

Nasopharyngeal Cancer in Patients Under Thirty Years of Age

Ki Jung Ahn, M.D., Eun Ji Chung, M.D., Hyung Sik Lee, M.D., Sun Rock Moon, M.D.
Jin Sil Seong, M.D., Gwi Eon Kim, M.D., Chang Ok Suh, M.D. and John Juhn Kyu Loh, M. D.

Department of Radiation Oncology, Yonsei University College of Medicine, Seoul, Korea

Between January 1971 and December 1987, 113 patients with nasopharyngeal cancer (NPC) were treated by radiation therapy with or without chemotherapy in the department of Radiation Oncology, Yonsei University Hospital. There were 19 patients under thirty years of age. The histology was undifferentiated carcinoma in 68% of the younger patients as compared to 47% of the older patients.

Sex, stage, initial symptoms and treatment modalities differed little from those of older patients.

In younger patients, the initial complete response rate was 79% as compared to older patients with 54%, distant metastases were more common and the overall five year survival rate was not significantly different between the two age groups (33.7% for the young vs. 37.4% for the old).

The five year survival rates for stage III and IV were 60.0% and 24.5%, respectively.

Histologic subtype was not correlated with survival. The best survival was found only in patients who obtained a complete clearance of disease after radiation therapy.

Adjuvant chemotherapy is suggested as an important target for further study.

Key Words: Nasopharyngeal carcinoma, Radiation therapy, Survival

INTRODUCTION

Although carcinoma of the nasopharynx (NPC) is a relatively rare tumor in children and young adults, studies from North America, Tunisia and India have demonstrated the greater relative occurrence in children and young adult¹⁾. No such age peak has been described in Chinese populations, possibly because NPC in the Chinese starts at an earlier age and may mask any younger age peak.

Histology of NPC in young patients is commonly the undifferentiated type and may have a more favorable prognosis, although not all authors agree.

Epidemiological, histological and prognostic distinctions of the two age groups may suggest that NPC in the younger age group is of a different etiology. Infection with oncogenic viruses, familial susceptibility and hormonal changes during the developmental period are of particular etiological interest in the young.

Distant metastases to bone, lung or liver are a common first relapse in the young²⁾.

Radiation treatment of nasopharyngeal carcinoma in the young produces prompt and complete

tumor regression in almost all patients and results in a cure in 30-50%. A few small pilot studies have suggested that the adjuvant chemotherapy may be of value³⁾.

Natural history and results of treatment for nasopharyngeal carcinoma in adults are well recognized. This review will attempt to elucidate some specific features such as clinicopathological features, response rate, survival rate and prognostic factors, in the clinical behavior of these tumors in the young which might suggest ways to improve treatment.

MATERIALS AND METHODS

The records of 113 patients with nasopharyngeal cancer who were treated at Yonsei University Hospital from 1971 to 1987 were reviewed. The age distribution is shown in Figure 1. There were 19 cases (17%) under 30 years of age, and the male to female ratio was 2.2:1 compared to 3.5:1 in older patients. There was a difference in the histological distribution between the two age groups; 68% (13/19) of younger patients showed the differentiated carcinomas as compared to 47% (44/94) of older patients. The symptoms at first examination are not very different from those of our older population; the two most frequent initial presenting symptoms were neck mass and nasal obstruction. Mean inter-

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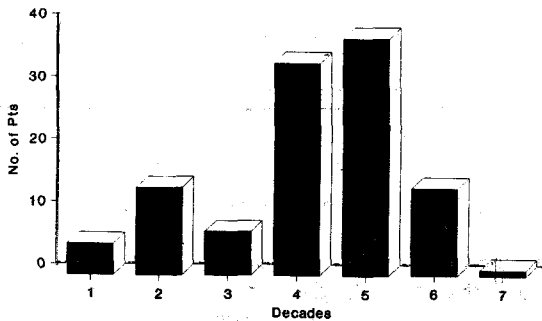


Fig. 1. Distribution of age.
(Total 113 from Jan. 1971 to Dec. 1987)

