Prognostic analysis of 152 patients with distant metastasis after intensity-modulated radiotherapy for nasopharyngeal carcinoma

Hua Yang
Department of Radiation Oncology ,First Affiliated Hospital of Air Force Medical University
Rui Ma
Department of Radiation Oncology,First Affiliated Hospital of Air Force Medical University
Yan Zhou
Department of Radiation Oncology,First Affiliated Hospital of Air Force Medical University
Yutian Yin
Department of Radiation Oncology,First Affiliated Hospital of Air Force Medical University
Lina Zhao
Department of Radiation Oncology,First Affiliated Hospital of Air Force Medical University
Mei Shi (mshi82@hotmail.com)
Department of Radiation Oncology, Xijing Hospital, Fourth Military Medical University
https://orcid.org/0000-0002-4937-405X

Research

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Abstract

Purpose The objectives of this study were to analyze the prognostic factors of patients with distant metastasis after intensity-modulated radiotherapy (IMRT) for nasopharyngeal carcinoma (NPC) and to provide a reference for the clinical treatment of these patients. Methods A retrospective analysis was conducted among 152 patients with distant metastasis after IMRT for NPC from January 2006 to December 2017 (median follow-up, 43 months). The survival rates were calculated and compared using the Kaplan-Meier method and log-rank tests, respectively. The Cox risk ratio model was used for univariateand multivariate analyses. Results Among all patients, the median interval from treatment completion to distant metastasis was 11.3 months. The median post-metastasis survival was 14 months, and the 1-, 2-, and 3-year survival rates were 60.4%, 40.2%, and 27.6%, respectively. Upon univariate analysis, overall survival was found to be related to the N stage and induction chemotherapy at initial diagnosis, time from initial radiotherapy completion to distant metastasis, liver metastasis, and chemotherapy and palliative radiotherapy after metastasis. Liver metastasis, multi-organ metastasis, chemotherapy after metastasis, and the time from radiotherapy completion to distant metastasis were independent prognostic factors for patient survival in the Cox regression analysis. Conclusions The prognosis of patients with distant metastasis after IMRT for NPC was related to the time from radiotherapy completion to distant metastasis, regardless of liver or multiple organ metastasis and adjuvant chemotherapy after metastasis. Adequate adjuvant chemotherapy and local palliative radiotherapy could potentially prolong the survival of patients with distant metastasis of NPC.

Introduction

Nasopharyngeal carcinoma (NPC) is a common head and neck malignant tumor. There is a significant regional difference in the incidence of NPC; high rates have been reported in Southeast Asia and southern Chin [1]. The nasopharynx has a complex structure and deep anatomic location, and it is surrounded by many organs and tissues, which makes it difficult to remove the tumor completely. The most common pathological type of NPC is poorly differentiated squamous cell carcinoma, which has a high malignancy rate. However, it is sensitive to radiotherapy, which is the primary treatment for NPC. In conventional 2-dimensional radiotherapy, local recurrence and distant metastasis are the main reasons for the failure of advanced local NPC [2, 3].With the development of 3-dimensional conformal intensity-modulated radiotherapy (IMRT), the local control rate of NPC has significantly improved (3-year local recurrence-free survival of > 90%). Distant metastasis has become the main factor affecting patient survival after IMRT in NPC [4, 5].

The prognosis of metastatic NPC is poor with a short median survival time [6, 7], and there is no standard treatment plan for this condition. Currently, chemotherapy-based comprehensive treatments are commonly used for metastatic NPC while considering various factors, such as the general condition of the patient, age, the time of metastasis, the metastatic site, the number of metastatic organs, and the number of metastases [4, 8–10]. In recent years, with the development of molecular biology, many anti-tumor molecular targeted drugs have been approved for marketing in the United States and Europe. These targeted drugs can prevent the toxic side effects of traditional chemotherapy and radiotherapy due to a

lack of specificity and provide better tolerance in patients with metastatic NPC. However, targeted therapy is still under investigation, and its efficacy and safety need to be confirmed by further clinical studies [11–14].Local palliative therapy is another important option for the treatment of metastatic NPC. Some patients with metastatic NPC can have long-term survival or even clinical cure upon receiving active and effective treatments. However, currently there is no standardized and reliable treatment strategy; only traditional 2-dimensional radiotherapy technology has been used in most previous studies. Very few studies have been conducted investigating the application of IMRT in distant metastatic NPC.

