

Original Articles

Treatment Outcomes of Patients with AJCC Stage IVC Nasopharyngeal Carcinoma: Benefits of Primary Radiotherapy

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Received October 2, 2005; accepted December 13, 2005; published online March 6, 2006

Background: There is no agreement on the optimal management of patients initially presenting with metastatic nasopharyngeal carcinoma. This study was performed to investigate the treatment outcomes and to assess whether radiotherapy to the primary tumors has survival benefits.

Methods: From 1993 to 2001, 806 consecutive patients with histology-proven nasopharyngeal carcinoma were registered at our department. Among them, 125 patients had distant metastases and fulfilled the criteria for stage IVC of the 1997 American Joint Committee on Cancer staging system. Tumor histology according to the World Health Organization classification was Type 2 in 67 patients and Type 3 in 58 patients. The most common site of initial metastasis was bone. A total of 28 patients refused any treatment, 39 received chemotherapy alone and 58 had radiotherapy to the primary tumor sites alone.

Results: The 1 year overall survival rates were 25, 36 and 48% for patients with no treatment, chemotherapy and radiotherapy, respectively. In multivariate analysis, age of diagnosis and treatment modality were confirmed as independent prognostic factors for overall survival.

Conclusions: Based on our results, radiotherapy to the primary tumor sites could be considered for patients with stage IVC nasopharyngeal carcinoma. A combination of radiotherapy and chemotherapy might have potential survival benefits. Further randomized prospective study is necessary to explore the optimal treatment strategy.

Key words: nasopharyngeal carcinoma – radiotherapy – chemotherapy – metastasis

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is highly prevalent in Taiwan. This disease is sensitive to both radiotherapy and chemotherapy (1–5). Owing to the high degree of radiosensitivity and anatomic restrictions, the standard treatment for NPC is definitive radiotherapy. It has been reported that NPC has the highest incidence of distant metastases among head and neck cancers (6–12). For patients presenting with distant metastases at initial diagnosis, the optimal treatment strategy remains a subject of debate. A major controversy concerns the necessity of treating the primary nasopharyngeal tumors. It is usually considered unnecessary to treat the prim-

ary tumor sites for patients with distant metastasis because of their short life expectancy. However, some physicians consider that local control of nasopharyngeal tumors and neck lymphadenopathy might improve the quality of life and also contribute to a prolonged survival.

This study was undertaken to investigate the treatment outcomes of patients with NPC and distant metastases at initial diagnosis. Treatment modalities and potential prognostic factors were evaluated to clarify their relationship to overall survival. These results might contribute to treatment recommendations and exploration of avenues of further research.

PATIENTS AND METHODS

Between March 1993 and September 2001, 806 consecutive, previously untreated patients with histology-proven NPC were registered at our department. Among them, 125 patients had

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Table 1. Patient characteristics according to treatment modality

	No treatment	Chemotherapy	Radiotherapy	P-value
Gender				0.738
Male	22 (79%)	31 (80%)	49 (85%)	
Female	6 (21%)	8 (20%)	9 (15%)	
Age (years)				0.032
≤65	23 (82%)	36 (92%)	41 (71%)	
>65	5 (18%)	3 (8%)	17 (29%)	
Histology				0.130
WHO Type 2	12 (43%)	19 (49%)	37 (64%)	
WHO Type 3	16 (57%)	20 (51%)	21 (36%)	
T-classification				0.149
T1	6 (21%)	8 (20%)	9 (15%)	
T2	10 (36%)	14 (36%)	14 (24%)	
T3	5 (18%)	12 (31%)	12 (21%)	
T4	7 (25%)	5 (13%)	23 (40%)	
N-classification				0.070
N0	2 (7%)	1 (3%)	9 (15%)	
N1	5 (18%)	6 (15%)	15 (26%)	
N2	12 (43%)	22 (56%)	15 (26%)	
N3	9 (32%)	10 (26%)	19 (33%)	

WHO, World Health Organization.

distant metastases at initial diagnosis and satisfied the criteria for stage IVC of the 1997 American Joint Committee on Cancer (AJCC) staging system (13). The 125 patients constituted the cohort of this study. There were 102 men and 23 women. All were ethnic Chinese. Their age ranged from 20 to 86 years (median, 53 years). All patients had a pre-treatment evaluation including complete history, physical examination, hematology and biochemistry profiles, chest radiographs, sonography of abdomen, whole-body bone scan and computed tomography (CT) scans of head and neck regions. Data were analyzed retrospectively by reviewing the medical records and imaging studies. Among the 125 patients, 28 patients refused any treatment, 39 patients received chemotherapy alone and 58 patients had radiotherapy alone. For those who wanted to receive treatment, the treatment modalities were selected according to the treating physician's policy of practice. The patient characteristics according to different treatment modalities are listed in Table 1. Most of these characteristics were evenly distributed except age of diagnosis.

