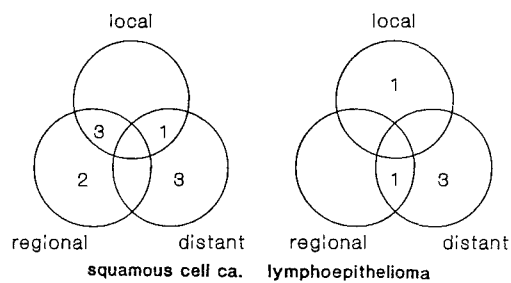
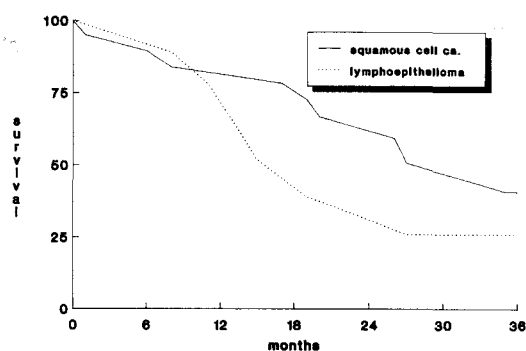
SCC : squamous cell carcinoma

LE : lymphoepithelioma

carcinoma in 31 patients (70.5%) and lymphoepithelioma in 13 patients (29.5%). Poorly differentiated squamous cell carcinoma was found in 44%. There was no well differentiated carcinoma. T- and N-stage were conjointly depicted in Table 3. There was no definite correlation between T stage and N stage. But the incidence of neck nodes metastases generally increased with advanced primary tumor status.

The tumor control rates among the 29 treated patients were illustrated in Table 4. The overall control rate was 2/2 in stage III, 22/27 in stage IV. In squamous cell carcinoma, the complete response rate was 75% (15/20). In lymphoepithelioma, all the treated patients showed complete disappearance of the tumor.

The pattern of failure is shown in Fig. 2. Among the 29 treated patients, 16 sites of failures in 13 patients were detected. The overall locoregional failure rate was 8/29 (27.6%). Most of the failure appeared within 24 months after completion of the treatment. In both histologies, distant metastases were the predominant feature. In lymphoepithelioma four out of six total failures were by distant metastasis. In squamous cell carcinoma the rate of distant metastasis was 40% of total failures. The most frequent metastasis appeared in liver (4

**Fig. 2.** Pattern of failure.**Fig. 3.** Survival rate according to histology.**Table 5.** Survival According to the Level of Neck Nodes

	Median (mon.)	3 year (%)
Level 1	20.9	32.3
Level 2	22.3	30.1
Level 3	27.5	28.6

cases), lung (3 cases), bone (2 cases), and bone marrow (1 case). Interestingly, there were two patients who later had adenocarcinoma of the stomach and died with stomach cancer.

The median survival time of the 13 untreated patients was 7.8 months, and there were no long-term survivors. The 3-year-survival-rate for the 20 treated squamous cell carcinomas was 40.5%, and for the 9 treated lymphoepitheliomas was 25.9%. These survival rates are depicted in Fig 3. The survival rates according to the modified Ho's neck nodes classification is shown in Table 5. Unfortunately, there was no significant difference because of the small sample size. But the metastatic potential was increased when the more lower neck nodes were involved.

There were no long-term complications except xerostomia and serous otitis media.

DISCUSSION

Though the survival rate has risen during the past several decades, a 5-year-survival-rate of about 40% and a tumor control rate of 30% generally may be expected with megavoltage radiotherapy for nasopharyngeal carcinomas¹¹. This is in general agreement with our survival results. But the local control rate was far higher than the reported data. Masashi et al² reported primary control rate of about 70%, which is similar to our 75% control rate. At the primary site, the treatment failure occurred in 27.6% as shown in Fig. 2. This is also in contrast to Petrivich's 83% primary failure rate¹².

Masashi² reported that there was no apparent correlation between the primary external dose and control rate. Petrovich¹² and Bedwinek⁶⁷ reported that a dose radiation of over 66 Gy was associated with a better survival rate than a dose of less than 60 Gy. They refrain from administering radiation beyond 70 Gy because administration of a radiation dose higher than 70 Gy failed to increase survival. However, Dexing et al¹³ suggested that, for those who have a residual tumor in the primary site when 70 Gy has been delivered, the total dose may be boosted to more than 90 Gy, he showed better results in the group of patients who received more than 90 Gy (64%, 39/61). Vikram et al¹⁴ also reported a higher control rate of recurrence in lower doses. The difference of the primary tumor control rate may be the result of the difference in the delivered radiation dose. In the current study, all the treated patients received over 70 Gy at the primary site, and the local control rate was 75% though all the patients had locally advanced diseases (stage III or IV). This fact supports Dexing's and Vikram's suggestions.

On the other hand, there is some problem of correlation of T-stage and control rate. As the nasopharyngeal region is the inaccessible location to examine, it is somewhat difficult to estimate of T-stage exactly even with computed tomography. However, Cooper et al¹⁵, and Park et al⁹ stated that primary persistence or recurrence of tumor in the nasopharynx correlated with the initial T-stage of disease.

