RESEARCH ARTICLE

Prognostic Factors on Overall Survival of Newly Diagnosed Metastatic Nasopharyngeal Carcinoma

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Abstract

Background: To investigate factors associated with overall survival in patients with newly diagnosed metastatic nasopharyngeal carcinoma. Materials and Methods: Two hundred and two consecutive patients with pathologically confirmed nasopharyngeal carcinoma with distant metastasis at diagnosis seen between December 2007 and May 2011 were reviewed. Patient, tumor and treatment factors were analyzed for their significance regarding overall survival. Results: The median follow-up time was 22 months. At the time of this report, 116 patients had died. For 112 patients, cause of death was nasopharyngeal carcinoma. The 1, 2, 3, and 4-year overall survival rates were 75.6%, 50.2%, 39.2%, and 28.2%, respectively. Cox regression multivariate analysis showed that T-stage (p=0.045), N-stage (p=0.014), metastasis number (p<0.001) and radiotherapy for nasopharynx and neck (p<0.001) were significant factors for overall survival. Conclusions: Early T-stage and N-stage, solitary metastasis in a single organ were good prognostic factors for patients with newly diagnosed metastatic nasopharyngeal carcinoma. Radiotherapy should be strongly recommended in systemic treatment.

Keywords: Nasopharyngeal neoplasm - metastatic - prognosis - radiotherapy

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Introduction

Nasopharyngeal carcinoma (NPC) has a distinct epidemiology compared with other head and neck squamous cell carcinomas. The annual incidence rate (per 100, 000 per year) ranged from <1 among whites to >20 among Southern Chinese male populations as reported (Parkin et al., 1997; Wei et al., 2010). Over two thirds of the patients are locoregionally advanced, but only 6% of cases are metastatic at initial diagnosis (Lee et al., 1992).

Distant metastasis in patients with NPC has conventionally been regarded as incurable and the aim of any form of treatment has been palliative. The median survival time ranges between 12.9-26.8 months (Toh et al., 2005; Cao et al., 2011; Lin et al., 2012). But a variable survival outcome is frequently observed in clinical practice. A few patients can survive for over 5 years or even longer time. What factors contribute to this difference? Up to now, the metastasis (M1) stage is still a 'catch-all' classification in TNM staging system for NPC, regardless of metastasis site and number, which has been found that outcomes are more favorable if metastases are limited to one organ or site in colon and rectal carcinoma (Sobin et al., 2009). Accordingly, we want to explore if the metastasis site and number will influence the prognosis in newly diagnosed metastatic NPC.

Besides, the role of chemotherapy is well established for metastatic NPC, but the objective response is still far from satisfied (Ngan et al., 2002; Chan et al., 2005; Leong et al., 2008). As NPC is highly sensitive to both chemotherapy and radiotherapy, whether local palliative radiotherapy for nasopharynx and metastatic tumors will provide additive value for overall survival when micro metastases are under control is a question worthy of consideration. In addition, intensity-modulated radiotherapy (IMRT) is a major breakthrough in the treatment of NPC. By conforming the dose to the irregularly shaped tumor, dose escalation is possible with IMRT (Phua et al., 2013). However, if there is an appropriate radiation dose and can IMRT improve the survival are largely unknown. The purpose of this study was to explore the predictive factors on overall survival of newly diagnosed metastatic NPC, and to investigate the effect of local palliative radiotherapy.

Materials and Methods

Patient characteristics

The study was approved by the Research Ethics Committee of Sun Yat-sen University Cancer Center. Between December 2007 and May 2011, 202 consecutive patients with NPC presenting with distant metastasis at diagnosis were evaluated. All patients were pathologically confirmed. The male to female ratio was 4.6 to 1.0, and their ages ranged from 17 to 73 years (median, 47.5

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years). Histological examination showed that 95.0% of patients were World Health Organization (WHO) III (undifferentiated carcinoma) and only 5.0% were WHO II (nonkeratinizing carcinoma).

Patients were staged with physical and neurologic examination, fiberoptic nasoendoscopy, MRI of nasopharynx and neck, chest X-ray (computed tomography scan was needed if suspicious lung metastasis), bone scintigraphy (MRI or X-ray was needed if suspicious bone metastasis), and ultrasonography of the abdominal region. The clinical stage was described according to the 2009 TNM staging system of the Union for International Cancer Control (Sobin et al., 2009).

