Survival Benefit with Palliative Local Radiotherapy in Metastatic Nasopharyngeal Carcinoma

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Abstract

Background: The purpose of this study was to evaluate the benefit to be gained from the addition of local radiotherapy to systemic chemotherapy in patients with newly diagnosed metastatic nasopharyngeal carcinoma in endemic areas of Southern China.

Methods: The data of patients with metastatic nasopharyngeal carcinoma (n = 649) were retrospectively analyzed: 313 patients received only chemotherapy and 336 received chemotherapy plus radiotherapy. The characteristics of the radiotherapy and chemoradiotherapy groups were compared using the chi-square test or Fisher exact test. Survival was analyzed using the Kaplan–Meier method. A Cox proportional hazard model was used to identify the factors independently associated with survival.

Results: Median follow-up was for 36 months. In univariate analysis, radiotherapy was significantly associated with improved survival (median OS 27 vs. 18 months; 5-year OS 36.4% vs. 20.1%; P < 0.001). In multivariate analysis, radiotherapy was an independent predictor of survival (HR, 0.65; CI, 0.53-0.79; P < 0.001). Other independent prognostic factors included number of metastatic organs, smoking, body mass index, hemoglobin, and N stage. In subgroup analysis, chemoradiotherapy was associated with improved survival in both the single-organ metastasis group (5-year OS, 38.5% vs. 25.1%; P < 0.001) and the multiorgan metastases group (5-year OS, 25.0% vs. 9.7%; P = 0.003).

Conclusion: The addition of local radiotherapy to chemotherapy appears to improve survival in patients with metastatic nasopharyngeal carcinoma. Even patients with multiorgan metastases may benefit from radiotherapy.

Introduction

Globally, about 86,500 new cases of nasopharyngeal carcinoma are diagnosed each year according to the data released by the International Agency for Research for Cancer in 2012.(1) About 6%-15% of NPC patients have distant metastasis at initial diagnosis.(2) Although significant progress has been made in long-term disease control in early and locally advanced NPC,(3) metastatic nasopharyngeal carcinoma (mNPC) is still considered incurable. The 5-year survival rate for metastatic nasopharyngeal cancer is about 20%, a relatively high figure compared to the rates in other M1 malignancies.(4) At present, there is no consensus on the best treatment for newly diagnosed metastatic nasopharyngeal carcinoma. NCCN guidelines recommend cisplatin-based chemotherapy as the primary treatment strategy.(5) NPC is a chemosensitive disease, with objective response rate of up to 80%; however, median survival of patients with mNPCs after chemotherapy is only 10–15 months, and median progression-free survival is only 6 months.(6, 7) After systemic chemotherapy, only 3%-8% of mNPC patients have complete remission, and most patients will still have residual primary foci.(8) These residual foci often become an important source of disease progression after chemotherapy is stopped.

Previously, low-dose radiotherapy was mostly used in metastatic nasopharyngeal cancer for relief of symptoms. In the absence of evidence from large-scale phase III clinical trials, the role of radiotherapy for

primary tumor remains debated. Recently, several retrospective studies(8–11) have shown that local radiotherapy can provide survival benefit in patients with metastatic nasopharyngeal carcinoma. However, these studies were mostly from non-high-incidence areas. The few studies from high-incidence areas had small sample sizes and even included patients with post-treatment metastasis. Therefore, the present study aimed to determine the value of local radiotherapy in newly diagnosed metastatic nasopharyngeal carcinoma, using a large sample of patients from an endemic area.

Materials And Methods

Patients

This retrospective study included 649 NPC patients with distant metastasis (including to noncervical lymph nodes) at diagnosis who were treated at Sun Yat-sen University Cancer Center between October 1989 and December 2014. The inclusion criteria were 1) pathologically confirmed nasopharyngeal carcinoma; 2) distant metastasis diagnosed by physical examination and imaging (computed tomography [CT], magnetic resonance imaging [MRI], electrical capacitance tomography [ECT], positron-emission tomography–computed tomography [PET/CT]); 3) no history of other cancers; 4) known TNM stage; 5) treated with systemic chemotherapy alone or chemotherapy plus nasopharyngeal and neck radiation; and 6) complete follow-up and clinical data available. The Ethics Review Committee of Sun Yat-sen University Cancer Center approved the study. Written informed consent was obtained from all patients before treatment

Pretreatment evaluation

Pretreatment evaluation included complete history, physical examination, complete blood counts, blood biochemistry, urine analysis, electrocardiography, nasal endoscopic biopsy, nasopharyngeal and neck MRI scan, bone scan, abdominal ultrasound, chest radiography, PET/CT, and dental evaluation.