In the current study, we analyzed the survival rate of patients with distant metastasis after radical IMRT, and investigated the characteristics and survival-related factors in patients with long-term survival.

Methods

Study Design

A retrospective analysis was conducted among 157 patients with distant metastatic NPC after IMRT that were admitted to the Department of Radiotherapy, The First Affiliated Hospital of Air Force Medical University, from January 2006 to December 2017.

Ethical approval

The present study was approved by the ethics committee of the First Affiliated Hospital of Air Force Medical University. The number of ethics committee approval is KY20172007-1.

Patient Inclusion Criteria

The inclusion criteria were as follows: explicit nasopharyngeal histopathology diagnosis before initial treatment; no distant metastasis observed by chest computed tomography (CT), abdominal B-ultrasound, and bone emission CT. If distant metastasis occurred after radical radiotherapy, the recurrence of tumors at the nasopharyngeal or cervical lymph nodes were excluded using physical examinations, nasopharyngeal fiberscope examinations, and nasopharyngeal + neck Magnetic Resonance Imaging (MRI) scans. In total, 152 patients who met the above criteria were included in the study, with a median follow-up of 43 months.

Radiotherapy

All patients were treated with radical IMRT. For CT simulation positioning, the patients were placed in the supine position and fixed using a head-neck-shoulder mold. The scanning ranged from the top of the head to 3cm below the clavicle, and venography was simultaneously given with a layer thickness of 3 mm and a layer spacing of 3mm.Patient images from the enhanced CT positioning and MRI were merged for target area delineation.

The gross tumor volume (GTV) was divided into the nasopharyngeal lesion as shown based on the videography (GTVnx) or as determined by the presence of an enlarged lymph node that met the diagnostic criteria (GTVnd). Clinical tumor volume(CTV)1is a high-risk clinical target area, which includes the entire

nasopharyngeal mucosa, posterior nasal cavity, 1/3 of the posterior maxillary sinus, posterior ethmoid sinus, parapharyngeal space, cranial base openings, inner and outer plates, slopes and the first 1/3 of the cervical vertebrae, part of the oropharynx, and the surrounding high-risk lymph node drainage area. CTV2 is a low-risk cervical lymphatic drainage area. Each of the above target areas were extended by 3 mm to form a respective plan tumor volume (PTV).

The prescription doses were as follows: GTVnx, 66.0-74.25Gy/30-33F;GTVnd, 66.0-72.4Gy/30-33F;PTV1, 56.0-63.5Gy/29-33F; and PTV2, 50.4-53.2Gy/28F. The requirements for the PTV dose were that an area <93% of the prescribed dose must be <3% by volume and an area that is >105% of the prescribed dose must be <20% by volume; an area that is >110% of the prescription dose was not allowed. The vital organ dose-volume limit was determined according to Radiation Therapy Oncology Group (RTOG) 0225 report: parotid gland, 50% volume ≤30Gy or an average dose ≤26Gy; brainstem, optic chiasm, and optic nerve, 54Gy or 1% volume ≤60Gy; spinal cord, 45Gy or 1cc volume ≤50Gy; mandible and temporomandibular joint, 70Gy or 1cc volume ≤75Gy; and temporal lobe, 60Gy or 1cc volume ≤65Gy.

Chemotherapy

The chemotherapy regimen used for patients in our institution was platinum (cisplatin)-based.

Follow-up

All patients received regular follow-up after radiotherapy either by telephone or hospital visits. The CTC 3.0 classification method was used to evaluate the standard for treatment side effects. The patients were followed up every 3 months in the first year after treatment, every 6 months in the second and third years, and annually after 3 years. Outpatient follow-up included general physical examinations, electronic nasopharyngoscopy, nasopharynx and neck enhancement CTs or MRIs, chest X-rays or CTs, abdominal B-ultrasounds, and a whole-body bone scans or a head MRI if necessary.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 software. Kaplan-Meier methods and log-rank tests were used to calculate and compare patient survival rates. P-values <0.05 were considered statistically significant.

Results

Clinical and Demographic Characteristics

Of the 152 patients included, 109 (71.7%) were men and the median age of all those enrolled at initial diagnosis was 48 years (13–81). Based on the American Joint Committee on Cancer (AJCC), 7th edition, 17 and 135 patients were classified as stages I–II and III–IV at initial diagnosis, respectively. The general clinical and demographic characteristics for patients are shown in Table 1.

