


Prognostic Relevance of Change in Body Mass Index in Patients With Nasopharyngeal Carcinoma Undergoing Volumetric Modulated Arc Therapy: A Retrospective Study

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Abstract

Objective: To assess the effect of pretreatment body mass index (BMI) and the extent of change in BMI (Δ BMI) during the treatment course on the treatment outcomes in patients with nasopharyngeal carcinoma (NPC) receiving volumetric modulated arc therapy (VMAT).

Methods: Data pertaining to 498 consecutive NPC patients with stage I–IVA disease who received VMAT between January 2010 and November 2011 at a single center were retrospectively analyzed. Univariate Kaplan-Meier and multivariate Cox regression analyses were used to evaluate the prognostic significance of pretreatment BMI and Δ BMI. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off point of Δ BMI.

Results: The 5-year loco-regional failure-free (L-FFR), distant failure-free survival (D-FFR), disease-free survival (DFS), and overall survival (OS) rates were 90.6%, 83.7%, 71.5% and 79.3%, respectively. The 5-year L-FFR, D-FFR, DFS, OS rates for NPC patients with Δ BMI ≤ 1 kg/m² vs Δ BMI > 1 kg/m² were 92.3% vs 89.3% ($P = .137$), 90.9% vs 78.5% ($P < .001$), 80.4% vs 65.1% ($P < .001$), and 88.0% vs 73.0% ($P < .001$), respectively. Δ BMI > 1 kg/m² was an independent predictor of D-FFR ($P = .002$), DFS ($P = .002$), and OS ($P = .001$).

Conclusions: Δ BMI during treatment course may have a significant impact on the prognosis of NPC patients receiving VMAT.

Keywords

body mass index, prognosis, nasopharyngeal carcinoma, volumetric modulated arc therapy

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Introduction

Nasopharyngeal carcinoma (NPC) is a particularly common high-grade malignant head and neck tumor in Southeast and East Asia.¹ Radiotherapy is the main treatment modality for NPC. Volumetric modulated arc therapy (VMAT), a novel form of intensity modulated radiation therapy (IMRT), has been widely accepted in lieu of static IMRT for NPC over the past years owing to the advantages of shortened treatment time and dosimetric benefits.^{2–4}

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Body mass index (BMI), which is calculated as weight in kilograms divided by the square of the height in meters (kg/m^2), is a simple index of nutritional status in adults. BMI has been shown to be associated with the prognosis of cancer; however, the relationship has not been fully elucidated. In some studies, higher BMI was found to be associated with a favorable prognosis for various tumors, such as head and neck cancer,⁵ esophageal cancer,⁶ and colon cancer.⁷ However, in some other studies, higher BMI was associated with a worse prognosis in patients with prostate cancer⁸ and breast cancer.⁹ The prognostic relevance of BMI in the context of NPC is not well characterized. To the best of our knowledge, no studies have addressed the prognostic relevance of the extent of decrease in BMI in NPC patients treated with VMAT. In a study by Huang et al,¹⁰ pretreatment BMI was found to be an independent prognostic factor for patients with locoregionally advanced NPC treated with chemoradiotherapy. Lin et al¹¹ found no significant relationship of BMI and percent weight loss on survival of NPC patients receiving IMRT. However the studies were based on conventional radiation therapy and IMRT, respectively. Currently, VMAT is being widely used in the treatment of NPC; therefore, further studies are required to assess the effect of BMI on outcomes of VMAT. The aim of this study was to assess the prognostic significance of BMI, including pretreatment BMI and the extent of decrease in BMI during treatment of NPC patients with VMAT.

Methods and Materials

Patients

Between January 2010 and November 2011, a total of 508 patients with newly-diagnosed NPC were treated primarily with VMAT at our institution. The inclusion criteria were: (1) stage I-IVA disease according to the 8th edition of the AJCC/UICC TNM staging system; (2) confirmed by pathology; (3) treated by VMAT. The exclusion criteria were as follows: (1) diagnosed with a previous malignancy or other concomitant malignant disease; (2) pregnancy or lactation; (3) metastatic disease at diagnosis. Based on the criteria, 498 patients were included in this retrospective study. The characteristics of patients are listed in Table 1. The study protocol was approved by the ethics committee of our institution. The participants were telephonically contacted to obtain verbal informed consent for retrospective analysis of the pertinent clinical information. Additionally, we de-identified all patient details. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.¹²

BMI Measurement

BMI was calculated as the patient's weight (in kilograms) divided by the patient's height squared (in meters). Pretreatment BMI was measured 1 week before the start of treatment. Posttreatment BMI was defined as the BMI at the last day of

Table 1. Patients' Characteristics.