Table 1. Patient Characteristics

	under 30 years (19 cases)	over 30 years (94 cases)
Age		
mean	23.1	56.5
median	25	50
Sex		
male	13	73
female	6	21
M/F ratio	2.2:1	3.5:1
Stage		
I & II	0	5 (5%)
III	5 (26%)	17 (18%)
IV	14 (74%)	72 (77%)
Histology		
squamous cell ca.	6 (32%)	50 (53%)
undifferentiated ca.	13 (68%)	44 (47%)
Initial symptoms		
neck mass	15	38
nasal obstruction	8	29
ear symptom	6	27
headache	4	15
epistaxis	4	8
cranial nerve symp.	1	4
others	2	11
Treatment modality		
RT + CT	8 (42%)	40 (43%)
RT only	11 (58%)	54 (57%)

val between initial symptoms and diagnosis was 7.5 months in younger patients as compared to 4.8 months in older patients. All patients were staged according to the American Joint Committee staging system using clinical and radiologic criteria.

Table 2. XRT Dose to Nasopharynx

Dose (cGy)*	No. of patients (%)	
	< 30 Yrs	> 30 Yrs
5,000–5,999	1 (5)	8 (9)
6,000–6,999	15 (79)	23 (77)
over 7,000	3 (16)	13 (14)

* 1.8 – 2 Gy/day, 5days/wk

Five patients (26%) had stage III and 14 (74%) had stage IV disease. There was no stage I, II in younger patients, and only 5% in older patients had stage I/II.

Eight (42%) of the younger patients and forty (43%) of the older patients received radiation therapy after the induction chemotherapy, and the remainder received radiation therapy only (Table 1).

All patients were treated with Co-60 teletherapy unit or 4MV X-ray. The nasopharynx, the base of skull and the upper part of the neck were irradiated by two lateral, shaped, parallel opposing portals. The dose to the primary site was 5,000–7,800 cGy, delivered in daily fractions of 180 to 200 cGy, treating 5 days per week. The posterior 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 AP field and the palpable nodes were given a boost treatment with an electron beam (Table 2, Figure 2).

All patients continued to be examined by physical and radiological examination every 3 months during the first two years and at six-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 was alive. The survival curves were plotted using the life table method.

RESULTS

The initial complete response rate for younger patients was 79% as compared to older patients with 54% (Table 3).

The overall five-year survival rates for the two age groups were 33.7% and 37.4%, respectively; there was no statistically significant difference (Figure 3). The five-year survival rate for undifferentiated carcinoma was 37.2% as compared to

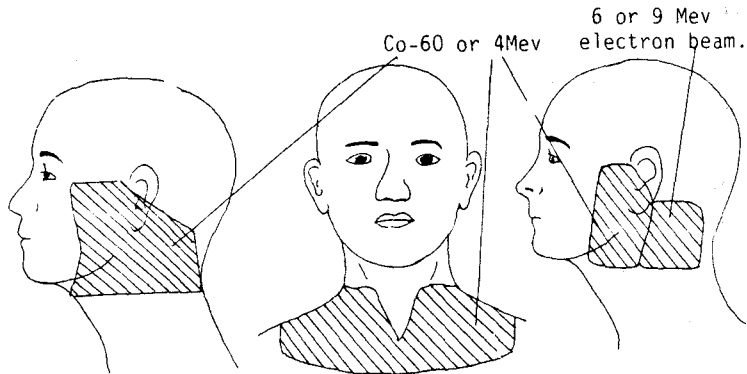


Fig. 2. Radiation field of nasopharyngeal carcinoma.