Chemotherapy

Overall, 136 (89.5%) received chemotherapy; 112 (73.7%) received 2–6 cycles of induction chemotherapy, including cisplatin + fluorouracil (n=28), docetaxel + cisplatin (n=50), docetaxel + cisplatin + fluorouracil (n=10), and gemcitabine + cisplatin (n=24).One hundred and thirty (85.5%) patients received concurrent chemotherapy with cisplatinfor an average of 2–3 cycles. Another 107 (70.4%) patients received 2–6 cycles of adjuvant chemotherapy, including cisplatin + fluorouracil (n=34), docetaxel + cisplatin (n=63), and gemcitabine + cisplatin (n=10).

Follow-up

As of December 2017, 98.7% of patients were retained in care; only two patients were lost to follow-up. The median overall follow-up was 43 months. Two patients were lost to follow-up. In total, 128 (84.2%) and 101 (66.4%) patients were followed for 3 and 5 years, respectively.

Efficacy

The median time from treatment completion to distant metastasis was 11.3 months. There were 71, 47, 48, and 34 cases of bone, lung, liver, and other metastases, respectively. The other metastatic sites included the axillary lymph nodes, mediastinal lymph nodes, the brain, spleen, adrenal glands, chest wall, and pleura. The median survival post-metastasis was 14 months and the 1-, 2-, 3-year survival rates were 60.4%, 40.2%, and 27.6%, respectively (Fig.1)

Prognostic factors

Upon univariate analysis, the overall survival of patients was related to the N stage and induction chemotherapy at initial diagnosis, the time interval from initial radiotherapy completion to distant metastasis (metastatic interval), multi-organ metastasis, liver metastasis, chemotherapy after metastasis, and palliative radiotherapy after metastasis. Based on the Cox regression analysis, the metastatic interval, liver metastasis, multi-organ metastasis, and chemotherapy after metastasis were independent prognostic factors for the survival of patients with metastatic NPC. In the multivariate analysis, patients with a short metastatic interval, multiple organ metastases, and no local palliative radiotherapy or chemotherapy had a significantly worse prognosis (Figs. 2a-2d).

Long-term survival analysis

In total, 21 (13.8%) patients (15 [71.4%] men) survived >3 years after the diagnosis of metastasis, with a median survival of 59.8 months (39.9–103.9). The average metastatic interval was 31.4 months and the median interval was 25 months (6–107). All patients received treatment for their metastases. Stereotactic body radiotherapy (SBRT) at 48Gy/6F was provided for three and two patients with lung and liver metastasis, respectively. One patient with liver metastases was treated with radiofrequency ablation. Patients with bone metastases were provided with palliative external beam radiotherapy (radiotherapy dose, 36–60 Gy).All patients were treated with systemic chemotherapy. The chemotherapy regimen included docetaxel + cisplatin (n=13), gemcitabine + cisplatin (n=5), and cisplatin + fluorouracil+ nimotuzumab (n=3). The median number of chemotherapy cycles for the entire group was four (2-6).

Discussion

In recent years, the radiotherapy techniques for NPC have advanced from 2- to 3-dimensional. The combined use of 3-dimensional conformal IMRT and MRI allows for the vital organs to be clearly defined and the dose to be properly distributed to the target area, leading to a significant increase in the local area control rate of NPC. Tumor centers in China and other countries have reported that the 5-year local area progression-free survival rate for NPC after IMRT was >90%[15, 16].IMRT significantly improved the local area control rate; however, it did not translate into improved patient survival due to the occurrence of distant metastases, which pose as challenges for patients with NPC [2-5]. We investigated the characteristics and prognostic factors of distant metastatic NPC after IMRT and provided experience for appropriate salvage therapies to improve the overall survival rate of NPC.

