Chemotherapy plus radiotherapy makes curability a possibility in nasopharyngeal carcinoma patients with distant metastasis at diagnosis

H Lin, HX Lin, XY Cai, T Jin, LB Guo, HZ Wang, R Sun, WH Hu

Abstract

Background
Systemic chemotherapy is the major treatment for nasopharyngeal carcinoma (NPC) patients with distant metastasis at diagnosis. Addition of radiotherapy has not been explored in these patients.

Methods
We retrospectively analysed 226 NPC patients with distant metastasis at diagnosis who received chemotherapy alone or chemotherapy plus radiotherapy. Survival was analysed using Kaplan–Meier analysis and the log-rank test.

Results
Median follow-up was 65.5 months (range, 27–113 months). Median overall survival (OS) was 16 months (95% CI, 14.3–17.7) for the chemotherapy group and 36 months (26.9–45.1) for the chemotherapy plus radiotherapy group (P < 0.001). Median progression-free survival (PFS) was 7 months (4.9–9.1) for the chemotherapy group and 28 months (18.2–37.8) for the chemotherapy plus radiotherapy group (P < 0.001). Cox multivariate analysis indicated that chemotherapy plus radiotherapy makes curability a possibility in these patients.

Conclusions
Adding radiotherapy to four to six cycles of paclitaxel-based chemotherapy significantly improved PFS and OS in distant metastatic NPC patients. Chemotherapy plus radiotherapy makes curability a possibility in nasopharyngeal carcinoma patients with distant metastasis at diagnosis.

Introduction
Nasopharyngeal carcinoma (NPC) is different to other head and neck cancers because of its extremely unbalanced endemic distribution. The incidence of NPC is lower than 1 per 10 000 in most regions of the world; however, there is a high incidence of this disease in southern China. The incidence of NPC in Guangdong province is up to 20–50 per 100 000 males. NPC has a high propensity to metastasize to other sites; the incidence of metastasis in NPC ranges from 20% to 41% (4–6). Compared with 5%–24% in other head and neck cancers. The most frequent sites of metastasis in NPC are the lung, liver and bones.

Palliative systemic chemotherapy is the primary treatment for NPC patients with distant metastasis at diagnosis (4–6). However, radiotherapy is the primary treatment for non-metastatic NPC because of its anatomic location and radiosensitivity. With recent advances in radiotherapy techniques, local control rates have improved for the early stages of NPC. The role of additional chemotherapy in the management of NPC patients at risk of developing metastases is well established because of the high chemosensitivity of NPC. However, the results of chemotherapy as an initial monotherapy in NPC patients with distant metastasis at diagnosis remain unsatisfactory, and the benefits of adding radiotherapy, which may potentially cure primary disease, have not yet been confirmed in NPC patients with distant metastasis at diagnosis.

Methods
Patients and methods
Between January 2003 and December 2010, 284 patients with an initial diagnosis of metastatic NPC were identified from the cancer registry database at Sun Yat-sen University Cancer Center. The inclusion criteria were: (i) patients with pathologically confirmed non-keratinizing NPC; (ii) those with distant metastasis at diagnosis; (iii) confirmation of distant metastatic lesion(s) via radiological examination; and (iv) patients treated with chemotherapy plus radiotherapy alone as an initial monotherapy in this group of NPC patients with distant metastasis at diagnosis. We also investigated the prognostic factors in order to improve the survival rate and identify the optimal strategy for this group of NPC patients.
Treatment approaches
All treatment approaches mentioned in this study were first-line therapy, which the patients received after an initial diagnosis of NPC with distant metastasis. When selecting treatment approaches, a comprehensive consideration of each individual patient, their economic situation and their treatment preferences was made by the multidisciplinary team at our cancer centre. Of the 212 patients, 105 underwent chemotherapy alone and 107 underwent chemotherapy plus radiotherapy. The chemotherapy regimens included: (i) PF regimen: 5-FU 1000 mg/m² administered by intravenous (i.v.) infusion daily on days 1–5 or by continuous intravenous (c.i.v.) infusion over 120 h and cisplatin 80 mg/m² administered by i.v. infusion in divided doses on days 1–3; (ii) TP regimen: paclitaxel 175 mg/m² administered by i.v. infusion on day 1 and cisplatin 80 mg/m² administered by i.v. infusion in divided doses on days 1–3; (iii) TPF regimen: paclitaxel 175 mg/m² administered by i.v. infusion on day 1, cisplatin 75 mg/m² administered by i.v. infusion in divided doses on days 1–3 and 5-FU 750 mg/m² administered daily by i.v. infusion on days 1–5; (iv) GP regimen: gemcitabine 1000 mg/m² administered by i.v. infusion on days 1 and 8 and cisplatin 80 mg/m² administered by i.v. infusion in divided doses on days 1–3; (v) BPF regimen: bleomycin 15 mg administered by intramuscular injection twice a week, cisplatin 75 mg/m² administered by i.v. infusion in divided doses on days 1–3 and 5-FU 750 mg/m² administered by i.v. infusion daily on days 1–5.

