

Clinical Research Article

## Prognostic Analysis in Patients with Metastatic Nasopharyngeal Carcinoma at Initial Diagnosis

Chengtao Wang M.D, Ph.D<sup>1,2</sup>, Peiyu Huang M.D, Ph.D<sup>2</sup>, Ling Guo M.D, Ph.D<sup>2</sup>, Zhenyu Wang Ph.D<sup>1</sup>, Tian Zhang M.D, Ph.D<sup>1</sup>, Jun Dong M.D, Ph.D<sup>1</sup>, Junli Shi M.D, Ph.D<sup>2</sup>, Yin Li M.D, Ph.D<sup>2</sup>, Xiang Guo M.D, Ph.D<sup>2</sup>, Kajia Cao M.D, Ph.D<sup>\*2</sup>, Bixiu Wen M.D, Ph.D<sup>\*1</sup>

<sup>1</sup>Department of Radiation Oncology, The First Affiliated Hospital of Sun Yat-sen University, China

<sup>2</sup>Department of Nasopharyngeal Carcinoma, Sun Yat-Sen University Cancer Center, China

\*Corresponding author: Dr. Bixiu Wen M.D, Ph.D, Department of Radiation Oncology, The First Affiliated Hospital of Sun Yat-sen University, 58 Zhongshan II Road, Guangzhou 510080, China, E-mail: wenbix@mail.sysu.edu.cn and Dr. Kajia Cao M.D, Ph.D, Department of Nasopharyngeal carcinoma, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, P.R. China, E-mail: caokj@sysucc.org.cn

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### Summary

The aim of this study was to investigate the prognostic factors and to provide a data foundation for the therapeutic decision in patients with metastatic nasopharyngeal carcinoma (NPC) at initial diagnosis. We did a retrospective study to explore 256 NPC patients with distant metastases at initial diagnosis (M<sub>1</sub> stage) between January 1997 and December 2004. Univariate and multivariate analyses showed that gender, N staging, and treatment modality were independent prognostic factors for M<sub>1</sub> stage NPC patients. Patients who received comprehensive treatment showed favorable prognosis, and some could achieve long-term survival.

### Abstract

**Background and purpose:** To investigate the prognostic factors in patients with metastatic nasopharyngeal carcinoma (NPC) at initial diagnosis.

**Materials and methods:** Between January 1997 and December 2004, 256 NPC patients with distant metastases at initial diagnosis (M<sub>1</sub> stage) were admitted for cancer treatment. Thirty-four patients did not undergo any treatment; 18 patients were treated with radiotherapy to the primary tumor, 96 with chemotherapy alone and 108 with comprehensive treatment.

**Results:** The 1-, 3-, and 5-year overall survival rates for the whole patients were 67.0%, 17.0%, and 7.0%, respectively, and the median survival time was 15.0 (range, 0-175) months. In patients without any treatment, the median survival time was 9.0 (range, 0-48) months and the 1-, 3-, and 5-year survival rates were 35.0%, 12.0%, and 0%, respectively. In patients with cancer treatment, the median survival time was 17.0 (range, 2-175) months and the 1-, 3-, and 5-year survival rates were 71.0%, 18.0%, and 8.0% ( $\chi^2=14.968$ ,  $p=0.000$ ), respectively. Univariate and multivariate analysis showed that gender, N stage, and treatment modality were independent prognostic factors for M<sub>1</sub> stage NPC patients.

**Conclusions:** The prognosis for M<sub>1</sub> stage NPC patients is relatively poor. Patients who received comprehensive treatment showed favorable prognosis, and some could achieve long-term survival.

**Keywords:** Nasopharyngeal Carcinoma; Distant Metastasis; Radiotherapy; Chemotherapy; Prognosis

## Background

Nasopharyngeal carcinoma (NPC) is an endemic disease in southern China [1, 2]. In endemic areas, most patients present with nonkeratinizing undifferentiated subtype with the propensity of distant metastasis [3-5]. Distant metastasis is the most common mode of failure in NPC patients after cancer treatment, followed by local recurrence [5-10]. Hitherto, there have been many reports on the treatment modality and prognosis of patients who developed distant metastasis after primary treatment [11-14]. Platinum-based palliative chemotherapy combined with palliative radiotherapy was the main modality based on the patient's physical condition [15-17]. The 3-year survival rate ranges from 17% to 34%, and a few patients could achieve long-time survival [14, 16, 18, 19].