Various survival rates for patients with distant metastatic NPC have been reported in previous studies. The median survival time and 2-year survival rate ranges from 9–15.6 months and 15.0–34.4%, respectively. The survival rate may be related to whether the patients received treatment and the treatment methods and intensity in the various studies [17-20]. Based on our findings, the median survival was 14 months, and the post-metastasis1-, 2-, and 3-year survival rates were 60.4%, 40.2%, and 27.6%, respectively. The most common metastatic sites were the bones, lungs, and the liver. The 2-year survival rate observed in this study was higher than that previously reported. There are two possible reasons for the differences in our findings and those previously reported. First, although this was a retrospective study, the treatment for all patients was selected by the Multiple Disciplinary Team (MDT), based on the patients' disease status and physical condition. Thus, there was no bias between different physicians regarding treatment options. Hence, our results are a good representation of the general situation regarding patients with metastatic NPC after IMRT. Second, most of the patients received local radiotherapy after disease remission or control by systemic chemotherapy. Radiotherapy eliminated local residual lesions that were not sensitive or resistant to chemotherapy. Furthermore, the combination of radiotherapy and chemotherapy reduced the overall tumor load and delayed the progression of disease.

The N stage at initial treatment independently affects the survival of patients with metastatic NPC [15].However, although induction chemotherapy and the N stage at initial diagnosis had effects on survival after metastasis upon univariate analysis, these factors were not found to be significant independent prognostic factors upon multivariate analysis. This could be explained by the fact that 71.1% of patients had N2 or N3 stages at initial diagnosis. Relatively high-risk N2 (>3 cm lymph node or with fusion necrosis) and N3 stage patients were provided 3–6 full cycles of treatment, in conjunction with an adequate amount of induction chemotherapy, which may have balanced the N-stage effects and improved the prognosis of high-risk N stage patients. Therefore, the N-stage did not have a critical impact on patient survival in the current study.

The findings from the multivariate analysis in this study were similar to those reported in previous studies [17-19]. Prognosis can vary according to the different metastatic sites. The median survival time of intrahepatic metastases was only 10.5 months, while that of extrahepatic metastases was 16 months. The median survival time of bone and lung metastases was 18 months and 16 months, respectively, whereas

that of multi-organ metastases was only 10 months. The survival rate of multiple organ metastases was significantly lower than that of any single organ metastasis. Previous studies have reported that patients with only lung or bone metastases have a better prognosis and long-term survival [17, 18], but no clear comparisons have been made in respective studies.

Local palliative therapy is a very important method for the treatment of metastatic NPC. For patients with bone metastases, radiotherapy after chemotherapy, combined with bisphosphonate treatment to inhibit osteoclast activity, can effectively relieve pain and prevent fractures. In patients with only lung metastases, chemotherapy combined with targeted therapy is an effective treatment option. After 4–6 cycles of chemotherapy, local radiotherapy is performed for intrapulmonary metastatic lesions. For a single lung metastatic lesion or multiple lesions in a single lobe, surgery or SBRT could also be considered if the patient is in good health. Liver metastasis generally involves multiple lesions and therefore, performing surgery is difficult. The liver poorly tolerates radiation; therefore, chemotherapy has always been used as the preferred treatment option. Patients with oligometastatic can also consider SBRT or radiofrequency ablation. In the current study, SBRT for metastatic lesions was performed in three and two patients with lung and liver metastases, respectively. Furthermore, one patient with liver metastasis was treated with radiofrequency ablation. All patients had long-term survival of >3 years.

Systemic chemotherapy is the preferred treatment choice for metastatic NPC [6, 7]. In this study, the median survival time of patients who received systemic chemotherapy was 18 months, which significantly differed from that of patients who did not receive chemotherapy (9 months). However, the efficacy of chemotherapy may depend on various patient factors. Previous researchers have shown that factors, such as the general condition of patients, hemoglobin levels, and body weight, can affect the treatment efficacy of metastatic NPC. The efficacy of different chemotherapy regimens can also vary. According to the results of multiple phase II clinical studies, the combination of two or three platinum-containing first-line drugs can achieve an efficiency of 50–80%, and a median progression-free and overall survival of 5-11 and 10-14 months, respectively [21-27]. The metastatic NPC chemotherapy regimens used in this study were docetaxel + cisplatin, gemcitabine + cisplatin or cisplatin + fluorouracil + nimotuzumab. There was no difference in the efficacy between these three regimens. However, prospective randomized controlled trials of these chemotherapy regimens are limited and therefore, prospective clinical trials to compare the efficacy between chemotherapy regimens are needed. We did not observe a prognostic effect of the targeted drugs upon univariate analysis; this may be due to the small number of patients (n=14) who underwent chemotherapy in addition to targeted therapy. Therefore, this finding may not reflect the true efficacy of targeted drugs used for metastatic NPC.