Tumor histology according to the World Health Organization classification (14) was Type 2 in 67 patients (54%) and Type 3 in 58 patients (46%). The T-classification and N-classification were re-evaluated according to the 1997 AJCC staging system. A total of 23 patients had T1, 38 had T2, 29 had T3 and 35 had T4 tumors; 12 patients had N0, 26 had N1, 49 had N2 and 38 had N3 diseases; 9 patients had pre-treatment excisional biopsy of neck lymph nodes (LN).

Distant metastases were diagnosed by imaging studies (bone scan, CT scan, sonography). The most common sites of initial metastases were bone (103 patients, 82%), followed by liver (44 patients, 35%) and lung (17 patients, 14%). Multiple metastases were observed in 35 patients, and 17 patients were found to have new distant metastases during the follow-up period.

RADIOTHERAPY

The treatment volume included the primary tumor sites and the neck lymphatics to the clavicle. The nasopharynx and upper neck were treated via bilateral opposed fields. The superior margin included the entire sphenoid sinus and the base of the skull with a 2 cm margin beyond the tumors visible on the CT scan. The posterior margin included 2 cm beyond the mastoid process and was extended further posteriorly with a 2 cm margin beyond any palpable neck LNs. Anteriorly, the field included the posterior third of the maxillary sinus and nasal cavity and was extended further anteriorly with a 2 cm margin beyond the tumors noted on the CT scan. The oral cavity was shielded as much as possible without compromising the margins around the tumors. Inferiorly, the field extended to the thyroid notch. A low anterior field with spinal cord shield, matched to the bilateral opposed portals, was employed to cover the lower neck and supraclavicular fossa. After 46.8 Gy was delivered, the initial bilateral opposed portals were reduced to spare the spinal cord. The beam quality was 6 MV photons for initial irradiation and 10 MV photons for off-cord boost. The total external radiation doses ranged from 66.6 to 75.6 Gy (median, 72 Gy). The neck lymphatics were boosted with electron beams of appropriate energy (9–12 MeV) determined by the depth and size of the neck lymphadenopathy. The doses of electron beams ranged from 12 to 24 Gy. External beam radiotherapy was delivered with daily fraction of 1.8 Gy for photon beams and 2 Gy for electron beams, five fractions per week. The median treatment duration was 62 days (range, 55–72 days). Intracavitary brachytherapy with a high-dose-rate remote after-loading ¹⁹²Ir unit was applied to 10 patients as part of boost irradiation. A total of 3–6 Gy with fraction size of 3 Gy was delivered to 2 cm off the midpoint of the ¹⁹²Ir source. Brachytherapy was delivered twice a week. Patients were offered intracavitary brachytherapy according to the treating physician's preference.

CHEMOTHERAPY

A total of 39 patients received two to four courses of chemotherapy. The regimen of chemotherapy consisted of cis-diamine-dichloroplatinum (CDDP) and 5-fluorouracil (5-FU). CDDP 100 mg/m² was given as a bolus infusion on day 1 and 5-FU 1000 mg/m²/day was delivered by 24 h continuous infusion, days 1–5. The cycle was repeated every four weeks. Patients with adequate renal, hepatic and bone marrow function were eligible for chemotherapy.

FOLLOW-UP

After completion of treatment, patients were examined at 4 week intervals until the acute reactions subsided. Subsequently, patients were followed up every 2 months. All patients except three were regularly followed up. Examination of the nasopharynx was performed at each follow-up visit. Before 1995, mirror examination was performed to evaluate the nasopharynx, oropharynx and nasal cavity. From 1995 onwards, fiberoptic nasopharyngoscopy was routinely performed instead of mirror examination. Hematology and biochemistry profiles, chest radiographs, sonography of abdomen, bone scan and CT scan were checked when there was any clinical indication. The radiation-related complications were recorded according to the Radiation Therapy Oncology Group (RTOG) grading system (15). Owing to the lack of a suitable scoring scheme for hearing impairment in the RTOG system, SOMA scales were employed (16). Current follow-up status was obtained by review of the medical records, written or telephone correspondence. At the time of this retrospective review, no patients were alive.