Treatment

All patients received systemic chemotherapy, with a median of five chemotherapy cycles per patient. The dose was reduced or the treatment terminated in patients who developed severe adverse reactions. Patients mostly received platinum-based chemotherapy. Cisplatin (20–30 mg/m^2 d1-d3) plus 5-fluorouracil (800–1000 mg/m^2 d1-d5) was the most common regimen. Other commonly used palliative chemotherapy regimens included platinum (20–30 mg/m^2 d1-d3) plus gemcitabine (800–1000 mg/m^2 d1, d8); gemcitabine (800–1000 mg/m^2 d1, d8) plus capecitabine (2 g/m^2 d1-d14); paclitaxel (135 mg/m^2 d1) plus platinum (20–25 mg/m^2 d1-d3) plus 5-fluorouracil (3-3.75 g/m^2, 120 h); and docetaxel (75 mg/m^2 d1) or paclitaxel (175 mg/m^2 d1) plus platinum (20–25 mg/m^2 d1). The above-mentioned regimens were administered intravenously every 3 weeks.

In addition to chemotherapy, 336 patients received radiotherapy—either two-dimensional conventional radiotherapy or intensity-modulated radiotherapy (IMRT). The median radiation dose to the primary tumor

was 70 Gy, and the median radiation dose to the positive region of metastatic lymph nodes in the neck was 62 Gy,. Radiotherapy was administered five times a week from Monday to Friday, with 1.8–2.2 Gy per fraction.

Statistical analysis

Categorical variables were classified according to clinical application. Continuous variables were transformed into categorical variables using cutoff points or findings reported in previous studies.(12) Clinicopathologic characteristics were compared between the two treatment groups by the chi-square test or Fisher exact test. Covariates deemed significant ($P < 0.05$) in univariate regression were entered into a multivariate Cox proportional hazards model to identify independent prognostic factors, using the forward stepwise method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Overall survival (OS) times were estimated by the Kaplan–Meier method, and the curves were compared using the log-rank test. Statistical analysis was performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA) or the rms package in R 3.3.2 (http://www.r-project.org/). All tests were two-tailed, and $P \leq 0.05$ was considered statistically significant.

Results

Patients

A total of 649 patients were included in this study: 313 in the chemotherapy-alone group and 336 in the chemoradiotherapy group. Table 1 shows the baseline characteristics of the patients. Patients younger than 45 were significantly more likely to receive radiotherapy (48.81% vs. 39.94%, $P = 0.034$). Radiotherapy was also significantly more likely in patients with single-organ metastasis than in those with multiorgan metastases (82.74% vs. 67.41%, $P < 0.001$). The other characteristics were comparable between the chemotherapy-alone group and the chemoradiotherapy group.

Table 1
Baseline characteristics of patients with metastatic nasopharyngeal carcinoma treated with chemotherapy alone or with chemotherapy plus radiotherapy

Characteristic	Total (N = 649)	Chemotherapy-alone group (n = 313)	Chemoradiotherapy group (n = 336)	P
Sex				0.675
Female	105 (16.18)	53 (16.93)	52 (15.48)	
Male	544 (83.82)	260 (83.07)	284 (84.52)	
Age				0.034
≤ 45	289 (44.53)	125 (39.94)	164 (48.81)	
> 45	360 (55.47)	188 (60.06)	172 (51.19)	
Histology (WHO)				1.000
Type I-II	31 (4.78)	15 (4.79)	16 (4.76)	
Type III	618 (95.22)	298 (95.21)	320 (95.24)	
Smoking				0.327
No	309 (47.61)	156 (49.84)	153 (45.54)	
Yes	340 (52.39)	157 (50.16)	183 (54.46)	
BMI, kg/m^2				0.868
< 18.5	105 (16.18)	49 (15.65)	56 (16.67)	
18.5–22.9	304 (46.84)	150 (47.92)	154 (45.83)	
≥ 22.9	222 (34.21)	106 (33.87)	116 (34.52)	
Unknown	18 (2.77)	8 (2.56)	10 (2.98)	
VCA-IgA				0.210

†Abbreviations: WHO, World Health Organization; BMI, body mass index; VCA, viral capsid antigen; IgA, immunoglobulin A; EA, early antigen; HGB, hemoglobin.