There were several limitations in the present study. First, the copy number of serum Epstein-Barr virus DNA is an important prognostic factor in patients with NPC [28]. However, only a small number of patients in this study had the pre-treatment serum Epstein-Barr virus Deoxyribonucleic acid (DNA) copy number and therefore, it was not included in the prognostic analysis of the patients.

In conclusion, the treatment of metastatic NPC remains challenging. Although the treatment has been improved, the overall prognosis of patients remains poor. Presently, systemic chemotherapy with a

platinum-based regimen remains an important first-line treatment. The combined application of localized radiotherapy and systemic chemotherapy requires further investigation. We found that there was a potential of cure or long-term remission after 4–6 cycles of chemotherapy and active local treatment of metastases for patients with only bone or lung metastases who were in good general health. For patients with multiple liver metastases or multiple organ metastases who had poor general health, the median survival time was relatively short, thus the best supportive care should be provided. The findings from this study can assist clinicians in more accurately determining the prognosis of patients with metastatic NPC. Additionally, they might provide guidance on the selection of individualized treatment plans, which can prevent excessive or ineffective treatment for patients.

Conclusion

The prognosis of patients with distant metastasis after IMRT for NPC was related to the time from radiotherapy completion to distant metastasis, regardless of liver or multiple organ metastasis and adjuvant chemotherapy after metastasis. Adequate adjuvant chemotherapy and local palliative radiotherapy could potentially prolong the survival of patients with distant metastasis of NPC.

Abbreviations

IMRT: intensity-modulated radiotherapy; NPC: nasopharyngeal carcinoma; CT: computed tomography; MRI: Magnetic Resonance Imaging; GTV: gross tumor volume; CTV: clinical tumor volume; PTV: plan tumor volume; RTOG: Radiation Therapy Oncology Group; AJCC: American Joint Committee on Cancer; SBRT: Stereotactic body radiotherapy; MDT : Multiple Disciplinary Team ;DNA: Deoxyribonucleic acid.

Declarations

Ethics approval and consent to participate

The present study was approved by the ethics committee of the First Affiliated Hospital of Air Force Medical University. The number of ethics committee approval is KY20172007-1.

Consent for publication

Not applicable.

Availability of supporting data

Materials in the manuscript are available by contacting the author at yanghuafmmu@163.com.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Drs. Mei Shi, and Lina zhao were principal investigators and contributed to the study design and approval of the final version of the manuscript. Hua yang and Rui ma contributed to manuscript writing and data interpretation. Yan zhou and Yutian Yin contributed to data analysis and collection. All authors read and approved the final manuscript.

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Authors' information

First Name	Last Name	Email	Institution
Hua	Yang	yanghuafmmu@163.com	Department of Radiation Oncology, First Affiliated Hospital of Air Force Medical University, Xi'an, Shaanxi
Rui	Ma	marui0913@163.com	Department of Radiation Oncology, First Affiliated Hospital of Air Force Medical University, Xi'an, Shaanxi
Yan	Zhou	382956462@qq.com	Department of Radiation Oncology, First Affiliated Hospital of Air Force Medical University, Xi'an, Shaanxi
Yutian	Yin	kaka212000@163.com	Department of Radiation Oncology, First Affiliated Hospital of Air Force Medical University, Xi'an, Shaanxi
Lina	Zhao	zhaolina@fmmu.edu.cn	Department of Radiation Oncology, First Affiliated Hospital of Air Force Medical University, Xi'an, Shaanxi
Mei	Shi	mshi82@hotmail.com	Department of Radiation Oncology, First Affiliated Hospital of Air Force Medical University, Xi'an, Shaanxi

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Table 1

Table 1 Clinical data of 152 patients with metastatic of NPC.