Characteristic	Number of patient (%)
Age (years)	
≤50	322 (64.7%)
>50	176 (35.3%)
Gender	
Male	383 (76.9)
Female	115 (23.1%)
T-stage	
T1	39 (7.8%)
T2	149 (29.9%)
T3	214 (43.0%)
T4	96 (19.3%)
N-stage	
N0	127 (25.5%)
N1	242 (48.6%)
N2	106 (21.3%)
N3	23 (4.6%)
TNM stage	
I	11 (2.2%)
II	128 (25.7%)
III	248 (49.8%)
IV	111 (22.3%)
Pretreatment BMI value	
<18.5 Kg/m^2	33 (6.6%)
18.5-22.9 Kg/m^2	232 (46.6%)
23.0-27.4 Kg/m^2	207 (41.6%)
≥27.5 Kg/m^2	26 (5.2%)
ΔBMI value	
≤1 Kg/m^2	209 (42.0%)
> 1 Kg/m^2	289 (58.0%)

Pre-RT BMI, pretreatment BMI; ΔBMI, Difference value of BMI before treatment and end of radiotherapy.

radiotherapy. Change in BMI value during treatment (ΔBMI) was calculated using the formula: pretreatment BMI minus posttreatment BMI. Patients were divided into four groups based on the pretreatment BMI: underweight ($\text{BMI}<18.5 \text{ kg}/\text{m}^2$), normal weight ($\text{BMI} 18.5\text{-}22.9 \text{ kg}/\text{m}^2$), overweight ($\text{BMI} 23.0\text{-}27.4 \text{ kg}/\text{m}^2$), and obese ($\text{BMI} \geq 27.4 \text{ kg}/\text{m}^2$) according to the World Health Organization classifications for Asian populations.

Radiotherapy

All patients in this study were treated with VMAT. The target volumes were outlined manually according to our treatment protocol described elsewhere.¹³ The primary gross tumor volume (GTV-P) and the cervical metastatic lymph nodes (GTV-N) included all gross disease as determined by imaging (CT and MRI fusion), clinical, and endoscopic findings. The clinical target volumes (CTVs) were designed to encompass microscopic disease including the high-risk region (CTV-1) and the subclinical prophylactic low-risk region (CTV-2). Levels II, III, IV, and V can be incorporated into CTV of

the neck nodal regions (CTV-N). The planning target volume (PTV) was created based on each volume with an additional 3-mm margin, allowing for setup variability. Organs at risk (OARs) included the brain stem, spinal cord, optic nerve, optic chiasm, temporal lobe, crystal, and parotid gland.

A total dose of 69.7-70 Gy administered in 31-35 fractions (2-2.25 Gy/fraction) was set to the PTV of GTV-P and GTV-N. While a total dose of 59.5-62 Gy at 1.7-2 Gy/fraction was set to the PTV of CTV-1 and 52.7-56 Gy at 1.6-1.8 Gy/fraction was set to the PTV of CTV-2 and CTV-N.

Chemotherapy

Patients with stage III-IV disease received 2-4 cycles of cisplatin-based neoadjuvant chemotherapy and 1-2 cycles of concurrent chemotherapy. Patients with stage T1-2N1 disease underwent 1-2 cycles of concurrent chemotherapy. Patients at stage T1-2N0 only received radiation. Neoadjuvant chemotherapy consisted of gemcitabine (1000 mg/m² on days 1 and 8) plus cisplatin (80 mg/m² on days 1-3) or paclitaxel (135 mg/m² on day 1) plus cisplatin (80 mg/m² on days 1-3). Concurrent chemotherapy based on cisplatin (80 mg/m² on days 1-3) was administered during the course of radiotherapy. Chemotherapy was repeated every 21 days.

Nutritional Support

This was a retrospective study, and there was no standardized protocol for nutritional support. All patients were encouraged to take regular meals during treatment. None of the patients received prophylactic or reactive feeding tubes during the treatment. Parenteral nutrition was not a routine nutritional support in this population either.

