Distant Metastases of Nasopharyngeal Carcinoma after Definite Irradiation

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One hundred and thirty five patients with carcinoma of the nasopharyx were treated by radiation therapy in the Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University between August 1977 and July 1987. Of the 30 patients omitted: 8 had distant metastases at initial diagnosis or during radiotherapy; 18 patients refused or did not receive a full course of radiation therapy, and four had not been confirmed histologically. The remaining 105 patients were analysed to determine the incidence and pattern of distant metastases.

Diagnosis of distant metastases was made based on clinical signs and radiography, even though histologic confirmation was not made. Twenty-six patients developed distant metastases after definite irradiation of nasopharyx and neck, an incidence rate of 24.8%. The common sites of distant metastases were, in descending order, bone, lung, liver, and brain. There was a strong correlation between Ho's N stage and distant metastases rate. But sex, age, histologic subtype (squamous cell and undifferentiated cell), AJC T and N stage, treatment modalities (radiotherapy alone and radiotherapy combined with chemotherapy) were not significant. Of those patients who developed distant metastases, 80.8% were discovered within 2 years of their radical radiotherapy.

The prognosis for nasopharyngeal carcinoma patients developing distant metastases was poor: median survival was nine months and 80% of those patients died within two years of the initial diagnosis of distant metastasis.

Key Words: Nasopharyngeal Carcinoma (NPC), Distant Metastases (DM), Ho's N stage

INTRODUCTION

Compared with other head and neck tumors, nasopharyngeal carcinoma has a higher incidence of distant metastases[1~3]. Based on clinical information without autopsy, 14.9~53% of distant metastases have been reported for NPC[4~12], compared with 5.3~23.6% reported for other head and neck cancers[2,3,13~16]. Among head and neck cancers, nasopharyngeal carcinoma (NPC) is a special entity with its anatomical constraints and radiosensitivity; radiotherapy remains the most important treatment modality. Recent reviews, however, indicate poor survival despite advanced radiographic imaging, radiation therapy machine and new techniques. One of the important causes of failure is distant metastasis[17,18]. So, we have reviewed and analysed our ten years' experience on the incidence and pattern of distant metastases in a consecutive series of patients with NPC who were treated with radiation. We have also evaluated the outcome of patients who developed distant metastases and tried to identify prognostic factors predictive of distant failure.

*연세대학교 의과대학 의학학술연구비에 의하여 이루어 졌음(1991).

MATERIALS AND METHODS

Between August 1977 and July 1987, 135 patients with carcinoma of the nasopharynx were treated in the Department of Radiation Oncology, Yonsei Cancer Center.

Thirty patients were excluded from the analysis for the following reasons: eight had distant metastasis at the time of diagnosis; another 18 patients refused treatment or did not complete the full course of radiation therapy, and four patients had not been proven histopathologically by nasopharynx or enlared neck node biopsy. The remaining 105 patients formed the basis of the present study.

There were 80 male and 25 female patients. Their ages ranged from 15 to 71 years with a median age of 48. All patients had histological confirmation by biopsy of the primary tumors in nasopharynx or enlarged neck nodes. Fifty of the tumors (47.6%) were classified as squamous cell carcinoma and 55

Table 1. Patients Characteristics in Nasopharyngeal Carcinoma (NPC)

Characteristics	No. of pts.	Freq.(%)
Sex		
Male	80	76.2
Female	25	23.8
Age		
Median	48 yrs (15–71)	
Histology		
Squamous cell	50	47.6
Undifferenciated	55	52.4
Treatment Modality		
Radiotherapy (RT) alone	55	52.4
Chemotherapy + RT	50	47.6

(52.4%) as undifferentiated carcinoma including lymphoepithelioma (Table 1). All patients were staged according to American Joint Committee (AJC) staging system (1988) and Ho's classification system (1970)[18] using clinical and radiologic criteria retrospectively, even if the separation of the neck into three distinct levels may be arbitrary and not always distinct in some patients. In Ho's stage, the T1 tumors are those confined to the nasopharynx; T2 tumors are those extending to the nasal fossa, oropharynx, and adjacent muscles and nerves below the base of skull, and T3 tumors are those extending beyond the T2 limit. For N stage grouping in Ho's system, the neck is divided into three regions by the skin crease extending from the laryngeal eminence laterally, and the line joining the upper margin of the sternal end of the clavicle and the apex of an angle formed by the lateral surface of the neck and the superior margin of the trapezius. Patients with no clinically palpable neck nodes are staged as NO. When the lowest lying node involved the uppermost, middle and the lowest regions of the neck, the patients was staged N1, N2 and N3 respectively. Bilateral nodal involvement does not influence the N stage (Fig. 1).