STATISTICS

The endpoints of this study were overall survival rates and treatment-related complications. The software SPSS (version 11) was utilized for statistical analysis. Survival rates were analyzed in relation to different treatment modalities, patient and tumor characteristics using univariate and multivariate analyses. Overall survival rates were calculated actuarially with Kaplan–Meier methods (17). Differences between potential prognostic subgroups were tested for statistical significance using the log-rank test, with $P < 0.05$ as the significance limit (18). All statistically significant prognostic variables in the univariate analysis were considered in the multivariate analysis. Multivariate analysis was performed with the Cox regression model to identify the independent prognostic factors (19).

RESULTS

The median survival of these 125 patients was 9.7 months. The 1 year and 2 year overall survival rates were 39 and 14%, respectively. In the multivariate analysis, age at diagnosis and treatment modality showed independent prognostic significance for overall survival rates. The 1 year overall survival rate was 25, 36 and 48% for patients receiving no treatment, chemotherapy alone and radiotherapy alone, respectively ($P = 0.0015$, Fig. 1). Among those treated with radiotherapy, patients receiving a radiation dose of 70.2–75.6 Gy survived longer than those receiving 66.6–68.4 Gy (median survival, 14 versus 8.9 months; 1 year overall survival rate, 53 versus 27%; $P = 0.0019$). The details of the univariate and multivariate analyses are listed in Tables 2 and 3.

Among those receiving radiotherapy, 38 patients developed xerostomia. The median interval between the initiation of

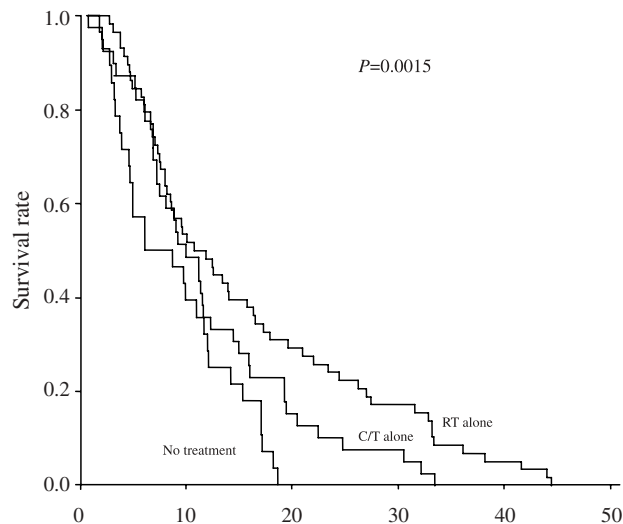


Figure 1. Overall survival rates according to the treatment modalities. Treatment modality: no treatment versus chemotherapy versus radiotherapy

Table 2. Univariate analysis of prognostic factors for overall survival rates

Variables	No.	1 year survival	2 year survival	P-value
Age (years)				0.0335
≤65	100	44%	15%	
>65	25	20%	12%	
Treatment modality				0.0015
None	28	25%	0%	
Chemotherapy	39	36%	10%	
Radiotherapy	58	48%	24%	
T-classification				0.8855
T1	23	48%	22%	
T2	38	42%	13%	
T3	29	35%	12%	
T4	35	35%	14%	
N-classification				0.5653
N0	12	42%	25%	
N1	26	45%	12%	
N2	49	37%	8%	
N3	38	37%	18%	
Histology				0.3431
WHO Type 2	68	36%	12%	
WHO Type 3	57	43%	18%	

radiotherapy and occurrence of xerostomia was 2 months (range, 0.2–10 months). Hearing impairment was observed in five patients (Grade 3, one patient). The median interval between the initiation of radiotherapy and occurrence of hearing impairment was 11 months (range, 6.5–27 months). Other radiation-related complications included neck fibrosis in

Table 3. Multivariate analysis of prognostic factors for overall survival rates

Variables	<i>P</i> -value	Hazard ratio (95% CI)
Age	0.001	2.165 (1.356–3.457)
Treatment modality	0.001	0.620 (0.481–0.798)

CI, Confidence interval.

Treatment modality: no treatment versus chemotherapy versus radiotherapy.

four patients, trismus in three patients, dysphagia in two patients, tinnitus in two patients and hoarseness in one patient. In summary, 40 of those treated with radiotherapy had at least one of the above-mentioned radiation-related complications and only one patient had a Grade 3 radiation-related complication.

Among those receiving chemotherapy, 26 patients had two cycles of chemotherapy and 13 patients had three or four cycles of chemotherapy (median survival, 9.3 versus 11.6 months; 1 year overall survival rate, 35 versus 39%; $P > 0.05$). The acute toxicities from chemotherapy were mainly nausea (80%), vomiting (78%), mucositis (75%) and myelosuppression (55%). All chemotherapy-related complications were reversible and no treatment-related death was noted.