Follow-Up

Follow-up was performed every 3 months for the first 2 years and every 6 months for the first 5 years. Thereafter, follow-up was performed once a year. Follow-up included complete physical, hematologic, and biochemical examinations, chest radiograph, abdominal ultrasonography, and nasopharyngoscopy examination. MRI/CT of the nasopharynx, CT chest, and abdominal ultrasound were performed every 6-12 months routinely. 18F-Fluorodeoxyglucose positron emission tomography and CT (PET-CT) was performed at the discretion of the treating physician as per need. All local or regional relapse was confirmed by pathology.

Statistical Analysis

Statistical analysis was performed using SPSS version 13.0 software (SPSS Inc. Chicago, IL) and R 2.15.3 software. Survival outcomes, including 5-year local failure-free rate (L-FFR), 5-year distant failure-free rate (D-FFR), 5-year disease-free survival (DFS), and 5-year overall survival (OS) were

calculated from the date of diagnosis to the most recent follow-up or to the date of recurrence, metastasis, or death. Kaplan-Meier method was used for survival analysis and between-group differences were assessed using the log-rank test. Cox proportional hazards regression analysis was performed to identify the prognostic factors. *P* values < .05 were considered indicative of statistical significance.

Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off point of Δ BMI to predict mortality. The optimal cut-off point was the minimal distance to the ideal point (sensitivity = specificity = 100%) on the ROC curve. It provides a criterion for choosing the "optimal" threshold value based on the Youden index.¹⁴ The study population was then stratified according to the optimal cut-off point.

Results

Baseline Characteristics and Follow-Up

The baseline characteristics of the 498 patients are summarized in Table 1. The mean pretreatment BMI in our cohort was 22.80 kg/m² (range 15.01-35.06). Patients were divided into four groups based on the pretreatment BMI according to the WHO BMI subgroups for Asian populations. A total of 33 patients (6.6%) were underweight, 232 (46.6%) had a normal BMI, and 207 (41.6%) were overweight; only 26 (5.2%) were obese. The mean Δ BMI was 1.29 kg/m² (range -1.65-5.75). The median duration of follow-up in our cohort was 68 months (range 4-110).

Optimal Δ BMI Cut-Off Point

The area under the ROC curve was .598 (95% CI 0.540-.656; *P* = .002). The cut-off point of Δ BMI was 1.04 kg/m² (sensitivity: 75.7%; specificity: 46.8%). Therefore, we selected the cut-off point as 1 kg/m² to classify patients into Δ BMI \leq 1 kg/m² group and Δ BMI > 1 kg/m² group for survival analysis.

Treatment Outcomes

The 5-year L-FFR, D-FFR, DFS, and OS rates in the overall cohort were 90.6%, 83.7%, 71.5%, and 79.3% respectively. Forty-seven patients had local or regional failure, 81 patients developed distant metastasis, and 10 patients had distant metastasis with local or regional failure.

The prognostic significance of age, sex, N-stage, T-stage, primary tumor volume (PTV), pretreatment BMI, and Δ BMI was analyzed. The results of univariate analysis are shown in Table 2. On multivariate analysis, age [relative risk (RR) = 2.457, *P* < .001], N-stage (RR = 1.807, *P* = .004), PTV (RR = 2.259, *P* < .001), and Δ BMI (RR = 2.197, *P* = .001) were adverse prognostic factors for OS (Table 3). None of these factors were independent prognostic factors for L-FFR.

Table 2. Univariate analysis of predictive factors for the patients with NPC.

Variable		5-year LFR (%)	P-value	5-year D-FFS (%)	P-value	5-year DFS (%)	P-value	5-year OS (%)	P-value
Gender	Male	90.3	.673	82.8	.240	70.0	.201	78.1	.179
	Female	91.3		87.0		76.5		83.5	
Age	≤50 y	92.3	.033	83.6	.863	76.2	<.001	84.5	<.001
	>50 y	87.4		84.0		62.9		69.7	
N-stage	N0	93.7	.325	92.1	<.001	81.1	<.001	85.0	.003
	N1	90.1		86.8		74.0		81.8	
	N2	88.7		69.8		56.6		69.8	
	N3	87.0		69.6		60.9		65.2	
T-stage	T1	94.9	.016	92.3	<.001	87.2	<.001	94.9	<.001
	T2	91.9		87.2		77.9		85.2	
	T3	92.1		85.5		73.8		80.8	
	T4	83.3		70.8		50.0		60.4	
PTV	≤15 mL	95.1	.188	91.3	<.001	81.6	<.001	87.4	<.001
	15-25 mL	89.2		86.5		76.6		82.9	
	25-50 mL	90.4		85.5		72.9		81.9	
	> 50 mL	88.1		72.0		55.9		65.3	
Pre-BMI	≤23 Kg/m ²	90.9	.864	82.3	.312	70.6	.520	79.2	.884
	>23 Kg/m ²	90.1		85.4		72.5		79.4	
ΔBMI	≤1 Kg/m ²	92.3	.137	90.9	<.001	80.4	<.001	88.0	<.001
	>1 Kg/m ²	89.3		78.5		65.1		73.0	