All patients were treated with Co-60 teletherapy unit or linear accelerator. The nasopharynx, the base of skull and the upper part of neck were irradiated by two lateral, parallel opposing faciocervial fields and one anterior lower neck field. The dose to the primary site as 6000~7500 cGy, delivered in daily fraction of 180 to 200 cGy, treating 5 days per week. The dose to the lower

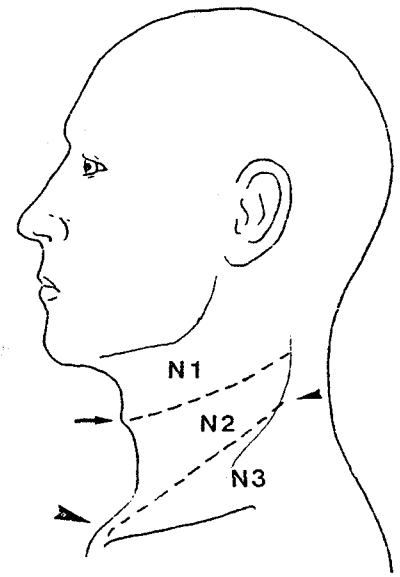

Fig. 1. Ho's cervical nodal stage level.

neck was 4500 cGy and the palpable nodes were given boost treatment with 9-15 Mev electorn beam. About half of the patients had received inducion chemotherapy irregularly. The chemotherapeutic regimen consisted of bleomycin alone or combined with vincristin, vinblastion, cisplatin, 5-FU and the courses of the treatment were one to three cycle.

After completion of radiotherapy, all patients were followed up every 4~8 weeks for the first year, then every 3 months for the second year and every 4~6 months thereafter. Unfortunately, more than half of the patients were not followed in this manner but were contactd by telephone or mail at their home addresses. Chest radiography was performed yearly. Other radiological and blood tests were done when clinical symptoms and signs indicated the need.

The duration of the median follow-up for the whole group of patients was 38 months, with a minimum of 6 months and a maximum of 112 months.

RESULTS

1. Incidence and Time of Distant Metastases

Among the 105 patients, twenty-six patients (24.8%) had distant metastases. These patients' metastases were diagnosed clinically and/or radio-

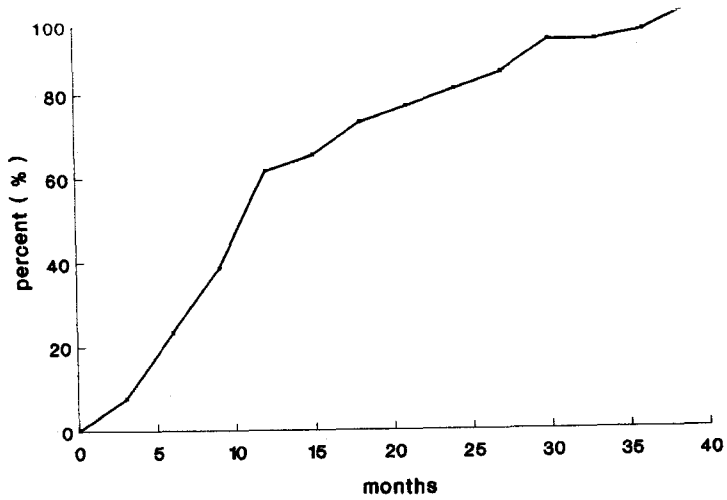

Fig. 2. Distant Metastases in NPC Interval between initial RT and first DM.

logically. The interval between the initial radical radiotherapy and the development of distant metastases was estimated. Of those patients who developed DM, 80.8% were discovered within two years of the initial treatment (Fig. 2).

2. Location of Distant Metastases

In the 26 patients in whom metastases developed, a total of 29 DM sites were found. Single organ metastasis occurred in 23 patients. Three patients had double organ involvement. All of them had bone and lung metastases. Since diagnosis of DM was made based on clinical and radiographic grounds, the extent of DM was almost certainly underestimated. Skeletal metastases occurred in 16 patients (16/29=55.2%). The subsites of bone involvement were, in descending order, T-L spine, pelvis, rib, C-spine, sternum, and humerus. Lung metastases occurred in 27.6%(8/29) of metastatic cases. Liver and brain involvement were present in 3 and 2 patients, respectively (Table 2).

3. Prognostic Factors Influencing to Distant Metastases

An attempt was made to detect whether any correlation existed between the development of DM and such factors as sex, age, histologic subtype, T and N stage at presentation (AJCC and Ho's classification), treatment modalities. Table 3 shows the distribution of the DM group of patients by sex and age grouped by decades. The frequencies by sex do not show any appreciable difference-26.3% in males and 20.0% in females.