Characteristic	Total (N = 649)	Chemotherapy-alone group (n = 313)	Chemoradiotherapy group (n = 336)	P
< 1:80	25 (3.85)	10 (3.19)	15 (4.46)	
1:80–1:320	345 (53.16)	177 (56.55)	168 (50.00)	
≥ 1:640	199 (30.66)	88 (28.12)	111 (33.04)	
unknown	80 (12.33)	38 (12.14)	42 (12.50)	
EA-IgA				0.615
< 1:10	102 (15.72)	46 (14.70)	56 (16.67)	
1:10–1:20	187 (28.81)	95 (30.35)	92 (27.38)	
≥ 1:40	299 (46.07)	142 (45.37)	157 (46.73)	
Unknown	61 (9.40)	30 (9.58)	31 (9.23)	
HGB, g/L				0.183
< 113	61 (9.40)	36 (11.50)	25 (7.44)	
113–151	424 (65.33)	203 (64.86)	221 (65.77)	
≥ 151	160 (24.65)	72 (23.00)	88 (26.19)	
Unknown	4 (0.61)	2 (0.64)	2 (0.60)	
T stage				0.217
T1-2	157 (24.19)	83 (26.52)	74 (22.02)	
T3-4	492 (75.81)	230 (73.48)	262 (77.98)	
N stage				0.104
N0-1	178 (27.43)	76 (24.28)	102 (30.36)	
N2-3	471 (72.57)	237 (75.72)	234 (69.64)	

†Abbreviations: WHO, World Health Organization; BMI, body mass index; VCA, viral capsid antigen; IgA, immunoglobulin A; EA, early antigen; HGB, hemoglobin.

Characteristic	Total (N = 649)	Chemotherapy-alone group (n = 313)	Chemoradiotherapy group (n = 336)	P
Metastatic organs				< 0.001
Single organ	489 (75.35)	211 (67.41)	278 (82.74)	
Multiple organs	160 (24.65)	102 (32.59)	58 (17.26)	

†Abbreviations: WHO, World Health Organization; BMI, body mass index; VCA, viral capsid antigen; IgA, immunoglobulin A; EA, early antigen; HGB, hemoglobin.

Prognostic factors

In univariate Cox regression analysis (Table 2), radiotherapy was a predictor of OS (HR = 0.61, 95% CI: 0.50–0.73, P < 0.001). Age, viral capsid antigen (VCA)-IgA, early antigen (EA)-IgA, and T stage were not associated with OS (P > 0.05 for all). In multivariate Cox regression analysis, independent predictors of better OS included radiotherapy (HR = 0.65, 95% CI: 0.53–0.79, P < 0.001) and single-organ metastasis (multiorgan metastases HR = 1.47, 95% CI: 1.18–1.84, P < 0.001). Four other independent predictors of good prognosis were nonsmoker status, BMI ≥ 22.9 kg/m^2, hemoglobin ≥ 113 g/L, and lower American Joint Committee on Cancer (AJCC) N stage (N0-1).

Table 2
Univariate analysis of overall survival in the 649 patients with metastatic nasopharyngeal carcinoma