Abbreviations: AJCC, American Joint Committee on Cancer, 7^{th} edition

Variable	Case (%)	Variable	Case (%)
Sex		**Adjuvant chemotherapy**	
Male	109 (71.7%)	≥4cycles	78 (51.3%)
Female	43 (28.3%)	<4cycles	74 (48.7%)
Age		**Induction chemotherapy**	
≤50years	86 (56.6%)	Yes	112 (73.7%)
>50years	66 (43.4%)	No	40 (26.3%)
T Stage		**Pathological type**	
T1	15 (9.8%)	Undifferentiated	75 (49.3%)
T2	40 (26.3%)	Differentiated	56 (36.8%)
T3	47 (30.9%)	Other types	21 (13.9%)
T4	50 (32.9%)		
N Stage		**Metastasis site**	
N0	16 (10.5%)	Single	112 (73.7%)
N1	28 (18.4%)	Multiple	40 (26.3%)
N2	55 (36.2%)		
N3	53(34.9%)		
AJCC Stage		**Metastatic organ**	
I	3 (2%)	Bones	71 (46.7%)
II	14 (9.2%)	Liver	48 (31.6%)
III	60 (39.5%)	Lungs	47 (30.9%)
IV	75 (49.3%)	Other	34 (22.4%)

Figures

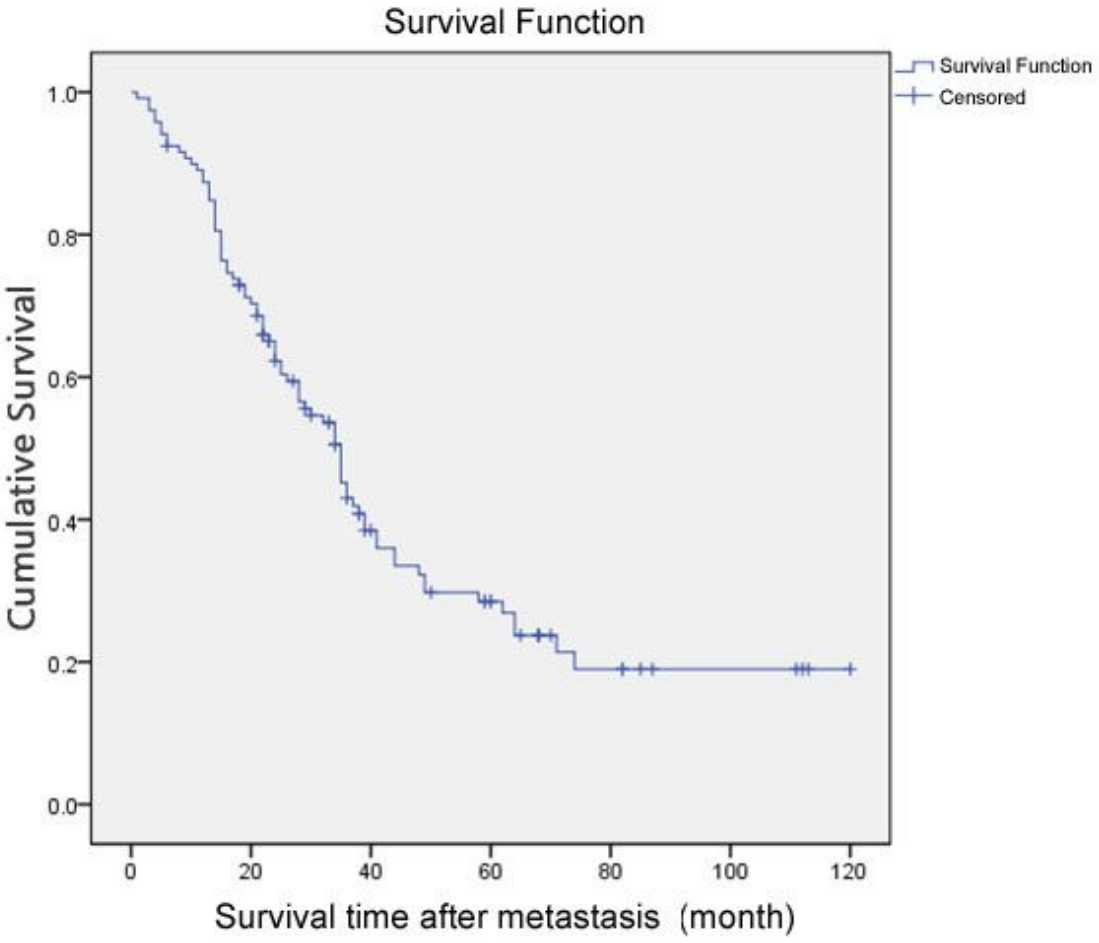

Figure 1

Survival curve of 152 patients with metastatic NPC.