The overall locoregional response rate to chemotherapy was 80%, but only 6% of those receiving chemotherapy achieved a complete locoregional response. On the other hand, a complete locoregional response was observed in 82% of patients treated with radiotherapy. For patients with bone metastasis alone, the 1 year overall survival rate was 36, 22 and 50% for patients receiving no treatment, chemotherapy alone and radiotherapy alone, respectively. For patients with liver, lung or multiple metastases, the 1 year overall survival rate was 22, 40 and 32% for patients receiving no treatment, chemotherapy alone and radiotherapy alone, respectively.

DISCUSSION

Conflicting results regarding the prognostic significance of age have been reported in the literature. Although it has been observed that age was a prognostic factor for survival (20–23), other studies failed to show its prognostic significance (24,25). In our study, multivariate analysis showed a clear correlation between increased age and decreased overall survival rate.

In this article, 28 patients (22%) refused any treatment. The ratio was higher than that of patients without distant metastasis at initial diagnosis. Most of them considered that they already had terminal diseases and refused any modern therapy such as radiotherapy and chemotherapy. On the other hand, only 58 patients received primary radiotherapy because many physicians considered only chemotherapy had benefits for patients with metastatic diseases. Furthermore, it was often considered inappropriate to give a prolonged course of radiotherapy to patients with stage IVC NPC because of their short life expectancy. The acute and subacute radiation-related morbidities

might persist for months and these patients might spend much of their residual life dealing with treatment-related complications. However, even though radiotherapy is hardly curative in patients with stage IVC NPC, it would produce significant regression of the primary tumors. If the primary tumors were left untreated, they might cause severe symptoms due to the mass effect. The nasopharyngeal tumors and neck mass might cause bleeding, nasal obstruction, severe headache, visual problems, hearing problems, neck pain and airway compression. Tumor necrosis might cause a fetid smell, local inflammation and systemic infection. Quality of life would be significantly compromised. The untreated tumors would make a greater impact on the quality of life than the radiation-related complications. Furthermore, with the advent of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy, the incidence and severity of acute and subacute radiation-related complications has been significantly reduced. With regard to late radiation-related complication, it would not be a major concern because long-term survival is still not achievable with current treatment modalities. In this study, primary radiotherapy was proved to be an independent prognostic factor for overall survival of patients with stage IVC NPC. Our study also demonstrated that the complete locoregional response rate was higher for patients treated with radiotherapy than for those treated with chemotherapy. Although 40 patients developed radiation-related complications during the follow-up period, only one of them had a Grade 3 complication. Our data might support the opinion that radiotherapy to the primary tumor sites offers certain survival benefits at the cost of mild radiation-related complications. With respect to the radiation dose–response relationship, the optimal radiation dose remains a subject of debate. A higher radiation dose was reported to have a positive impact on overall survival (26,27), but other authors showed that radiation dose was not related to overall survival (23). Our results supported the opinion that a higher radiation dose was associated with higher overall survival rate and 70 Gy was suggested while primary radiotherapy was delivered.

NPC is also sensitive to chemotherapy. In general, combination regimens are believed to be more active than a single drug, and cisplatin-based regimens are considered to be more active than non-cisplatin-based combinations (1,28,29). Currently, cisplatin plus a 5-FU infusion is most widely used (5). Other active combination regimens have been investigated and promising results have also been noted (30–33). Uncertainties regarding the optimal time sequence and number of cycles of chemotherapy persist and most of the reported articles concentrated on patients without distant metastasis at initial diagnosis. In our study, there was a trend for patients receiving three or four cycles of chemotherapy to survive longer than those undergoing only two cycles of chemotherapy, but this trend did not achieve statistical significance. Owing to the retrospective nature of this study, it was hard to know whether the patients receiving three or four cycles of chemotherapy lived longer because of more cycles of

chemotherapy or whether they received more cycles of chemotherapy because they lived longer.

CONCLUSION

In the endemic area of NPC, patients with stage IVC diseases might account for approximately 10% of all NPC cases. Choosing the appropriate primary treatment modality is based on several factors, mainly the survival impact, treatment-related complications and quality of life. Our results show that radiotherapy alone to the primary tumor sites could offer higher overall survival rates compared with chemotherapy alone. The radiation-related complications were limited. It is also reasonable to assume that a combination of chemotherapy and radiotherapy might have potential survival benefits for selected patients with stage IVC NPC. The issue of quality of life of these patients should be explored in the future. Prospective randomized studies are needed to optimize treatment strategy.

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