Treatment

DCF [Docetaxel 60 mg/m^2 day1, DDP 60 mg/m^2 day1 and 5-Fu 550 mg/ (m^2·d) day1-5, 120h] was the main regimen in sequential chemotherapy or chemotherapy alone, while cisplatin alone (80 to 100 mg/m^2/3w) was usually applied in concurrent chemotherapy.

Radiotherapy was delivered with 6MV photons for the nasopharynx and neck. The majority (66.7%) were treated with conventional two-dimensional radiotherapy and 3.3% received 3-dimensional conformal radiotherapy. The most common schedule was 2Gy/fraction daily, with a total dose of 70Gy. Thirty percent of patients were treated with IMRT, and the prescribed dose was usually 68Gy to the planning target volume (PTV) of primary nasopharyngeal tumor (GTVnx), 60Gy to the PTV of clinical target volume1 (CTV1, defined as the GTVnx plus a 5 to 10mm margin), 54Gy to the PTV of CTV2 (defined as the CTV1 plus a 5 to 10mm margin and encompass the lymphatic regions), and 64-66Gy to the PTV of the GTV for the involved cervical lymph nodes in 30 fractions.

Patients with metastatic foci in bone, lung, and noncervical lymph nodes amenable to local therapy were offered radiation therapy, surgery, and/or interventional treatments at the attending physicians' discretion.

Patient evaluation and follow-up

All patients were evaluated at least once a week during the treatment. After the treatment completion, the patients were subsequently followed up monthly in the first 3 months, every 3 months during the first 3 years, every 6 months during the next 2 years, and then annually. During every follow-up visit, disease status (nasoendoscopy and radiological information of the metastatic tumors) and treatment toxicity were assessed. MRI of the nasopharynx and cervical region were ordered yearly or as clinically indicated.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 package (SPSS Standard version 16.0, SPSS Inc, Chicago, IL). Chi-square test was used to compare the difference of categorical variables. Overall survival (OS) was defined as from the date of diagnosis until death or the last follow-up. The survival curves were calculated by the Kaplan-Meier method and compared using the log-rank test. Multivariate survival analysis was performed on all parameters that were found significant on univariate analysis using the Cox regression model. All statistical tests were two-sided, and a p value of <0.05 was considered to indicate statistical significance.

Results

Treatment modalities

One hundred and ninety-seven patients (97.5%) received chemotherapy. Among them, 77 patients were treated with chemotherapy alone, and the others (120 patients) received concurrent with or without sequential (induction/adjuvant) chemotherapy. The median courses of chemotherapy was 6 (95% range, 2-16).

One hundred and twenty patients (59.4%) received radiotherapy in the nasopharynx and neck. The median dose for the primary tumors was 70Gy (95% range, 60-76.7Gy), and the median overall treatment time was 51 days (95% range, 40-62d).

Fourteen patients (6.9%) received interventional treatments or operations for the metastatic tumors. Forty-five patients (22.3%) with metastatic foci in bone, liver,

Table 1. Summary of Univariate Analysis of Prognostic Factors in Patients with Newly Diagnosed Metastatic NPC*

Factors	Cases (n)	Median Survival (mo)	p
Age (years)			0.276
<48	95	28	
≥48	98	22	
Gender			0.176
Male	158	24	
Female	35	25	
T stage			0.077
T1	26	46	
T2	19	25	
T3	72	22	
T4	76	25	
N stage			<0.001
N0	5	42	
N1	39	19	
N2	99	23	
N3	50	16.5	
Metastasis site			<0.001
Single organ	122	25	
Bone	77	46	
Liver	20	23	
Lung	17	29	
Distant lymph nodes	8	22	
Multiple organs	71	16	
Metastasis number			<0.001
Single organ with solitary metastasis	44	46	
Single organ with multifocal metastases	78	28	
Multiple organ involved	71	16	
Courses of chemotherapy			0.046
<6	53	18	
≥6	133	28	
Radiotherapy for nasopharynx			<0.001
No	76	15	
Conventional RT	82	46	
IMRT	35	45	
Radiotherapy dose to nasopharynx			0.133
≤70Gy	76	46	
>70Gy	41	50	
Radiotherapy for metastatic tumors			0.012
Yes	43	45	
No	150	22	