Table 2. Distant Metastases in NPC Metastases Organ Involved

Organ	No. of pts.	(%)
Bone	13	50.0
Lung	5	19.3
Bone and Lung	3	11.5
Liver	3	11.5
Brain	2	7.7
Total	26	100.0

Table 3. Distant Metastases in NPC Sex and Age Group

	No. DM pts.	No. all pts.	(%)
Sex			
Male	21	80	26.3
Female	5	25	20.0
Age group (yrs)			
10 – 19	1	5	20.0
20 – 29	4	10	40.0
30 – 39	4	12	33.3
40 – 49	10	32	31.2
50 – 59	6	30	20.0
60 –	1	16	6.3

The frequencies of DM developing in each of the age groups were approximated to the overall fre-

quency, except for the seventh decades. Only one patient in the seventh decade developed DM.

Table 4. Distant Metastases in NPC AJCC T and N Stage

	T1	T2	T3	T4	DM/Nx	(%)
N0	0/2	2/4	0/9	0/7	2/22	9.1
N1	1/3	0/1	2/12	2/8	5/24	20.8
N2	2/4	1/9	6/14	5/20	14/47	29.8
N3	0/0	2/4	3/6	0/2	5/12	41.7
DM/Tx	3/9	5/18	11/41	7/37	26/105	
(%)	33.3	27.7	26.8	18.9		24.8

* DM : distant metastases
* univariate analysis in T stages : $p > 0.1$
N stages : $p > 0.05$

Table 5. Distant Metastases in NPC Ho's T and N Stage

	T1	T2	T3	DM/Nx	(%)
N0	1/4	1/11	0/7	2/22	9.1
N1	0/10	4/25	4/19	8/54	14.8
N2	1/3	3/7	2/7	6/17	35.3
N3	2/2	6/6	2/4	10/12	83.3
DM/Tx	4/19	14/19	8/37	26/105	
(%)	21.1	28.6	21.6		24.8

* DM : distant metastases
* univariate analysis in T stages . $p > 0.1$
N stages : $p < 0.05$

However, the number of patients in each of these groups is too small for statistical assessment. Table 4 and 5 show the percentage 'risk' of DM developing in each of the grouping by T (primary tumor) and N (cervival lymphadenopathy) stage by AJCC and Ho's staging system. Using the 'Chi-square' test, the differences between the Ho's N stages (NO, N1, N2) are significant at the 5% level ($p<0.05$). Although N stage by AJC does not show the statistical significance, it does show the trend of the increasing 'risk' of DM by increasing the N stages from NO to N3.

When the rates of DM were analyzed by histologic subtype, squamous cell and undifferentiated carcinoma had the similar incidence of DM, 20%

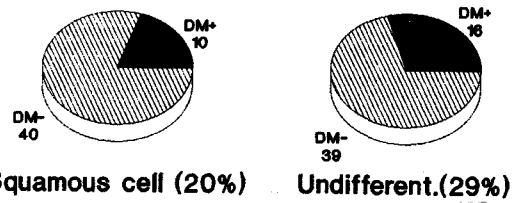

Fig. 3. Distant metastases in NPC histologic subtype.

Table 6. Distant Metastases in NPC Treatment Modalities

	No. DM pts.	No. all pts.	(%)
RT alone	14	55	25.5
Chemotherapy+RT	12	50	24.0
Total	26	105	24.8

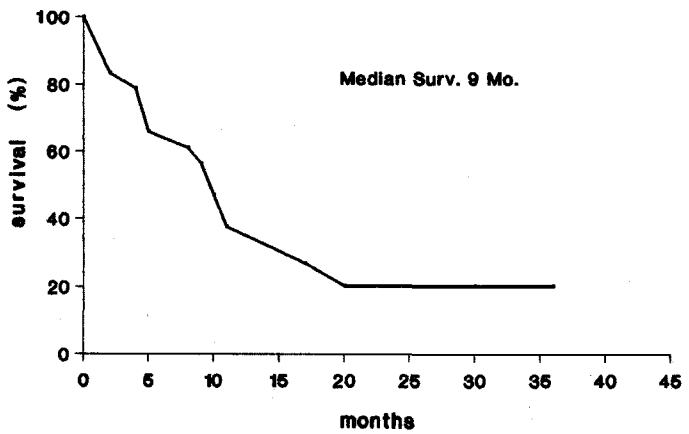

Fig. 4. Distant Metastases in NPC Survival after development of first DM.

and 29% respectively (Fig. 3). We try to detect whether any correlation existed between the development of DM and the treatment modalities, radiotherapy alone and induction chemotherapy and radical radiotherapy group. But there was no significant difference in the rate of DM (Table 6).