Characteristic	n (%)	HR (95% CI)	P
Sex			0.010
Female	105 (16.2)	Reference	
Male	544 (83.8)	1.42 (1.09, 1.85)	
Age			0.116
≤ 45	289 (44.5)	Reference	
> 45	360 (55.5)	1.16 (0.96, 1.41)	
Histology (WHO)			0.334
Type I-II	31(4.8)	Reference	
Type III	618(95.2)	0.81 (0.52, 1.25)	
Smoking			0.007
No	309(47.6)	Reference	
Yes	340(52.4)	1.30 (1.07, 1.57)	
BMI, kg/m^2			0.018
< 18.5	105 (16.6)	Reference	
18.5–22.9	304 (48.2)	0.93 (0.71, 1.21)	
≥ 22.9	222 (35.2)	0.71 (0.53, 0.95)	
VCA-IgA			0.418
< 1:80	25 (4.4)	Reference	
1:80–1:320	345 (60.6)	0.81 (0.49, 1.35)	
≥ 1:640	199 (35)	0.92 (0.55, 1.54)	
EA-IgA			0.741
< 1:10	102 (17.3)	Reference	
1:10–1:20	187 (31.8)	0.90 (0.66, 1.21)	
≥ 1:40	299 (50.9)	0.96 (0.73, 1.26)	
HGB, g/L			< 0.001

†Abbreviations: OS, overall survival; NPC, nasopharyngeal carcinoma; HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; BMI, body mass index; VCA, viral capsid antigen; IgA, immunoglobulin A; EA, early antigen; HGB, hemoglobin; Chemo, chemotherapy; RT, radiation therapy.

Characteristic	n (%)	HR (95% CI)	P
< 113	61(9.5)	Reference	
113–151	424 (65.7)	0.55 (0.40, 0.75)	
≥ 151	160 (24.8)	0.46 (0.33, 0.66)	
T stage			0.250
T1-2	157 (24.2)	Reference	
T3-4	492 (75.8)	0.88 (0.71, 1.09)	
N stage			0.001
N0-1	178 (27.4)	Reference	
N2-3	471 (72.6)	1.42 (1.14, 1.76)	
Metastatic organs			< 0.001
Single organ	489 (75.3)	Reference	
Multiple organs	160 (24.7)	1.65 (1.33, 2.04)	
Treatment			< 0.001
Chemo alone	313 (48.2)	Reference	
Chemo + RT	336 (51.8)	0.61 (0.50, 0.73)	

†Abbreviations: OS, overall survival; NPC, nasopharyngeal carcinoma; HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; BMI, body mass index; VCA, viral capsid antigen; IgA, immunoglobulin A; EA, early antigen; HGB, hemoglobin; Chemo, chemotherapy; RT, radiation therapy.

Table 3
Multivariate analysis of overall survival in the 649 patients with metastatic nasopharyngeal carcinoma

Variable	HR (95% CI)	P
Sex		
Female	Reference	
Male	1.33 (0.98,1.79)	0.065
Smoking		
No	Reference	
Yes	1.29 (1.04,1.60)	0.020
BMI, kg/m^2		
< 18.5	Reference	
18.5–22.9	0.87 (0.66,1.14)	0.303
≥ 22.9	0.68 (0.51,0.91)	0.010
HGB, g/L		
< 113	Reference	
113–151	0.60 (0.43,0.83)	0.002
≥ 151	0.52 (0.36,0.75)	< 0.001
N stage		
N0-1	Reference	
N2-3	1.30 (1.04,1.62)	0.023
Metastatic organs		
Single organ	Reference	
Multiple organs	1.47 (1.18,1.84)	0.001
Treatment		
Chemo alone	Reference	
Chemo + RT	0.65 (0.53,0.79)	< 0.001

†Abbreviations: OS, overall survival; NPC, nasopharyngeal carcinoma; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HGB, hemoglobin; Chemo, chemotherapy; RT, radiation therapy.

Survival

Median follow-up time for the entire group was 22 months, and median survival time was 21 months. The study sample was divided into subgroups according to the independent prognostic factors, and the survival rates were compared between the subgroups (Fig. 1). The 3-year and 5-year OS rates were significantly higher in the patients receiving chemoradiotherapy than in patients receiving chemotherapy alone (47.9% vs. 26.9% and 36.4% vs. 20.1%, respectively; both $P < 0.001$; Fig. 1A). The 3-year and 5-year OS rates were significantly higher in the single-organ metastasis subgroup than in the multiorgan metastases subgroup (41.8% vs. 25.7% and 32.9% vs. 15.2%, respectively, both $P < 0.001$; Fig. 1B). Similarly, 3-year and 5-year survival rates were significantly higher in patients with AJCC N0-1 stage, no smoking history, hemoglobin ≥ 113 g/L, and BMI ≥ 22.9 kg/m^2 (Fig. 1C-F). In the hemoglobin subgroups, 3-year and 5-year survival rates were similar in the 113–151 g/L subgroup and the ≥ 151 g/L subgroup ($P = 0.142$; Fig. 1D).