Radiotherapy and chemotherapy
In patients who received radiotherapy plus chemotherapy, radiotherapy was started after four to six cycles of chemotherapy. All patients who were treated with radiotherapy received high palliative intent radiation therapy. Megavoltage photons (6 MV or cobalt-60) were used to irradiate the primary tumour and neck lymph nodes. The patients were treated by conventional fractionation (radiotherapy was given five times a week at 2 Gy/day). The irradiation fields were defined according to tumour extension. The target volume, the entire tumour with a 2-cm margin in each direction, received at least 90% of the mid-depth central axis dose. An anterior cervical field was used to treat the whole neck with a laryngeal block. The accumulated radiation dose to the primary tumour was 68–72 Gy. The accumulated dose to the involved areas of the neck was 60–62 Gy and 50 Gy to the uninvolved areas, as described in our previous study.

Evaluation protocol and follow-up
Treatment efficacy was assessed after every two cycles of chemotherapy and at 3 months after radiotherapy using spiral MRI scans for the nasopharyngeal area and triphasic enhanced CT scans for the sites of metastasis. Long-term efficacy was evaluated using PFS and OS. PFS was defined as the time from the first day of treatment to newly occurring expansion of the primary lesion, recurrence or metastatic lesion. OS was calculated from the first day of treatment to death. Patients were followed up every 3 months after treatment until 1 July 2012. Nasopharyngeal and neck MRI scans, abdominal ultrasonography or a CT scan, serum Epstein–Barr virus measurement and liver function tests were performed during each visit.

Statistical analysis
Statistical analysis was performed using SPSS 19.0 software (SPSS, Chicago, IL, USA). Clinicopathological features were analysed using the chi-square test. Survival rates were analysed using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis using a Cox proportional hazards model was used to test independent significance by backward elimination of insignificant explanatory variables. The criterion for statistical significance was set at \( Z = 0.05 \); all \( P \) values were based on two-sided tests.

Results
Descriptive characteristics
Of the 226 NPC patients with distant metastasis at diagnosis, 111 patients received chemotherapy alone and 115 patients received chemotherapy plus radiotherapy. In total, 82.3% (187/226) of the patients were male. The mean patient age was 48 years (range, 13–78 years). At the time of diagnosis, 145 of 226 (64%) patients had isolated metastasis in a single organ. Of all patients, 47 of 226 (21%) had lung metastases, 85 (38%) had liver metastases, 29 (22.8%) had lymph node metastases and 151 (67%) had bone metastases. The patients’ clinicopathological characteristics are shown in Table 1. In the 115 patients who received chemotherapy plus radiotherapy, the mean number of cycles of chemotherapy received was 4.4 (CI, 4.0–4.7).

Treatment efficacy
Follow-up lasted till 1 July 2012; OS data were collected for 212 patients and the data for 14 patients were censored. The median follow-up time was 65.5 months (range, 27–117 months). Improved PFS and OS were obtained in the chemotherapy plus radiotherapy group compared with the chemotherapy alone group (\( P < 0.001 \), Figure 1, Table 2). The 1, 2, 3, 4, 5 and 7 year OS rates of the chemotherapy plus radiotherapy group were higher than those in the chemotherapy alone group. Multivariate analysis demonstrated that radiotherapy plus chemotherapy improved OS and PFS compared with chemotherapy alone (\( P < 0.001 \), Table 2).

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than those of the chemotherapy alone group ($P < 0.001$, Figure 2, Table 2).