4. Survival after Development of Distant Metastases

Median survival in those who developed DM was 9 months, and 80% of those patients had died within 2 years of the first diagnosis of their metastasis (Fig. 4).

DISCUSSION

Previous reports from several institutions show the incidence of distant metastases (DM) for nasopharyngeal carcinoma (NPC) from 14.9 ~53%[1~13]. Our data shows an incidence of 24.8%, comparable to that reported in the literature, but appears apparently be less frequent than some other series. Strict comparison is not possible because of the difference in stage distribution, stage classification used, and histology distribution and other possible differences in natural history of this tumor. The predilection of this tumor to metastases to bone is further confirmed by this study. This is in contrast to most head and neck cancers where lung is the most common metastasis site[3,6,10,12,20]. Huang[17] reported the axial skeleton and the long bones as the most common involvement sites. Sham et al[21] analyaed the pattern of skeletal metastases in NPC and confirmed the general bony metastases pattern, with the spine and pelvis being the common sites. In that analysis, the first region of involvement was lumbar spine (28.4%), then dorsal spine (27.7%), sacrum and pelvis (16.3%), femur (9.9%), rarely rib, sternum, humerus, cervical spine and skull vault. In this study, subsites of bone metastases were T-L spine, pelvic bone, ribs, C-spine, sternum, femur, humerus. Other organ commonly involved were lungs, liver and brain, in that order.

We calculated the incidence of distant metastases as a function of time from the initial radical radiotherapy. Of those who developed distant metastases, 80.8% were already discovered by 2 years. Khor et al[7] calculated the interval between the initial treatment and the development of first distant metastasis, 68.5% of distant metastases were found within 12 months and 92.7% within 24 months.

When we analyzed different subgroups of patients according to several factors such as sex, age, locoregional extent (AJC anc Ho stage), histologic subtype, and treatment modalities, there was a very interesting observation. There was no significant prognostic factor predictive of distant metastases except Ho's N sage.

Anwar Ahmad[11] reported that correlation between histologic subtype and pattern of distant metastases. In undifferentiated carcinoma, the incidence of bone metastases was highest, while lung metastases was lowest. But we did not observe such difference between histologic subtype and incidence or pattern of distant metastases.

We observed in this paper that there is a statistically significant correlation of Ho's node stage at presentation with the risk of distant metastases developing. The distant metastasis rate increased as cervical lymph node metastases progressed from NO stage to N3. This fact was confirmed previously in other studies of distant metastases in NPC[12].

Berger and Fletcher[8], Bedwink et al.[10], Mesic et al.[16] found such a close correlation only between N stage and distant metastases and not between T stage and metastases. Probert et al.[2] on the other hand, reported a statistically significant higher risk of distant metastases developing in T4 lesions when compared with other T stages at presentation but without a significant connection between N stage and subsequent development of metastases. Some other reports by Khor[7], Van Andel[11], A. Ahmad[12] and Sham[22] suggests that the incidence of distant metastases is correlated with the T stage and N stage. No correlation between T stage by AJC, Ho and distant metastasis incidence was observed in the present study.

The parameters underlying the N stage classification adopted by Bedwink et al.[8] and Mesic et al.[10] are the size of the nodes and contralateral neck involvement (American Joint Committee for Cancer Staging and End Result Reporting, 1978). This is similar to the stage classification of other head and neck tumors. The importance of node size and contralaterality was embedded in AJC classification of node involvement, and we have shown that it was positively correlated with distant failure although there was no statistical significance. We have, however, found that the Ho stage classification of N stage is superior as a prognostic factor predictive of distant failure.

Nasopharyngeal carcinoma has a high propensity for lymph node metastasis compared with

other head and neck tumors. It is centrally situated in the head, often with bilateral cervical node involvement: most of the time the first clinically palpable nodes are in the high cervical chain and then spread downward to the supraclavicular fossae[26]. In the Ho stage classification of N stage, by dividing the neck into 3 regions, and ranking the involvement from above downwards, it is hoped that the ranking will measure the propensity for spread and the actual extent of spread via the lymphatics. It is also hoped that such a measure of spread via the lymphatics will be useful as an indicator of distant metastasis. In a recen study of neck node involvement and the pattern of distant failure in NPC by Sham et al[12], the incidence of DM is correlated with the Ho's T stage, N stage and the characteristics of the cervical nodes (size, movable or fixed), although there was no correlation with bilaterality of neck node involvement.