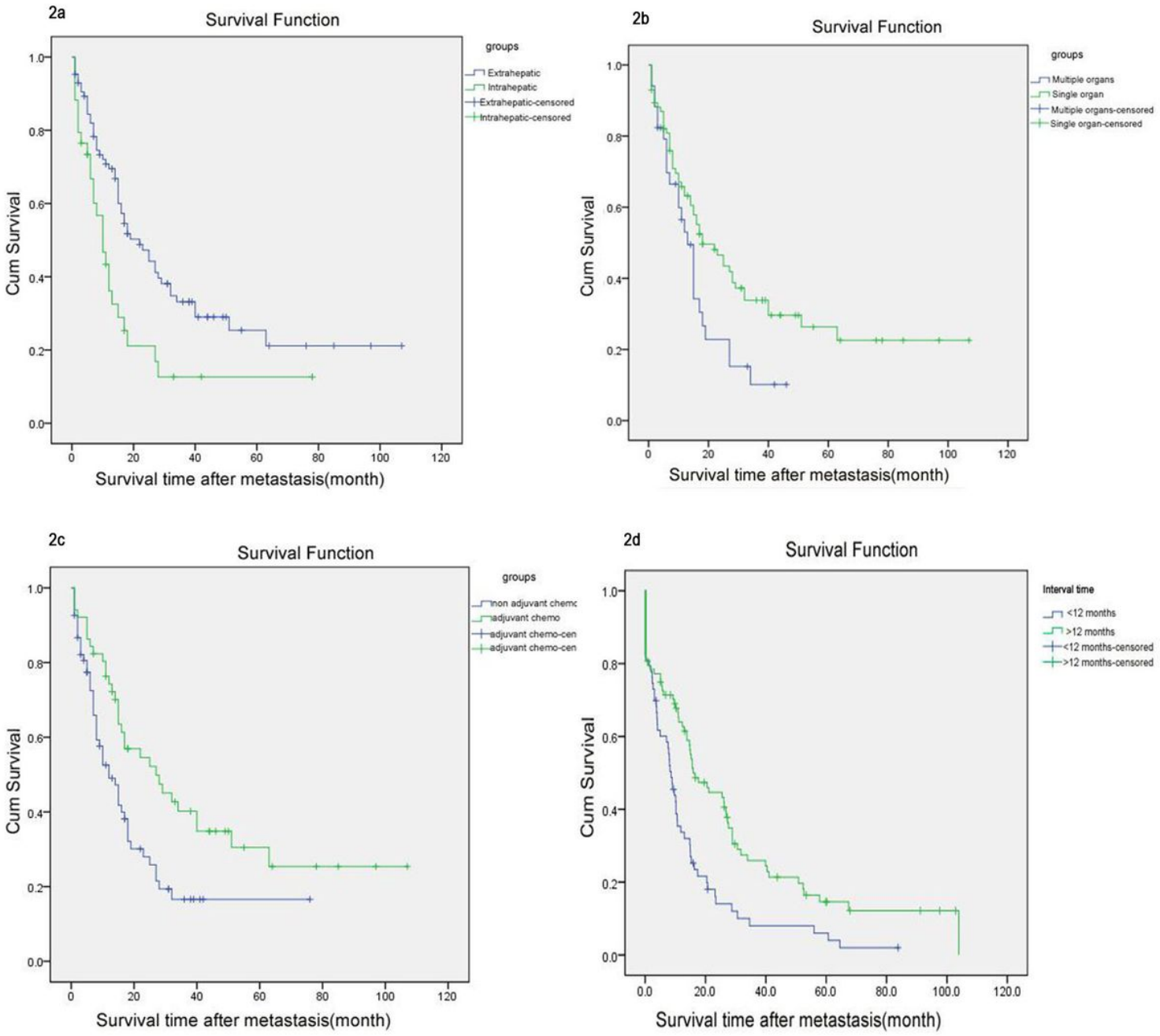

Figure 2

Effect of different grouping factors on survival curve of patients with metastatic NPC. a:Extrahepatic metastasis significantly improved patient survival compared to liver metastasis(P=0.005), b:Single-organ metastasis significantly improved patient survival compared to multi-organ metastasis(P=0.0028). c:Chemotherapy after metastasis significantly improved patient survival compared to without chemotherapy(P=0.005). d:Patients with a short metastatic interval (<12 months) had a significantly worse prognosis compared to long metastatic interval(≥12months)(P=0.000).