Table 3. Initial Response Rate

Response	No. of patients (%)		Total
	<30Yrs	>30 Yrs	
CR	15 (79)	51 (54) p<0.05	66 (58)
PR	4 (21)	40 (43) p<0.1	44 (39)
Unknown		3 (3)	3 (3)
Total	19	94	113

Table 4. Analysis of Prognostic Factors

Factors	< 30 Yrs		> 30 Yrs	
	No	5YRS(%)	No	5YRS(%)
Sex				
male	13	30.8	73	32.8
female	6	44.4	21	45.1
Stage				
I & II	0	60.0	5	66.7
III	5	24.5	17	64.6**
IV	14		72	28.7
Histology				
sq. cell ca.	6	33.3	50	36.6
undiff. ca	13	37.2	44	38.3
XRT dose				
5,000-5,999	1	30.0	8	18.8
6,000-6,999	15	50.0	73	38.2
over 7,000	3	50.0	13	57.1
Chemotherapy				
RT + CT	8	41.6	40	58.0
RT only	11	41.6	54	27.9
Initial Response				
CR	15	45.7*	51	63.7*
non CR	4	0	40	3.8

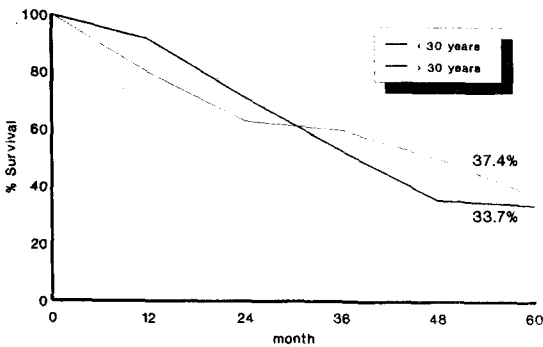


Fig. 3. Overall 5-year survival rate.

33.3% for squamous cell carcinoma. No correlation between histologic subtype and survival was found. The five year survival rates for stage III and IV were 60.0% and 24.5%, respectively.

The best survival was found in patients who obtained a complete clearance of disease after radiation therapy. The five year survival in complete responders was 45.7%, 0% in partial responders and non-responders. Thus, the status of complete response of locoregional disease after completion of radiation therapy is of paramount importance in

* P < 0.05, ** P < 0.005 by log rank test

predicting survival and the chance of remaining relapse-free (Table 4).

Fourteen of 19 patients (73.7%) failed and six of 19 patients (31.6%) developed distant failures with or without primary failure. Locoregional recurrence alone was 42.1% (Table 5). The common site of distant metastasis were bone, lung and liver with a decreasing order of frequency. A higher incidence

Table 5. Patterns of Failure

Failure	No. of patients (%)		p
	< 30 Yrs	> 30 Yrs	
Locoregional	8/19 (42.1)	38/94 (40.4)	>.05
Distant	4/19 (21.1)	10/94 (10.6)	>.05
Locoregional & Distant	2/19 (10.5)	6/94 (6.4)	>.05

of distant metastases was observed in undifferentiated carcinomas (38%) in comparison to squamous cell carcinoma (17%).

DISCUSSION

The curve representing the age distribution of NPC in "high risk" areas such as southern china, Hong Kong, etc., rises sharply after the age of thirty years; it reaches a plateau between the 45th and 54th year of age and falls slowly thereafter. Only a few patients with NPC are under the age of thirty years in china. In Africa, however, there is a second peak in the second decade, while in Birmingham the peak is prominent around the age of twenty years. In America Martin and Blady reported that 18% of their patients were under thirty years of age, while Cammoun et al. reported a rate of 21% in Tunisia similar to the United States, a post-adolescent age peak for cancer of the nasopharynx has been observed in other parts of the world including Algeria, Uganda, India, Greece and Puerto Rico⁴⁾. In our study 17% (19/113) of all patients were under the age of thirty years at diagnosis.

Epithelial malignancies occurring at a younger age are very rare. The nasopharynx, paradoxically, is one of the more common sites of epithelial malignancy in children⁵⁾. The age distribution of patients for three separate sites of head and neck malignancy who were registered at P.M.H. from 1958 to 1972, revealed a distinct younger age peak only in NPC. No younger age peak was demonstrated for oropharynx and hypopharynx²⁾.

An interesting and perhaps significant finding in the younger patients with NPC is the relatively high familial incidence of the neoplasms⁵⁾.