Single-organ vs. multiorgan metastases

In patients with single-organ metastasis, the 3-year and 5-year OS rates in chemotherapy-alone group and the chemoradiotherapy group were 30.6% vs. 49.9% and 25.1% vs. 38.5%, respectively ($P < 0.001$; Fig. 2A). The survival curves of the chemotherapy-alone group and the chemoradiotherapy group were well separated in the patients with multiorgan metastases ($P = 0.003$; Fig. 2B).

Discussion

RT is an effective palliative treatment in mNPC patients and can often relieve symptoms such as bleeding, nasal congestion, headaches, vision and hearing problems, neck pain, and airway compression.(13) Many studies have shown that addition of radiotherapy to chemotherapy can improve prognosis. Verma et al. analyzed the data of 555 patients in the National Cancer Database (NCDB) and reported that additional radiotherapy was an independent prognostic factor for improved OS: median OS was 25.8 months in patients receiving chemoradiotherapy vs. 13.7 months in patients receiving chemotherapy alone ($P < 0.001$).(14) Rusthoven et.al also reported improved survival with the addition of radiotherapy (median OS, 21.4 months vs. 15.5 months).(9) In NPC patients with lung metastasis, Cao et al. found significantly higher median OS in patients treated with chemoradiotherapy than in patients treated with only chemotherapy (73.7 months vs. 46.2 months, $P < 0.001$).(15) In the present study on 649 newly diagnosed mNPC patients from an endemic area, the addition of radiation significantly improved OS; the median OS was 27 months for patients receiving chemoradiotherapy vs. 18 months for patients receiving chemotherapy alone; this is similar to the results of previous studies.(11, 16) Thus, primary disease control appears to significantly improve prognosis, probably via reduction of the number of circulating tumor cells, and tumor promoters and immunosuppressive factors.(10) However, the evidence so far is from retrospective studies. Prospective randomized trials are needed to validate the efficacy and benefits of local radiotherapy treatment.

Hu et al. found higher survival rate for patients with a single metastatic focus than for those with multiple metastatic foci (3-year OS: 61.1 vs. 31.2%, $P = 0.016$).(17) Yin et al. reported significant difference in 2-

year OS between patients with single-organ metastasis and patients with multiorgan metastases (67.5% and 0%, respectively; P = 0.039).(18) Wei et al. showed that among patients with and without multi-metastasis, survival was significantly better for those receiving chemoradiotherapy than for those receiving chemotherapy alone; moreover, prognosis was better for patients with oligometastasis.(19) To date, however, no studies have reported the efficacy of radiotherapy for improving survival in mNPC patients with single-organ vs. multiorgan metastases. In the clinic, the attending doctor tends to choose patients with single-organ metastasis for primary local radiotherapy, because these patients have better treatment tolerance and better prognosis, and are more likely to have a longer survival time. This was apparent in our sample also, where the proportion of patients with single-organ metastasis was as high as 82.74% in the chemoradiotherapy group. Our retrospective study found significantly higher 3-year and 5-year survival rates in patients with single-organ metastasis than in patients with multiorgan metastases (41.8% vs. 25.7% and 32.9% vs. 15.2%, P < 0.001). Subgroup analysis showed that addition of radiotherapy improved survival in patients with single-organ metastasis as well as in those with multiorgan metastases. Thus, the evidence from this study supports the use of radiotherapy for all mNPC patients who can tolerate the treatment.

For metastatic head and neck cancers, including NPC, there is still no consensus on optimal dose and fraction for palliative radiotherapy,(20) primarily because of the heterogeneity among the patients and the lack of data on the benefits and toxicity of radiotherapy. In one study that included 158 patients with metastatic head and neck squamous cell carcinomas treated with 50 Gy (in 16 fractions), the complete response rate was 45% and the total response rate was 73%, indicating that response to palliative radiation was dose dependent.(21) Another retrospective study showed significantly improved survival with a defined dose of > 65 Gy to the primary disease area than with lower doses.(11) In the present study, most of the chemoradiotherapy patients received a radiation dose > 65 Gy to the primary foci, and so subgroup analysis could not be performed.