Pre-BMI, pretreatment BMI; ΔBMI, Difference value of BMI before treatment and end of radiotherapy; 5-y L-FFR, 5-year local-regional failure-free rate; 5-y D-FFS, 5-year distant failure-free survival; 5-y DFS, 5-year disease free survival; 5-y OS, 5-year overall survival.

Table 3. Multivariate Analysis of Predictive Factors for the Patients With NPC.

Variable	5-year L-FFR		5-year D-FFS		5-year DFS		5-year OS		
	RR,95% CI	P	RR,95% CI	P	RR,95% CI	P	RR,95% CI	P	
Age	≤50 vs >50	1.607	.155	1.183	.476	1.942	<.001	2.457	<.001
		.836-3.091		.745-1.879		1.388-2.716		1.654-3.650	
T-stage	T1-2 vs T3-4	1.511	.261	1.377	.139	1.377	.139	1.648	.058
		.736-3.105		.902-2.103		.902-2.103		.984-2.763	
N-stage	N0-1 vs N2-3	1.475	.222	2.623	<.001	1.880	<.001	1.807	.004
		.791-2.749		1.683-4.087		1.330-2.658		1.203-2.715	
PTV	≤50 mL vs >50 mL	1.607	.155	1.900	.007	1.990	<.001	2.259	<.001
		.836-3.091		1.190-3.034		1.389-2.852		1.398-3.465	
Pre-BMI	≤23 Kg/m ² vs >23 Kg/m ²	.977	.938	.746	.746	.830	.291	.881	.538
		.536-1.778		.472-1.180		.588-1.173		.588-1.319	
ΔBMI	≤1 Kg/m ² vs >1 Kg/m ²	1.438	.258	2.306	.002	1.800	.002	2.197	.001
		.767-2.699		1.350-3.939		1.233-2.628		1.379-3.500	

RR, risk ratio; CI, confidence interval; Pre-BMI, pretreatment BMI; ΔBMI, Difference value of BMI before treatment and end of radiotherapy; 5-y L-FFR, 5-year local-regional failure-free rate; 5-y D-FFS, 5-year distant failure-free survival; 5-y DFS, 5-year disease free survival; 5-y OS, 5-year overall survival.

N-stage (RR = 2.623, $P < .001$), PTV (RR = 1.900, $P = .007$), and ΔBMI (RR = 2.306, $P = .002$) showed an independent association with D-FFR. Age (RR = 1.942, $P < .001$), N-stage (RR = 2.623, $P < .001$), PTV (RR = 1.900, $P = .001$), and

ΔBMI (RR = 1.800, $P = .002$) were adverse prognostic factors for DFS. Pretreatment BMI was not found to be an independent prognostic factor for L-FFR, D-FFR, DFS, or OS in our cohort.

Prognostic Value of the Δ BMI Cut-Off Point

In the study, the 5-year L-FFR, D-FFR, DFS, OS rates for NPC patients with a Δ BMI ≤ 1 kg/m² vs Δ BMI > 1 kg/m² were 92.3% vs 89.3% ($P = .137$), 90.9% vs 78.5% ($P < .001$, Figure 1), 80.4% vs 65.1% ($P < .001$), and 88.0% vs 73.0% ($P < .001$, Figure 2), respectively. Overall, patients with a Δ BMI > 1 kg/m² had significantly poorer D-FFR, DFS, and OS than patients with Δ BMI ≤ 1 kg/m². In multivariate analysis, Δ BMI using the cut-off point was an independent prognostic factor for D-FFR ($P = .002$), DFS ($P = .002$), and OS ($P = .001$).

Discussion

In the study, we investigated the prognostic relevance of BMI in NPC patients treated with VMAT. In our cohort, pretreatment BMI had no significant effect on treatment outcomes. However, Δ BMI was associated with D-FFR, DFS, and OS. To the best of our knowledge, this is the first study to investigate the prognostic value of change in BMI during the treatment course in NPC patients undergoing VMAT.