*Data was available for 193 cases

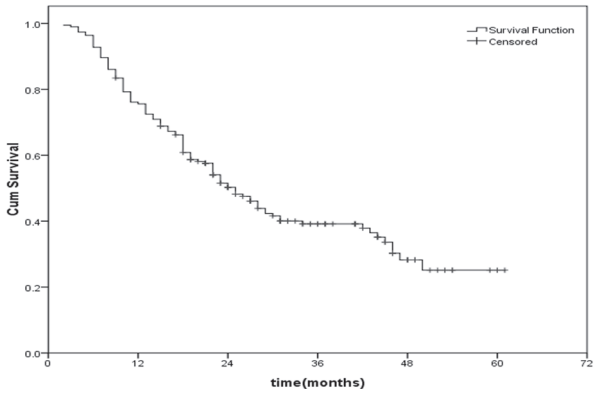

Figure 1. Overall Survival of 193 Patients with Newly Diagnosed Metastatic NPC

Table 2. Summary of Multivariate Analysis of Prognostic Factors in Patients with Newly Diagnosed Metastatic NPC

Factors	χ^2	p*
T stage	3.948	0.047
N stage	5.993	0.014
Metastasis site	1.382	0.24
Metastasis number	13.301	<0.001
Courses of chemotherapy	2.896	0.089
Radiotherapy for nasopharynx	21.651	<0.001
Radiotherapy for metastatic tumors	0.675	0.411

*: Wald test.

and distant lymph nodes were treated with radiotherapy. The median dose for the metastatic tumors was 40Gy (95% range, 25-60Gy).

Survival

One hundred and ninety-three patients (95.5%) were observed until death or the time of analysis. The median follow-up time was 22 months (range: 2 to 61 mo). At the time of this report, 116 patients had died. For 112 patients, cause of death was NPC. Two cases died without definite cause during the treatments. Of the remaining two, one was attributed to aneurysm rupture, and one to hemorrhage of nasopharynx. The 1, 2, 3, and 4-year OS rates were 75.6%, 50.2%, 39.2%, and 28.2%, respectively (Figure 1).

Adverse events

All patients tolerated the treatments well and completed their planned therapy except two. The Common Terminology Criteria for Adverse Events (CTCAE) was used to evaluate the acute toxicity. The most commonly observed severe acute toxicities included grade 3 leukocytopenia, mucositis and skin desquamation, which occurred in 39 (19.3%), 13 (6.4%), and 9 (4.5%) patients, respectively. No patient experienced grade 4 acute toxicity. Fifty-seven patients (28.2%) required intravenous hydration support at some point of their treatments. Long-term adverse events were not analyzed in this study because of the relatively short survival time.

Prognostic factors of survival

Univariate analysis: Potential prognostic factors for OS, including age, gender, T-stage, N-stage, sites and numbers of metastases, courses of chemotherapy, radiotherapy for nasopharynx or metastatic tumors and radiation dose were evaluated using log-rank comparisons (Table 1). It showed that N-stage, metastasis site and number, radiotherapy for nasopharynx and metastatic tumors were significantly associated with overall survival. T-stage and courses of chemotherapy were marginally significant.

Multivariate analysis: Cox regression multivariate analysis showed that T-stage, N-stage, metastasis number and radiotherapy for nasopharynx and neck were significant factors (p<0.05) (Table 2). Early T-stage and N-stage, solitary metastasis in single organ, and a combination of radiotherapy for nasopharynx were significant predictors for favorable survival.

Discussion

Although the prognosis of metastatic NPC is still quite poor, it has been well accepted that the survival can be highly variable and long-term survival is possible in some patients (Teo et al., 1996; Fandi et al., 2000; Khanfir et al., 2006). But most of the reports included patients who developed metastasis (es) after primary treatment, few explored the prognosis of newly diagnosed metastatic NPC specially. The identification of prognostic factors of this group may be of great importance for clinical therapy and scientific research. In this study, we presented the long-term outcome and prognostic indicators of survival in a large cohort of newly diagnosed metastatic NPC patients.