However, for patients with distant metastasis at initial diagnosis ( $M_1$  stage), what are the prognostic factors? Can radiotherapy of primary nasopharyngeal tumor and cervical lymph nodes improve the survival for these patients? All of those questions remain unresolved.

The management of nasopharyngeal cancer in patients with metastatic disease at presentation is highly variable. There are no phase III trials addressing therapeutic approaches, and the optimal sequencing of chemotherapy and radiation therapy remains unresolved. Although chemoradiation is standard of care for patients with locoregionally advanced nasopharyngeal cancer, its role in the metastatic setting is controversial.

In the present study, we carried out a retrospective study of 256 patients with NPC with distant metastases at initial diagnosis to investigate the prognostic factors and the effective treatment approach for these patients.

## Materials and methods

### Case information and diagnosis of distant metastasis

Between January 1997 and December 2004, a total of 256 previously untreated NPC patients with distant metastasis at initial diagnosis were systemically investigated. Pathological diagnosis was made according to the World Health Organization (WHO) criteria. Every patient received routine systemic physical examination; nasopharyngeal endoscopy and nasopharyngeal biopsy; hematology and biochemistry profiles; enhanced CT scan or/and MRI scan of the nasopharynx and neck; chest radiographs; ultrasonography of abdomen; and whole body bone scan before treatment. UICC TNM staging system (2002) was used for analysis.

Chest CT or PET-CT was performed in patients with abnormal finding in chest radiographs; and abdominal CT, MRI, or PET-CT in patients with abnormal finding in abdominal ultraso-

nography. Plain X-ray, CT, MRI, or PET-CT was taken for definite diagnosis in patients with abnormal whole body scan. Pathological evaluation for metastatic disease was performed in some of the patients.

### Treatment modality

Conventional two-dimensional radiotherapy was delivered to the nasopharynx, cervical lymph nodes and metastatic lesion(s) with 2 Gy per fraction, 5 fractions a week in patients who underwent radiotherapy alone or comprehensive treatment. The median dose was 70 Gy (range, 36-84 Gy) to the primary nasopharyngeal lesion, 62 Gy (range, 36-78 Gy) to the cervical lymph nodes, 55 Gy (range, 36-64 Gy) to the lung metastasis and 40 Gy (range, 12-50 Gy) to the bone metastasis.

Platinum-based chemotherapy was administered in patients who received chemotherapy alone or comprehensive treatment. The regimen of cisplatin and 5-Fluorouracil was most commonly used. Other regimens included cisplatin+5-Fluorouracil+leucovorin, cisplatin+5-Fluorouracil+bleomycin, taxol+cisplatin, cisplatin+ capecitabine, and gemcitabine + navelbine. The median period of chemotherapy was 4 cycles (range, 1-16 cycles).

Among the patients with bone metastasis, 12 were treated with external beam radiation therapy to the bone metastasis, and 4 with radioisotopes therapy. Among the patients with lung metastasis, 4 were treated with external beam radiotherapy to the metastatic lesions in the lungs and one patient with surgical treatment. Among the patients with liver metastasis, 3 were treated with radiofrequency ablation. Among patients with multiple organ metastases, 2 were treated with radiofrequency ablation for liver metastasis tumor and 6 with external beam radiation therapy to the bone metastasis.

### Statistical analysis

Survival time was defined as the duration from the date of metastasis diagnosis to the date of death or the date of last follow-up. SPSS v.16.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. The survival rate was calculated using the Kaplan-Meier method, and a log-rank test was applied for the comparison of the differences in survival rates among the groups. Multivariate survival analysis was carried out using Cox regression.

## Results

### Patient Characteristics

Between January 1997 and December 2004, 256 NPC patients with distant metastases at initial diagnosis were admitted to our institute. Among them, 219 were males and 37 were fe-

males. The median age was 49 years (range, 15-78 years). 248 patients were diagnosed as WHO type III and 8 WHO type II. The baseline characteristics of all patients are shown in Table 1.