The EBV is suspected to be etiologic in carcinoma of the nasopharynx. Elevated titers of anti-EBV antibodies have been found in patients with Burkitt's lymphoma and NPC. Although significantly high antibody titers to EBV are present in only 45% of patients with stage I carcinoma of the nasopharynx,

the titers are elevated in 100% of patients with stage IV lesions. Patients without evidence of recurrence have lower titers. The role of the EBV in the etiology of carcinoma of the nasopharynx is obscured by the fact that the virus may be present in lymphoid tissue for a long period as a latent infection.

Therefore, its presence in this disease may be based on a previous EBV infection. But, there is no reference about the difference of titers of anti-EBV antibodies between two age groups. Although the EBV may not be the etiologic agent in carcinoma of the nasopharynx. Although the EBV may not be the etiologic agent in carcinoma of the nasopharynx, it appears to be a necessary factor for carcinoma of the nasopharynx. There is apparently another unidentified necessary factor⁶⁾.

The rarity of NPC in young patients leads to problems in diagnosis and management, but these are not dissimilar to those problems related to the same malignancy in adult patients. The presenting signs and symptoms are similar in both age groups; ie, cervical adenopathy, nasal obstruction, disturbances in vision or hearing, and epistaxis. These findings are often mistakenly interpreted as innocuous in a young patients which may lead to a delay in the establishment of a histological diagnosis. The most common area of primary involvement is the lateral wall of the nasopharynx with extension into the fossa of Rosenmuller. The narrowness of the nasopharyngeal space in young patients makes examination and identification of the primary site difficult. As a result, repeated examinations and biopsies may be necessary, thereby constituting another delay before the initiation of treatment⁵⁾. Therefore, the majority of the patients had advanced disease at diagnosis. In our study, all of the patients under 30 years were stage III or IV.

Approximately 90% of malignant tumors arising in the nasopharynx are epidermoid or undifferentiated carcinomas. Within the category of epidermoid and undifferentiated carcinoma, four morphologic entities have been described: squamous cell carcinoma, transitional cell carcinoma, lymphoepithelioma, and undifferentiated carcinoma. The term "lymphoepithelioma" was first employed by Regaud and Schmincke in 1921 to describe certain "highly radiosensitive" tumors of the nasopharynx and tonsillar regions that they believed to possess sufficiently distinctive clinical and pathological features. The chief histological feature consisted of (1) syncytial strands or bands of isolated, separate transitional cells, and (2) penetration of the tumor cell mosaic by

lymphocytes. Recently, many authors have rejected the distinct tumor entity. Therefore, it is reasonable to consider that lymphoepithelioma is nothing but a histological picture of undifferentiated carcinoma infiltrating the pre-existing lymphoid tissue of the nasopharynx⁷⁾. Different authors used different criteria for designating the histologic classifications of NPC. However, they observe the valid distinction, as far as prognosis and clinical course is concerned, between the classical epidermoid type and the undifferentiated one⁴⁾. In our study using the classification system of Yeh et al., 68% (13/19) were undifferentiated carcinomas, which is in agreement with other studies. There was no difference in survival between the two histologic subtypes.

Standard therapy for NPC in younger patients generally followed the guideline established for adults. Young patients with an advanced disease showed a better response than older patients. There are two explanations for a better response to radiation therapy in younger patients. First, undifferentiated tumors may be more radiosensitive, and secondly, young patients may tolerate radiation better than older age groups as their tissues, particularly the vessels, have not been altered by aging and atheromatosis⁴⁾. In our study initial complete response rate in younger patients was 79% as compared to 54% in older patients. These response rate were strongly related to survival.

The most important prognostic factor was represented by the extent of primary tumor growth in the nasopharynx. Radiotherapy was able to control the nasopharyngeal tumor and the metastases in the cervical nodes in the majority of young patients, but distant metastases were responsible for the final adverse outcomes in younger patients with advanced primary tumor⁸⁾. Because the main cause of treatment failure is distant metastasis in the young, treating these patients with adjuvant chemotherapy appears to be justified. Adjuvant therapy may prevent or eradicate occult metastatic disease and prolong survival⁹⁾.