The aim of the TNM staging system is to aid medical staff in planning treatment, assessing prognosis, evaluating the results of treatment and providing facilities around the world to collate information more productively. A series of modifications have been introduced to the TNM staging system for NPC, while mostly focusing on the primary tumor (T) and local node (N) components (Teo et al., 1996). However, the metastasis (IVc) stage is still an 'all-embracing' classification, no matter any T, any N, and the metastasis site or number. But metastatic NPC makes a very heterogeneous group, of which the overall survival can range from weeks to years (Toh et al., 2005). As there was no great difference in the institutional treatment protocols, it cannot be satisfactorily explained by the therapies. Maybe patients with certain characteristics were potentially curable. Our data indicated that early T-stage and N-stage, single organ with solitary metastasis were significant predictors for favorable survival, which concurred closely with other studies. In a study (Lin et al., 2012) of 170 NPC patients with lung metastasis alone, it was found that the disease-free internal was longer in patients with early T-stage (p=0.001) or N-stage (p=0.002). Another study (Pan et al., 2012) suggested patients with metastasis to the lung and/or solitary lesions have a more favorable prognosis compared with those patients with multiple metastases located in other anatomic sites. T-stage, N-stage and metastasis number are all the representations of tumor burden. A lot of articles reported that the greater the tumor load, the worse the prognosis in NPC (Chen et al., 2004; Lee et al., 2008; Chen et al., 2011). Increased number of clonogenic tumor cells is related to tumor hypoxia and possibly alters levels of intercellular

communication factors, which are associated with insensitivity to radiotherapy or chemotherapy (Johnson et al., 1995). Accordingly, aggressive treatments for patients with a poorer prognosis are necessary.

Chemotherapy remains the main therapeutic approach for metastatic NPC, with a number of reports confirming of its efficacy (Siu et al., 1998; Leong et al., 2008; Chen et al., 2013). However, the median survival was short, and there was no randomized study that compared palliative chemotherapy versus other palliative care. Almost all patients (97.5%) in our series received chemotherapy, which is hard to compare the survival rate between patients treated with and without chemotherapy. How many circles of chemotherapy are associated with better prognosis has been explored in some studies. Cao et al. (2011) found no significant better overall survival in patients received more than 6 circles of chemotherapy. Lin et al. (2012) chose 4 circles as the cut-off point, and the result was negative, too. Our data showed the prognosis of patients with more than 6 courses was better in univariate analysis (p=0.046), but no statistical significance in multivariate analysis. Perhaps it could be attributable to the affect of radiotherapy. The percentages of patients received radiation in group ≥6 courses and <6 courses are 63.2% and 59.3%, and proportion of total radiation dose >70Gy are 24.1% and 16.7%, respectively. Though the disproportion is not significant (p=0.381), it is enough to make the litter superiority of more chemotherapy courses less obvious.

In the past years, the National Comprehensive Cancer Network (NCCN) guideline suggested radiotherapy to primary and neck could be applied after chemotherapy if complete clinical response was attained. Since 2011, concurrent chemo/radiotherapy has been another choice for selected patients (patients with distant metastasis in limited site or with small tumor burden, or patients with symptoms in the primary or any nodal site) in the guideline, emphasizing the importance of multidisciplinary therapy in newly diagnosed metastatic NPC. Concurred closely with other studies (Cao et al., 2011; Lin et al., 2012), we found a combination of radiotherapy for nasopharynx improved the OS. But the prognosis did not significantly relate to different radiation doses and techniques. It could be ascribed to 88.7% of patients received more than 68Gy in radiation group and the median dose in group ≤70Gy was 70Gy. In other words, the great majority of patients in group ≤70Gy still receive a radical treatment dose, so it's not surprising the radiation dose was not an independent predictor for OS in our series. As the radiation techniques, there was few chance to apply IMRT on patients with metastatic NPC because of the limited medical resources until 2009. The proportions of patients diagnosed later than Jan 1st, 2010 in conventional RT group and IMRT group are 37.2% and 62.9%, respectively. IMRT was found that it could improve the overall survival in non-metastatic NPC patients (Peng et al., 2012). Maybe we can expect the result in stage IVc patients with longer follow-up time.

In conclusion, our study investigated the prognostic factors of newly diagnosed metastatic NPC with the newest staging system and treatments in a large cohort. Based on our results, early T-stage and N-stage, solitary metastasis in single organ, and a combination of radiotherapy for nasopharynx were significant predictors for favorable survival. Further work is needed to evaluate the clinical benefit of IMRT in metastatic NPC.

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