**Table 1.** Baseline characteristics of 256 patients with metastatic NPC at initial diagnosis.

| Characteristics                | No. of patients | Percent |
|--------------------------------|-----------------|---------|
| <b>Gender</b>                  |                 |         |
| Male                           | 219             | 85.5%   |
| Female                         | 37              | 14.5%   |
| <b>Age</b>                     |                 |         |
| Median(range)                  | 49 (15-78)      |         |
| <60 year                       | 212             | 82.8%   |
| ≥60 year                       | 44              | 17.2%   |
| <b>Histology</b>               |                 |         |
| WHO II                         | 8               | 3.1%    |
| WHO III                        | 248             | 96.9%   |
| <b>T stage</b>                 |                 |         |
| T1                             | 16              | 6.2%    |
| T2                             | 56              | 21.9%   |
| T3                             | 116             | 45.3%   |
| T4                             | 68              | 26.6%   |
| <b>N stage</b>                 |                 |         |
| N0                             | 8               | 3.1%    |
| N1                             | 67              | 26.2%   |
| N2                             | 87              | 34.0%   |
| N3                             | 94              | 36.7%   |
| <b>Metastatic distribution</b> |                 |         |
| Bone alone                     | 87              | 34.0%   |
| Lung alone                     | 45              | 17.6%   |
| Liver alone                    | 56              | 21.9%   |
| Other single organ             | 17              | 6.6%    |
| Multi-organ                    | 51              | 19.9%   |
| Bone+ lung                     | 7               | 2.7%    |
| Bone+ liver                    | 18              | 7.0%    |
| Lung+ liver                    | 1               | 0.4%    |
| Bone+ lung+ liver              | 5               | 1.9%    |
| Other multi-organ              | 20              | 7.8%    |
| <b>Therapy modality</b>        |                 |         |
| No treatment                   | 34              | 13.3%   |
| Radiotherapy alone             | 18              | 7.0%    |
| Chemotherapy alone             | 96              | 37.5%   |
| Combination therapy            | 108             | 42.2%   |

**Table 1.** Baseline characteristics of 256 patients with metastatic NPC at initial diagnosis.

The states of distant metastasis were as follows: bone metastasis in 87 patients, lung metastasis in 45 patients, liver metastasis in 56 patients, lymph node metastasis in the mediastinum (6 patients), in the axilla (4 patients), and in the paraortic region (4 patients), spleen metastasis in 3 patients, and multiple-organ metastases in 51 patients.

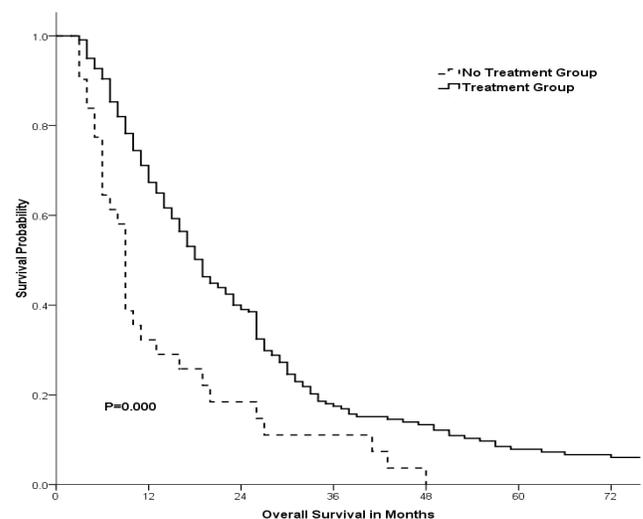
Thirty-four patients did not undergo any treatment, 222 patients received radiotherapy and/or chemotherapy. Eighteen out of the 222 patients were treated with palliative radiother-

apy to the nasopharynx and cervical lymph nodes, 96 with cisplatin-based chemotherapy, and 108 patients with comprehensive treatment of chemoradiotherapy.

Among those who received radiotherapy and/or chemotherapy, the N<sub>0</sub>, N<sub>1</sub>, N<sub>2</sub> and N<sub>3</sub> stage was 2 (0.9%), 43 (19.4%), 74 (33.3%) and 72 (32.4%), respectively for male patients; 3 (1.4%), 7 (3.2%), 10 (4.5%) and 11 (4.9%) respectively for female patients. The difference in N stage distribution between male and female was statistically significant (p=0.013). The difference in treatment modality between male and female was not statistically significant (p=0.373).