There are conflicting reports regarding the prognostic significance of age.(22–28) In our study, older age was not associated with shorter OS. History of smoking was a predictor of poor survival in the present study. Smoking has been previously shown to be associated with increased the risk of death in multiple cancers (including NPC).(29–31) In our study, where smokers accounted for 52.4% of the total cohort, the 5-year OS rate was 23.6% for smokers vs. 34.2% for nonsmokers (P = 0.007). Thus, a history of smoking can be a useful predictor of treatment outcome in patients with mNPC.

EA-IgA and VCA-IgA, which are used for screening for NPC, were not associated with prognosis in the present study cohort. Circulating Epstein–Barr virus (EBV)-DNA load has been previously shown to be an independent prognostic factor for mNPC;(32) however, EBV-DNA data was not available for most patients in our cohort, and so we did not assess its prognostic significance.

Our study has some limitations. First, this is a retrospective study and a selection bias is inevitable. Second, the addition of radiotherapy to the treatment regimen was at the discretion of the attending

physician, and so the treatment choice was highly subjective. Third, our series only compares single- and multiple-organ metastases, but does not take into consideration the total metastatic load.

Conclusions

In patients with mNPC being treated with chemotherapy, addition of radiotherapy to the primary cancer appears to improve survival. Local radiotherapy may provide survival benefit even in patients with multiorgan metastases.

Abbreviations

AJCC, American Joint Committee on Cancer

BMI, body mass index

CI, confidence interval

CT, computed tomography

EA, early antigen

EBV, Epstein-Barr virus

ECT, electrical capacitance tomography

HR, hazard ratio

IMRT, intensity-modulated radiotherapy

mNPC, metastatic nasopharyngeal carcinoma

MRI, magnetic resonance imaging

NCDB, National Cancer Database

NPC, nasopharyngeal carcinoma

OS, overall survival

PET/CT, positron-emission tomography–computed tomography

VCA, viral capsid antigen

Declarations

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Ethical approval and consent to participate

The Ethical Committee and Institutional Review Board of the Sun Yat-sen University Cancer Center reviewed and approved this study protocol (grant number GZR2017-024).

Authors' contributions

HXL and HQM conceived and designed this study; WW, QNT, ZQL and SYX acquired the data; JJY, YNJ , HYH and WWZ analyzed the data and results; WW, JJY, QNT and XH wrote the manuscript; and HXL , HQM ,LG and ZYH improved and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset used during the study are available from the corresponding author on a reasonable request.

Consent for publication

Not applicable.

Competing interests

All authors have none to declare.