**Univariate analysis of prognostic factors for OS**
The patients’ features (age group, gender), disease factors (presence of more than one site of metastasis, jugular node diameter >3 cm, specific sites of metastases, skull base involvement) and treatment factors (radiotherapy, whether the first-line chemotherapy included paclitaxel) were included in the univariate analysis. Univariate analysis indicated that the presence of more than one site of metastases, a jugular node diameter >3 cm and liver metastases were significant negative prognostic factors for OS. The addition of radiotherapy to chemotherapy was associated with a good prognosis. In addition, first-line chemotherapy including paclitaxel was associated with a good prognosis.

**Multivariate analysis of prognostic factors for OS**
Cox multivariate analysis identified that receiving chemotherapy plus radiotherapy (HR = 0.341, $P < 0.001$) and first-line chemotherapy including paclitaxel (HR = 0.678, $P < 0.03$) were associated with a good prognosis, demonstrating that these factors were independent positive prognostic factors for OS (Table 3).

**Discussion**
NPC patients tend to exhibit a higher risk of metastasis compared with other head and neck squamous cell carcinoma patients. The most common sites for distant metastasis in NPC include the bones, lung and liver. NPC patients with distant metastasis at diagnosis usually receive palliative treatment. Palliative systemic chemotherapy, mainly cisplatin-based chemotherapy, is the major treatment modality. However, after several courses of chemotherapy, the median PFS rate is only 5–7 months. It is unknown whether effective local
control of gross residual disease provides additional value and improves outcome in NPC when micrometastasis is under control. This is the first study to reveal that radiotherapy combined with chemotherapy is superior to chemotherapy alone for treating NPC patients who have metastasis at diagnosis, as the addition of radiotherapy significantly improved PFS and OS after chemotherapy \( (P < 0.001) \).

Univariate analysis demonstrated that NPC patients with distant metastasis to only one organ or site had better outcomes compared with patients with distant metastasis to multiple organs or sites. In addition, the univariate analysis indicated that the presence of liver metastases was a negative prognostic factor. In agreement with this result, Boussen et al.\(^\text{13}\) designed a prognostic index score for metastatic NPC, which showed that liver metastasis was a negative prognostic factor.

Unless contraindicated, more than four cycles of chemotherapy are recommended for disseminated NPC in patients developing distant metastasis\(^\text{14}\). In this study, the patients received a mean of 4.4 cycles of chemotherapy before radiotherapy. The ability of chemotherapeutic treatment to reduce the tumour burden at the sites of distant metastases is important for the control of subclinical disease. Our results suggested that the addition of radiotherapy significantly improved PFS in NPC patients with distant metastasis at diagnosis who received a mean of 4.4 cycles of chemotherapy compared with patients who received chemotherapy alone. Jin et al.\(^\text{15}\) reported that systemic chemotherapy is the mainstream therapy for non-Hodgkin lymphoma. However, radiotherapy was shown to increase regional control in non-Hodgkin lymphoma, which may make it worthwhile to consider radiotherapy in NPC patients with distant metastases.

**Figure 1:** Kaplan–Meier PFS curves for 226 NPC patients with distant metastasis at diagnosis treated with chemotherapy plus radiotherapy or chemotherapy alone. Median PFS was 28 ± 9.8 (95% CI, 18.2–37.8) months in the chemotherapy plus radiotherapy group and 7 ± 2.1 (95% CI, 4.9–9.1) months in the chemotherapy alone group \((P < 0.001, \text{log-rank test})\).

**Table 2** Survival rate, PFS and OS of the 212 NPC patients with distant metastasis at diagnosis treated with chemotherapy plus radiotherapy or chemotherapy alone

<table>
<thead>
<tr>
<th>Group</th>
<th>Survival rate (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-year 2-year 3-year 4-year 5-year 7-year</td>
<td>Median ± SE (95% CI)</td>
<td>Median ± SE (95% CI)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>65 23 12 8 0 0</td>
<td>7 ± 2.1 (4.9–9.1)</td>
<td>16 ± 1.7 (14.3–17.7)</td>
</tr>
<tr>
<td>Chemotherapy plus radiotherapy</td>
<td>88 70 66 43 38 18</td>
<td>28 ± 9.8 (18.2–37.8)</td>
<td>36 ± 9.1 (26.9–45.1)</td>
</tr>
</tbody>
</table>

CI, confidence interval.

lead to improved survival. Achievement of local control may be a surrogate for improved survival\textsuperscript{15}. Radiotherapy is an effective local treatment modality for NPC. In a study conducted by dos Santos et al., durable complete response rates were reported to be greater than 80\% with conventional radiation techniques\textsuperscript{16}. Teo et al.\textsuperscript{6} suggested that locoregional control improved OS in NPC patients with distant metastasis. In our study, the median PFS of the chemotherapy alone group was only 7 ± 2.1 months compared with 28 ± 9.8 months in the chemotherapy plus radiotherapy group. Therefore, local treatment of the primary disease to improve local disease control is important for NPC patients with distant metastasis. The results of this study suggest that radiotherapy significantly improved local control and led to improved survival in NPC patients with distant metastases, as the median OS improved from 16 ± 1.7 months to 36 ± 9.1 months.