### Survival analysis

The period of the follow-up time ranged from 0 to 175 months with a median of 23 months. The median survival time was 15.0 (range, 0-175) months. The 1-, 3-, and 5-year survival rates for the whole group of patients were 67.0%, 17.0%, and 7.0%, respectively. As shown in Figure 1, the median survival time for 34 patients who did not receive any treatment was 9.0 (range, 0-48) months, and the 1-, 3-, and 5-year survival rates were 35.0%, 12.0%, and 0%, respectively. The median survival time of the 222 patients who underwent treatment was 17.0 (range, 2-175) months, and the 1-, 3-, and 5-year survival rates were 71.0%, 18.0%, and 8.0% ( $\chi^2=14.968$ , p=0.000), respectively.



**Figure 1.** Overall survival rates according to treatment or not.

### Univariate analysis

Univariate analysis was carried out for 222 patients who received cancer treatment. The results showed that gender, N staging, and treatment modality were independent prognostic

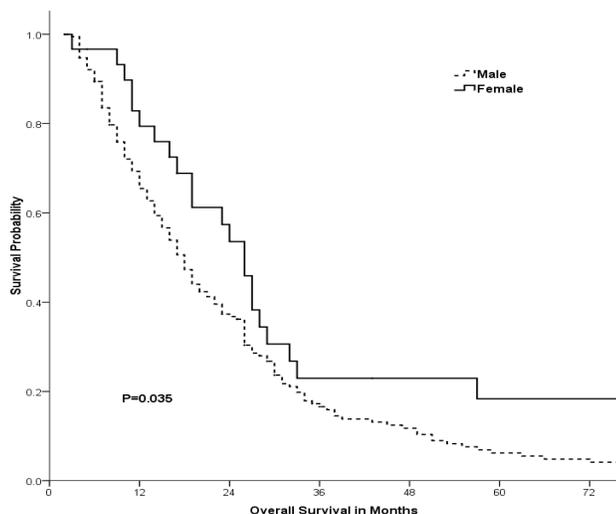
factors. The detailed analysis is shown in Table 2.

**Table 2.** Univariate prognostic analysis of 222 metastatic NPC at initial diagnosis who were treated with radiotherapy and/or chemotherapy.

| Variables                     | Cases | survival rate (%) |        |        | $\chi^2$ | P value |
|-------------------------------|-------|-------------------|--------|--------|----------|---------|
|                               |       | 1 year            | 2 year | 3 year |          |         |
| Gender                        |       |                   |        |        | 4.437    | 0.035   |
| Male                          | 191   | 70.0              | 37.0   | 18.0   |          |         |
| Female                        | 31    | 83.0              | 58.0   | 23.0   |          |         |
| Age                           |       |                   |        |        | 0.491    | 0.484   |
| <60 year                      | 190   | 73.0              | 40.0   | 19.0   |          |         |
| ≥60 year                      | 32    | 62.0              | 38.0   | 13.0   |          |         |
| Metastatic organ              |       |                   |        |        | 8.678    | 0.070   |
| Bone alone                    | 78    | 62.0              | 34.0   | 12.0   |          |         |
| Lung alone                    | 40    | 87.0              | 54.0   | 27.0   |          |         |
| Liver alone                   | 44    | 66.0              | 35.0   | 24.0   |          |         |
| Other single organ            | 16    | 81.0              | 47.0   | 20.0   |          |         |
| Multi-organ                   | 44    | 77.0              | 42.0   | 15.0   |          |         |
| Therapy modality <sup>a</sup> |       |                   |        |        | 24.802   | 0.000   |
| RT alone                      | 18    | 50.0              | 17.0   | 6.0    |          |         |
| CT alone                      | 96    | 59.0              | 33.0   | 13.0   |          |         |
| RT + CT                       | 108   | 87.0              | 51.0   | 26.0   |          |         |
| T stage                       |       |                   |        |        | 4.874    | 0.181   |
| T1                            | 13    | 52.0              | 26.0   | 5.0    |          |         |
| T2                            | 49    | 71.0              | 41.0   | 14.0   |          |         |
| T3                            | 98    | 75.0              | 42.0   | 22.0   |          |         |
| T4                            | 62    | 70.0              | 39.0   | 19.0   |          |         |
| N stage                       |       |                   |        |        | 8.951    | 0.030   |
| N0                            | 6     | 100.0             | 83.0   | 33.0   |          |         |
| N1                            | 57    | 75.0              | 49.0   | 27.0   |          |         |
| N2                            | 79    | 74.0              | 40.0   | 17.0   |          |         |
| N3                            | 80    | 64.0              | 30.0   | 12.0   |          |         |