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Figures

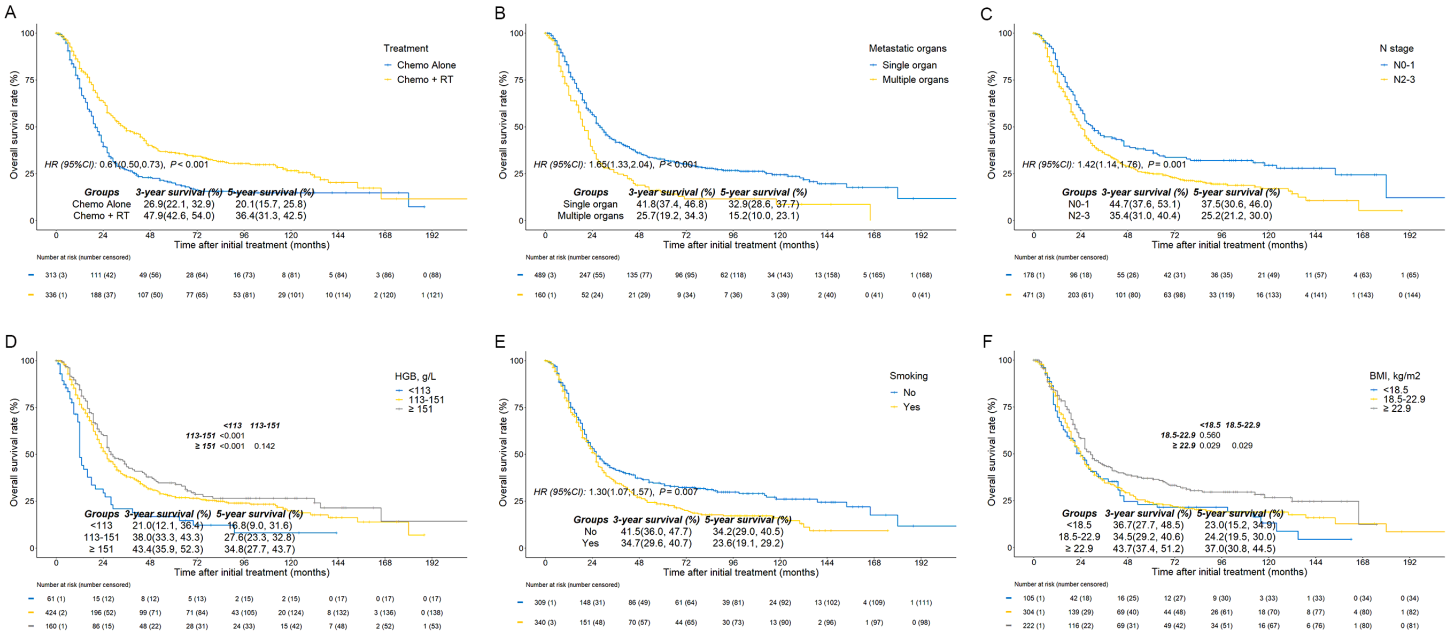

Figure 1

Survival outcomes of patients with newly diagnosed metastatic nasopharyngeal carcinoma stratified by treatment (A), metastatic organs (B), N stage (C), BMI (D), HGB (E), and smoking history (F). NPC, nasopharyngeal carcinoma; BMI, body mass index; HGB, hemoglobin; Chemo, chemotherapy; RT, local radiation therapy.

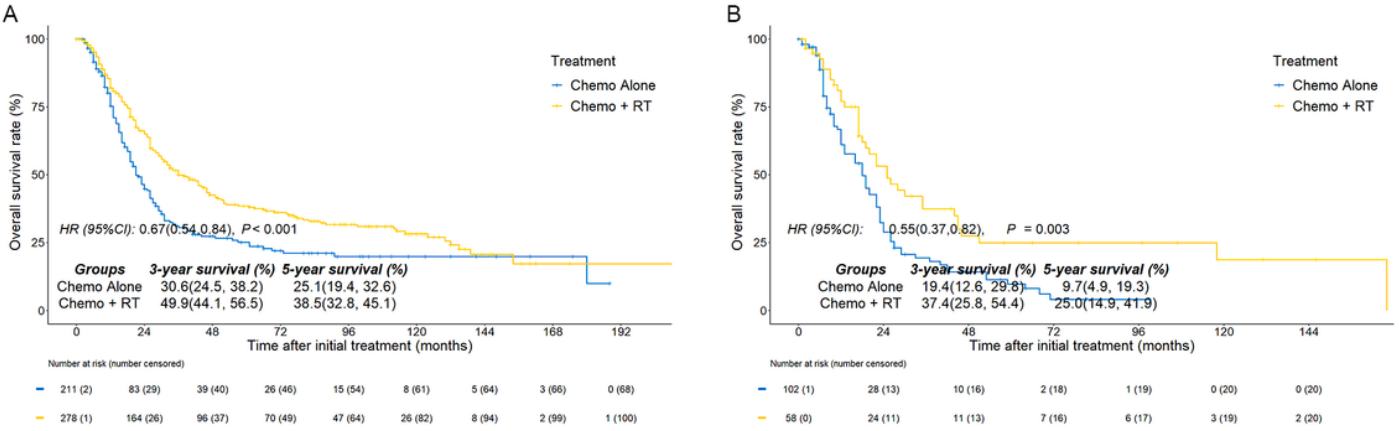

Figure 2

Kaplan–Meier curves of overall survival for single-organ metastasis group (A) and multiorgan metastasis group (B) with chemotherapy alone or chemotherapy + radiotherapy. Chemo, chemotherapy; RT, local radiation therapy.