By 1 July 2012, none of the patients in the chemotherapy alone group had achieved 5 year OS. However, the 5- and 7-year OS rates of the patients in the chemotherapy plus radiotherapy group were 38\% and 18\%, respectively. Locoregional disease control is important for NPC patients with distant metastasis at diagnosis in order to obtain long-term survival. The failure to maintain long-term local response in the chemotherapy alone group makes curability impossible; however, the addition of radiotherapy as primary treatment modality makes curability a possibility in NPC patients with distant metastasis at diagnosis.

The Cox proportional hazard regression model revealed that first-line chemotherapy, which included paclitaxel, was associated with a good

![Figure 2: Kaplan–Meier OS curves for 226 NPC patients with distant metastasis at diagnosis treated with chemotherapy plus radiotherapy or chemotherapy alone. Median OS was 36 ± 9.1 (95\% CI, 26.9–45.1) months in the chemotherapy plus radiotherapy group and 16 ± 1.7 (95\% CI, 14.3–17.7) months in the chemotherapy alone group (P < 0.001, log-rank test).](image)

### Table 3 Multivariate analysis of prognostic factors for survival outcome in NPC patients with distant metastasis at diagnosis

<table>
<thead>
<tr>
<th>Item</th>
<th>P*</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver metastasis</td>
<td>0.623</td>
<td>1.093</td>
<td>0.766–1.560</td>
</tr>
<tr>
<td>Diameter of jugular node &gt;3 cm</td>
<td>0.169</td>
<td>1.264</td>
<td>0.905–1.767</td>
</tr>
<tr>
<td>Chemotherapy including paclitaxel</td>
<td>0.030</td>
<td>0.678</td>
<td>0.478–0.963</td>
</tr>
<tr>
<td>Radiotherapy plus chemotherapy</td>
<td>0.000</td>
<td>0.341</td>
<td>0.237–0.489</td>
</tr>
<tr>
<td>Multiple sites of metastases</td>
<td>0.237</td>
<td>1.254</td>
<td>0.862–1.824</td>
</tr>
</tbody>
</table>

HR, hazards ratio; CI, confidence interval.

*P < 0.05 was considered statistically significant.
prognosis in NPC patients with distant metastasis at diagnosis. Lee et al.\(^1\) and Teo et al.\(^2\) reported that induction chemotherapy with the addition of docetaxel significantly improved PFS and OS in patients with unresectable squamous cell carcinoma of the head and neck. Chemotherapy regimens with paclitaxel are suggested to be more effective for disease control. For example, Posner et al.\(^3\) reported a statistically significant improvement in the cumulative incidence of distant metastases in the docetaxel induction chemotherapy arm compared with the PF arm. Consistent with these observations, in this study, the localregional control rate was better in the TPF group than in the PF group (\(P = 0.004\)).

Like many other retrospective studies, the interpretation of our results may be hampered by a number of potential biases such as treatment approach selection. To date, no research has yet explored the effect of adding radiotherapy to chemotherapy in NPC patients with distant metastases at diagnosis. Both treatment approaches in our study may be adopted in clinical practice. When selecting treatment approaches, a comprehensive consideration of each individual patient, their economic situation and their treatment preferences was made by the multidisciplinary team at our cancer centre. The characteristics of the patients were relatively well balanced between the two groups. Despite these limitations, the results obtained from this study are interesting as a relatively large number of patients were analysed. In conclusion, we consider that the addition of four to six cycles of paclitaxel-based chemotherapy to radiotherapy can improve PFS and OS in NPC patients with distant metastases at diagnosis. Chemotherapy plus radiotherapy makes curability a possibility in these patients. Our results provide a strong support to further prospective studies for NPC patients with distant metastases at diagnosis.

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References