a: RT: radiotherapy; CT: chemotherapy;

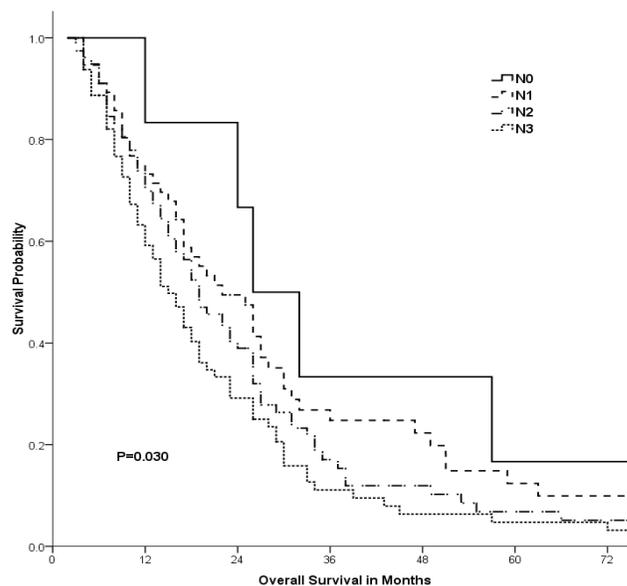
**Table 2.** Univariate prognostic analysis of 222 metastatic NPC at initial diagnosis who were treated with radiotherapy and/or chemotherapy.



**Figure 2.** Overall survival rates according to gender in treatment group.

The median survival time for female patients was 26 (range, 3-175) months, and the 1-, 2- and 3-year survival rates were 83.0%, 58.0%, and 23.0%, respectively. The median survival time of male patients was 18.0 (range, 3-157) months, and the 1-, 2- and 3-year survival rates were 70.0%, 37.0%, and 18.0% ( $\chi^2=4.437$ ,  $p=0.035$ ), respectively. The detailed results are shown in Figure 2.

As shown in Figure 3, the prognosis was poor in patients with advanced N staging. The 1-, 2-, and 3-year survival rates were 100.0%, 83.0%, and 33.0%, respectively for N<sub>0</sub> patients; 75.0%, 49.0%, and 27.0%, respectively for N<sub>1</sub> patients; 74.0%, 40.0%, and 17.0%, respectively for N<sub>2</sub> patients; 64.0%, 30.0%, and 12.0%, respectively for N<sub>3</sub> patients. The difference in overall survival according to N staging at initial diagnosis was statistically significant ( $\chi^2=8.951$ ,  $p=0.030$ ).



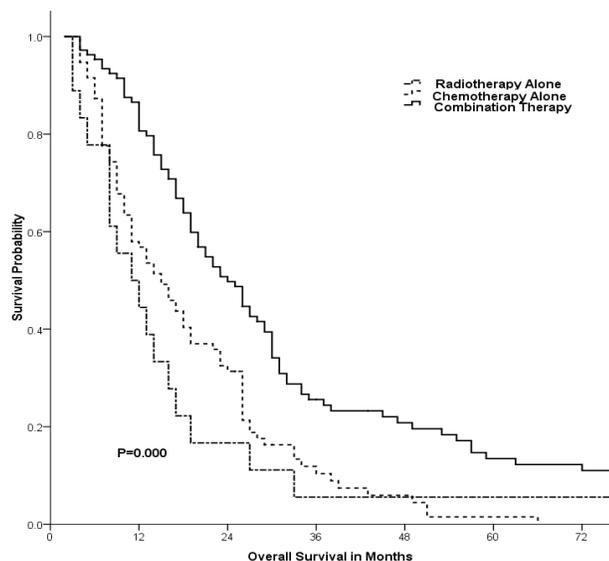
**Figure 3.** Overall survival rates according to N stage in treatment group.