The results of the present study support the above literature reviews.

It is interesting to note no significant difference between the T stage in either the AJC or Ho stage systems, as far as the distant metastasis is concerned. This lack of difference may reflect the inadequacy of clinical examination in detecting details of adjacent tissue extension of tumor without the use of computed tomography. (about half of present analyzed cases).

As radiotherapy is a locoregional form of treatment, improvement in survival rates for patients with high risk of distant failure is not expected when reliance is entirely on radiotherapy. The integration of chemotherapy into the primary treatment of NPC is accepted as a theoretical means to improve current results of radiotherapy. Unfortunately, there is no standard regimen for NPC. Preradiotherapy induction chemotherapy trial results showed that the high rate of tumor response, but did not appear to convey long-term benefit to patients treated with radiation therapy alone[23]. Other adjuvant to patients treated with combination chemotherapy after radiotherapy in NPC had been tried to find the benefit of chemotherapy on the survival, locoregional and distant failure[24].

The pattern of relapse was similar in the two treatment arms (RT alone and RT followed by combination chemotherapy). The rate of distant metastases in the group of adjuvant chemotherapy patients also similar. In our study, treatment modalities-whether by radiotherapy alone or combined chemoradiotherapy-did not affect the incidence of distant metastases. But because the chemotherapy regimen, dose and schedule were irreguar and inadequate, it is difficult to conclude that induction chemotherapy did not play a role in preventing distant failure. Even though the result of adjuvant chemotherapy for nasopharyngeal carcinoma has been disappointing and the late toxicity was not slight, the high incidence of distant metastasis warrants further clinical trials in this direction[23,25]. Patients at a very high risk of such failure, those with lower lying and bulky neck nodes, should be recruited into properly controlled randomized trials of combined radiochemotherapy.

The prognosis for patients with nasopharyngeal carcinoma developing distant metastases is poor; 80% of the patients die within two year of diagnosis of first metastases, and the overall median survival is nine months. This result is more favorable than Khor's study[7]: 90% of the patients dying within a year of diagnosis of first DM. Probert et al.[2], in their series of head and neck cancer patients, gave a fatality rate of 90% within two years.

CONCLUSION

1. The incidence of distant metastasis in nasopharyngeal carcinoma after definite radiotherapy was 24.8%.
2. The common sites of distant metastases were, in descending order, bone, lung, liver and brain.
3. There was a strong correlation between Ho's N stage and incidence of development of distant metastases of nasopharyngeal carcinoma.
4. Of those patients with distant metastases, 80.8% were discovered within 2 yeas or earlier from definite radiotherapy.
5. The prognosis of nasopharyngeal carcinoma patients on development of distant metastases was poor; 80% died within two years from diagnosis of first metastasis, and the median survival was nine months.

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=국문초록=

근치적 방사선 치료를 받은 비인강암 환자의 원격전이 빈도 및 양상에 관한 고찰

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1977년 7월부터 1987년 6월까지 10년간 연세대학교 의과대학 치료방사선과에서 방사선 치료를 받았던 135명의 비인강암 환자 중 치료시작 당시 조직학적으로 확진되지 않았던 환자, 원격전이를 동반하고 있었던 환자 및 방사선 치료를 완료하지 못한 환자 30명을 제외한 105명 환자를 대상으로 원격전이의 빈도, 양상 및 예후를 분석하였다.

원격전이 진단은 임상증상과 방사선 소견으로 하였으며, 대상환자 105명중 원격전이를 보인 환자는 26명으로 원격전이율 24.8%였으며, 원격전이의 장기는 이전의 다른 보고들에서와 마찬가지로 골전이(50.0%)가 가장 많았고, 다음이 폐(19.3%), 간(11.5%), 뇌(7.7%) 순서였다.

원격전이에 영향을 미치는 인자로 연령, 성별, AJC의 T병기, N병기, Ho의 T병기, N병기, 조직세포유형 및 치료방법등을 분석해 보았으나 Ho의 N병기에서만 N0, N1, N2, N3로 감에따라 원격전이율이 증가하는 양상을 보였다($p<0.05$).

원격 전이 발생시기는 환자의 80.8%에서 방사선 치료시작부터 2년이내에 일어나는 것을 보여 비교적 조기에 발생함을 알 수 있었다. 원격전이가 발생한 26명의 환자에 있어서, 원격전이후 생존율을 살펴보면 중앙 생존치가 9개월이었고 1년생존율 60%, 2년 생존율 20%를 보여 비인강암 환자에서 일단 원격전이가 발생하면 그 예후가 불량함을 알 수 있었다.