CONCLUSIONS

From the analysis of our own experience and literature review, we concluded as follows;

A higher initial response rate was observed in younger patients.

More frequent distant metastasis was observed in younger patients.

No difference in survival was observed between the older and younger age groups.

REFERENCES

1. **Bala Krishnan V:** An additional younger age peak for cancer of the nasopharynx, *Int J Cancer* 15:651-657, 1975
2. **Berry MP, Smith CHR, Brown TC, Jenkin RDT, Rider WD:** Nasopharyngeal carcinoma in the young. *Int J Radiat Oncol Biol Phys* 6:415-421, 1980
3. **Jenkin RDT, Anderson JR, Jereb B, Thompson JC, Pyesmany A, Wara WM, Hammond D:** Nasopharyngeal carcinoma-A retrospective review of patients less than thirty years of age: A report from Childrens Cancer Study Group. *Cancer* 47:360-366, 1981
4. **Papavisioliou C, Paulatou M, Pappas J:** Nasopharyngeal cancer in patients under the age of thirty years. *Cancer* 40:2312-2316, 1977
5. **Ronald HN, John GB, Don KW:** Nasopharyngeal carcinomas in children. *Arch Surg* 94:214-217, 1967
6. **James BSJ:** Carcinoma of the nasopharynx in children. *Ann Otol* 84:817-826, 1975
7. **Shu Yeh, MD:** A histological classification of carcinoma of the nasopharynx with a critical review as to the existence of lymphoepitheliomas. *Cancer* 15:895-920, 1961
8. **Gasparini M, Lombardi G, Rottoli L et al:** Combined radiotherapy and chemotherapy in stage T3 and T4 nasopharyngeal carcinoma in children. *J Clin Oncol* 6:492-494, 1988
9. **TH Kim, John M, Carlos SA, John BW et al:** Adjuvant chemotherapy for advanced nasopharyngeal carcinoma in childhood. *Cancr* 63:1922-1926, 1989

= 국문초록 =

30세 이전에 발생한 비인강암의 임상적 고찰

연세대학교 의과대학 치료 방사선과학교실

안기정 · 정은지 · 이형식 · 문성록

성진실 · 김귀언 · 서창옥 · 노준규

비인강암은 해부학적으로 두개저부 및 중추신경계와 인접하고 있어 수술적 접근이 어렵고, 또 최근 항암제요법의 발달로 복합항암제를 이용한 항암제요법으로 반응율을 높이기 위한 여러 연구들이 진행되고 있지만, 아직까지 비인강암에 대한 치료는 방사선치료가 그 근간을 이루고 있다.

비인강암의 연령분포곡선은 30세 이후에 급격히 증가하여 45세에서 54세까지에서 수평을 이룬 후 서서히 감소하는 곡선을 그리는데, 10대 내지 20대에서도 작은 증가곡선을 나타내어 bimodal curve를 그리게 된다. 30세 이전에 생긴 비인강암은 그 빈도가 매우 적어서 이에 대한 연구보고가 많지 않지만 일반적으로는 30세 이후에 생긴 비인강암과는 다른 임상양상을 보이는 것으로 보고되어 있다.

이에 저자들은 1971년부터 1987년까지 연세대학교 의과대학 치료방사선과에서 치료받았던 113명의 비인강암 환자들을 30세 이전과 30세 이후 환자군으로 구별하여, 임상적 특성 및 치료에 대한 관해율, 이에 따른 생존율 및 생존에 영향을 미치는 인자들, 그리고 치료실패양상 등을 분석 비교하여 향후 30세 이전의 비인강암 환자의 치료에 지침을 마련하고자 본 연구를 시행하여 다음과 같은 결과를 얻었다.

1. 30세 이전의 비인강암 환자에서 치료에 대한 초기반응율이 높았다
2. 30세 이전의 비인강암 환자에서 통계적 의의는 없었으나 원격전이가 많았다.
3. 두 연령군간에 생존율의 차이는 없었다.