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

| Characteristics  | $\beta$ value | SE    | Wald   | P value | RR    |
|------------------|---------------|-------|--------|---------|-------|
| Gender           | -0.602        | 0.229 | 6.899  | 0.009   | 0.548 |
| N stage          | 0.229         | 0.087 | 6.929  | 0.008   | 1.257 |
| Therapy modality | -0.588        | 0.115 | 26.201 | 0.000   | 0.555 |

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

Patients who underwent comprehensive treatment had better prognosis than patients who underwent chemotherapy or radiotherapy alone as shown in Figure 4.



**Figure 4.** Overall survival rates according to treatment modality in treatment group.

The median survival time of patients who underwent radiotherapy alone was 11 (range, 3-87) months, and the 1-, 2-, and 3-year survival rates were 50.0%, 17.0%, and 6.0%, respectively. The median survival time of patients who underwent chemotherapy alone was 15.0 (range, 4-66) months, and the 1-, 2-, and 3-year survival rates were 59.0%, 33.0%, and 13.0%, respectively. The median survival time of patients who underwent comprehensive treatment was 24 (range, 4-175) months, and the 1-, 2-, and 3-year survival rates were 87.0%, 51.0%, and 26.0% ( $\chi^2=24.802$ ,  $p=0.000$ ), respectively.

### Multivariate analysis

Multivariate survival analysis was carried out using Cox regression for gender, N staging, and treatment modality. The results are shown in Table 3. Gender ( $p=0.009$ ), N staging ( $p=0.008$ ), and treatment modality ( $p=0.000$ ) were independent prognostic factors of NPC with initial distant metastasis.

### Relationship between the metastatic site and the prognosis

The prognosis was further analyzed in 222 patients who were treated with radiotherapy and/or chemotherapy according to the metastatic sites. The median survival time was 22.0 (range, 2-175) months for 40 patients with lung metastasis; and the 1-, 3-, and 5-year survival rates were 87%, 27%, and 12%, respectively. For the remaining patients the median survival was 16.0 (range, 3-157) months, and the 1-, 3-, and 5-year survival rates were 68%, 17%, and 7% ( $\chi^2=5.796$ ,  $p=0.016$ ), respectively.

### Relationship between the cycles of chemotherapy and

### prognosis

The efficacy of chemotherapy on prognosis was analyzed in 96 patients who were treated with chemotherapy alone. There were 75 patients were treated with chemotherapy with less than 6 cycles; The median survival for this group of patients was 11.0 (range, 2-51) months, and the 1-, 2-, and 3-year survival rates were 50%, 23%, and 11%, respectively. 21 other patients were treated with chemotherapy more than 6 cycles; the median survival was 26.0 (range, 6-66) months, and the 1-, 2-, and 3-year survival rates were 90%, 65%, and 18% ( $\chi^2=6.149$ ,  $p=0.013$ ), respectively.

### Discussion

Patients with metastatic NPC at initial diagnosis present both primary tumor and distant metastasis. There is no recommended standard of care for this group of patients. Some patients may withdraw treatment due to poor prognosis[14]. Our study showed that appropriate treatment may extend the survival time for patients who present distant metastatic disease at initial diagnosis and a few patients would achieve long term survival. The median survival time of the 222 patients who received radiotherapy and/or chemotherapy was 17.0 months, and the 1-, 3-, and 5-year survival rates were 71.0%, 18.0%, and 8.0%, respectively. Univariate and multivariate analyses showed that gender, N staging, and treatment modality were independent prognostic factors for M<sub>1</sub> stage NPC patients. Whereas, 34 other patients who did not receive any treatment showed worse prognosis with median survival of 9.0 months and none of these patients would survived up to 5 years.

It is generally believed that the prognosis of patients who presented with distant metastasis at initial diagnosis is relatively poor compared to those who developed metastases after primary radiotherapy[14]. However, our study demonstrated the outcome for this group of patients is very similar to the reports in patients had distant metastasis after primary radiotherapy [14, 18]. Therefore, comprehensive treatment should be considered for NPC patients with distant metastasis at initial diagnosis to prolong their survival, some of these patients may achieve long term survival.