The local control rate of lymphoepithelioma was excellent. All nine/treated patients achieved complete local control despite a 5 Gy lower dose than the dose for squamous cell carcinoma. Mesic et al⁸

reported a similar excellent local control rate in lymphoepithelioma (only 5.6% primary failure). Million¹⁶ suggested that a 5 Gy less dose than for squamous cell carcinoma was sufficient for stage by stage control of the primary tumor.

Rehima et al¹ reported that the lymphoepithelioma had 61.8% 5-YSR which is significantly different from the 32.7% 5-YSR of squamous cell carcinoma. This differs slightly from our results. The 3-YSR of lymphoepithelioma were 25.9%, as shown in figure 3. This phenomenon seems to be the result of ineffective chemotherapy and a more frequent distant metastases in lymphoepitheliomas. The rate of distant metastasis was 4 out of 6 total failures after treatment of lymphoepithelioma (Fig. 2). The rate of distant metastasis in squamous cell carcinoma was also high, measuring 4 out of 10 failures which influenced the survival as did locoregional failures (Fig. 2, 3) this despite an excellent local control rate.

O'conner et al¹⁷ reported that their 21 patients with nasopharyngeal tumors had a significantly improved survival at the 7 years' follow-up using VBM chemotherapy. This improved survival was due, however, to improved locoregional control; whereas the observed rate of distant metastasis was similar to other head and neck tumors. Rahima et al¹ also found that their data were in accordance with previous studies of nasopharyngeal tumors in that their patients with squamous cell carcinoma did not benefit from adjuvant chemotherapy. Interestingly, Baker and Wolfe¹⁸ found that duration of treatment was related to survival that is, longer periods offered better 5-YSR in their review of prognostic factors affecting the outcome of treatment of nasopharyngeal tumors. Thus, more prudent chemotherapy would be necessary to reduce the incidence of distant metastasis and to improve survival in squamous cell carcinoma as well as in lymphoepithelioma.

The two clinical staging systems in use for nasopharyngeal carcinoma - AJC and UICC - have been questioned, and new proposals have been made^{9,10,19}. According to AJC and UICC classification, most of the patients with neck metastasis were allocated to stage IV, irrespective of any other feature of the nodes. Stage I, II included less than 10% of the cases. This is similar to our data. In the original Ho's classification⁹, the neck was divided into 3 levels by the skin creases. This seems to be impractical because the skin creases might be obscured when the node becomes very large. Cesare et al¹⁰ proposed an alternative classifica-

tion based on a prognostic scoring system directly derived from the Weibull model. Without regard to the size, number, and fixation of the neck nodes, they found that only the level of the involved nodes was a significant variable with regard to nodal extent. In their new proposal, the neck was divided into 3 levels with two imaginary horizontal lines, the upper one passing on the hyoid bone and the lower one crossing the inferior border of the thyroid cartilage as shown in Fig 1. This might be more practical than the original Ho's clasification because the thyroid bone and hyoid bone are easily palpable. According to this classification, our results unfortunately showed no satisfactory correlation with the level of the neck diseases. Small sample size and retrospective determination of the neck levels through the description in the chart might lead to inaccurate results. It is thought to be necessary to consider the nature and location of neck nodes in staging the nasopharyngeal cancer.

In conclusion, though no significant results were obtained from our data analysis, both the squamous cell carcinoma and the lymphoepithelioma of the nasopharynx require more prudent and aggressive chemotherapy to achieve better long-term survival. And new staging classification would be necessary. Larger and randomized multi-institutional studies should be carried out to reach conclusions regarding the efficacy of treatment in nasopharyngeal cancer.

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= 국문초록 =

비인강암의 치료 결과 분석

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박 준 식

경북대학교병원 치료방사선과에서 1984년부터 1988년까지 치료를 받은 비인강의 편평 상피 세포암과 림프 상피종 42예를 대상으로 치료 결과를 분석하였다. 치료를 거부한 13명의 중앙 생존 기간은 7.8개월이었다. 원발 병소에 적어도 70 Gy이상, 그리고 경부 임파절에 60 Gy이상 투여된 환자는 29명이었고, 이들은 모두 제 3 혹은 제 4병기에 속하였다. 20예의 편평 상피 세포암의 국소 관해율은 75%였고, 림프 상피종 9예는 모두 완전 관해를 보였다. 원발병소와 임파절의 재발율은 27.6%였으며, 원격 전이가 치료 실패의 주종을 이루어서, 림프 상피종에서는 6예의 치료 실패 중 4예, 편평 상피 세포종에서는 10예 중 4예에서 나타났다. 3년 생존율은 편평 상피 세포종에서 40.5%였고, 림프 상피종에서는 25.9%였다. 이는 림프 상피종의 국소 관해율이 더 높았으나 원격전이가 더 빈번하고 비효율적인 화학요법의 결과라 생각된다. 경부 임파절의 위치와 생존율과의 상관 관계는 발견하지 못하였다. 이상으로 미루어, 보조적 화학 요법이 생존에 큰 이득이 없는 것으로 받아들여지고 있으나, 더 신중하고 적극적인 화학요법이 필요할 것으로 생각된다.