The treatment modality is related to the prognosis of NPC patients with distant metastasis at initial diagnosis. Some physicians may consider that the survival time of these patients is limited and that radiotherapy to the primary lesion in the nasopharynx and the complications caused by radiotherapy may affect the quality of life. As a result, these physicians forgo radiotherapy to the primary lesion in the nasopharynx and just choose chemotherapy alone. In the current study, both the univariate and multivariate analyses showed that the treatment modality is a prognostic determinant for NPC patients with distant metastasis at initial diagnosis.

The prognosis of patients who underwent comprehensive treatment was better than that of patients who underwent radiotherapy for primary tumor alone ( $\chi^2=14.390$ ,  $p=0.000$ ) and that of patients who underwent chemotherapy alone ( $\chi^2=19.214$ ,  $p=0.000$ ). We consider that the tumor burden is large in NPC patients with distant metastasis at initial diagnosis, and chemotherapy alone cannot control the tumor completely. Radiotherapy to the primary lesion in the nasopharynx may not only relieve symptoms such as nasal congestion, headache, and tinnitus, etc, but also reduce tumor burden to enhance the chance of successful chemotherapy to distant metastasis. In patients who undergo radiotherapy to the primary lesion in the nasopharynx, the prognosis is relatively poor because the systemic disease is not fully controlled. Therefore, combination of radiotherapy and chemotherapy should be considered for patients with NPC with distant metastasis at initial diagnosis to improve the local tumor control and prolong the survival. The result is consistent with previously reported study [20, 21].

Most NPCs in endemic areas are undifferentiated and, thus relatively sensitive to chemotherapy. As a systemic treatment method, chemotherapy plays an important role in the treatment of NPC patients with metastatic disease. At present, it is generally believed that platinum-based regimens are better than non-platinum-based regimens [22-24]. The commonly used combined regimen is cisplatin and 5-fluorouracil. In the present study, our data showed that for patients who underwent chemotherapy the survival time was much longer in those who underwent  $\geq 6$  cycles chemotherapy compared to those  $< 6$  cycles chemotherapy ( $p=0.013$ ). Limited with the nature of retrospective study, it is difficult to distinguish which patients might have extended survival due to chemotherapy and which patients received more cycles of chemotherapy due to the relatively long survival. Therefore, further prospective studies are needed to verify these observations.

The current results indicated that the distribution of metastatic lesions in NPC patients with distant metastasis at initial diagnosis were similar to that in patients who had distant metastases after radiotherapy [5]. The most common site of metastasis was bone (34.0%), followed by liver metastasis and lung metastasis. Multiple-organ metastases are also common (19.9%). The site of metastatic lesion is related to patients' prognosis. Our data showed that the median survival time of patients with lung metastasis was 22.0, much long than those who presented with distant metastasis other than lung. It suggests that patients with lung metastasis have a better prognosis than patients with metastasis in other places, which is similar to that reported by Hui *et al* [25]. Though the mechanism underlying this phenomenon is not yet clear, it may be related to the special anatomical structures of lung tissues, and further clinical studies should be investigated.

The incidence rates in male populations are commonly 2 to 3 fold that of female population in NPC. The present study showed in those who were treated with radiotherapy and/or chemotherapy that incidence in male population is 6 fold that of female population. For patients who received cancer treatment, there is difference in N stage distribution between male and female but no difference in treatment modality between male and female patients. The unbalanced distribution in N stage may be one of the potential reasons responsible for better outcomes in female patients. However, after adjusting for N stage and treatment modality, cox regression analysis showed that the gender was still an independent prognostic factor for M<sub>1</sub> stage nasopharyngeal carcinoma. It consists with some Chinese series (1-3), female gender was a favorable factor on overall survival for M0 stage nasopharyngeal carcinoma.

In conclusion, the prognosis in NPC patients with distant metastasis at initial diagnosis is relatively poor. Patients received aggressive comprehensive treatment have favorable prognosis and some could achieve long-term survival. The optimal sequencing of chemotherapy and radiation therapy is needed for further study.

### Conflicts of Interest

No potential conflicts of interest were disclosed.

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