Numerous studies have confirmed that IMRT is an outstanding radiotherapeutic technique for NPC. Nonetheless, the prolonged treatment time of IMRT may limit the radiotherapy accuracy because of increased intra-fractional patient movements.¹⁵ Additionally, the increased dose to OARs, compared with VMAT, may increase the incidence of radiation-induced secondary cancers.¹⁶⁻¹⁸ Therefore VMAT has gradually replaced IMRT due to shortened treatment time and dosimetric benefits. Several studies have found that VMAT can deliver dosimetric benefits to some extent compared with static IMRT in treatment plan.^{3,4} Although many studies have indicated the relationship of BMI and percent weight loss with survival of NPC patients, there is a paucity of published data pertaining to VMAT. Thus we conducted this study to assess the correlation between BMI and prognosis in NPC treated with VMAT.

Park et al⁶ found that higher pretreatment BMI may be associated with better prognosis in Korean patients with head and neck cancer. In the studies by Hung et al¹⁰ and Shen et al,¹⁹ pretreatment BMI was an independent prognostic factor for patients with NPC treated with chemoradiotherapy, which was contrary to our results. In our study, multivariate analysis showed no significant influence of pretreatment BMI

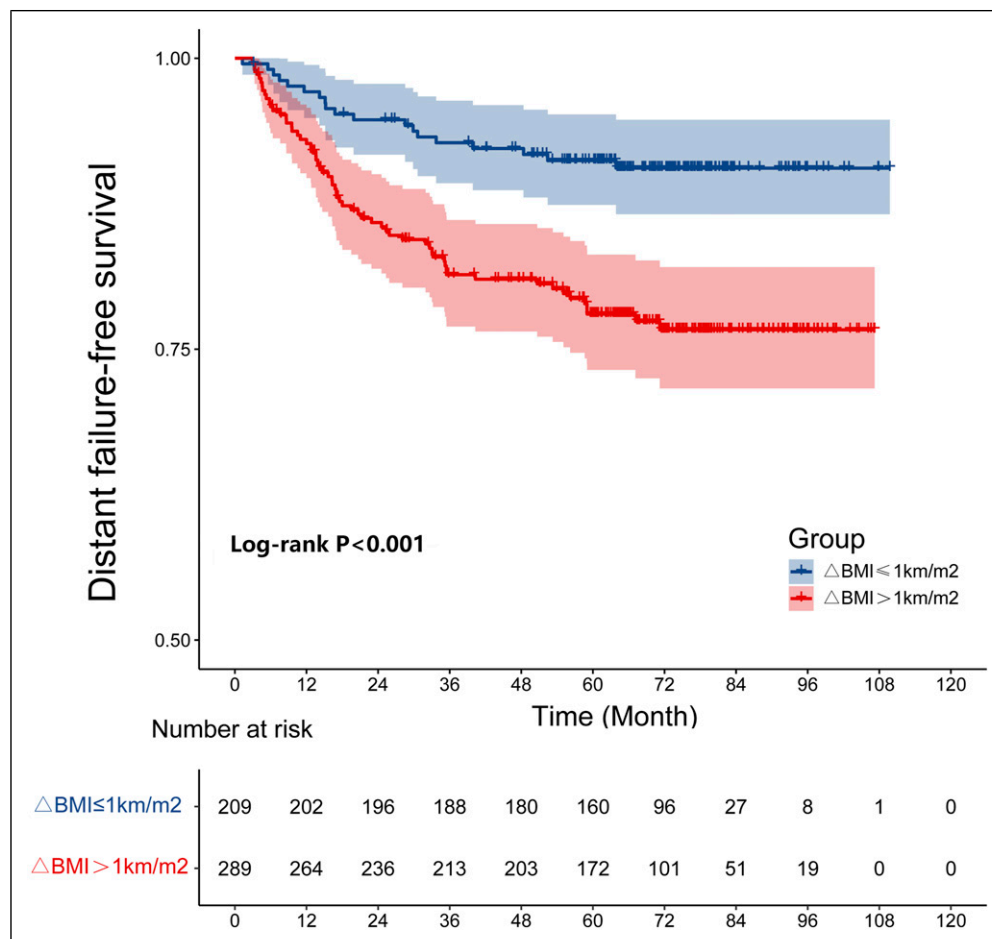


Figure 1. The cumulative distant failure-free survival curves by Δ BMI (≤ 1 and > 1 Kg/m²).

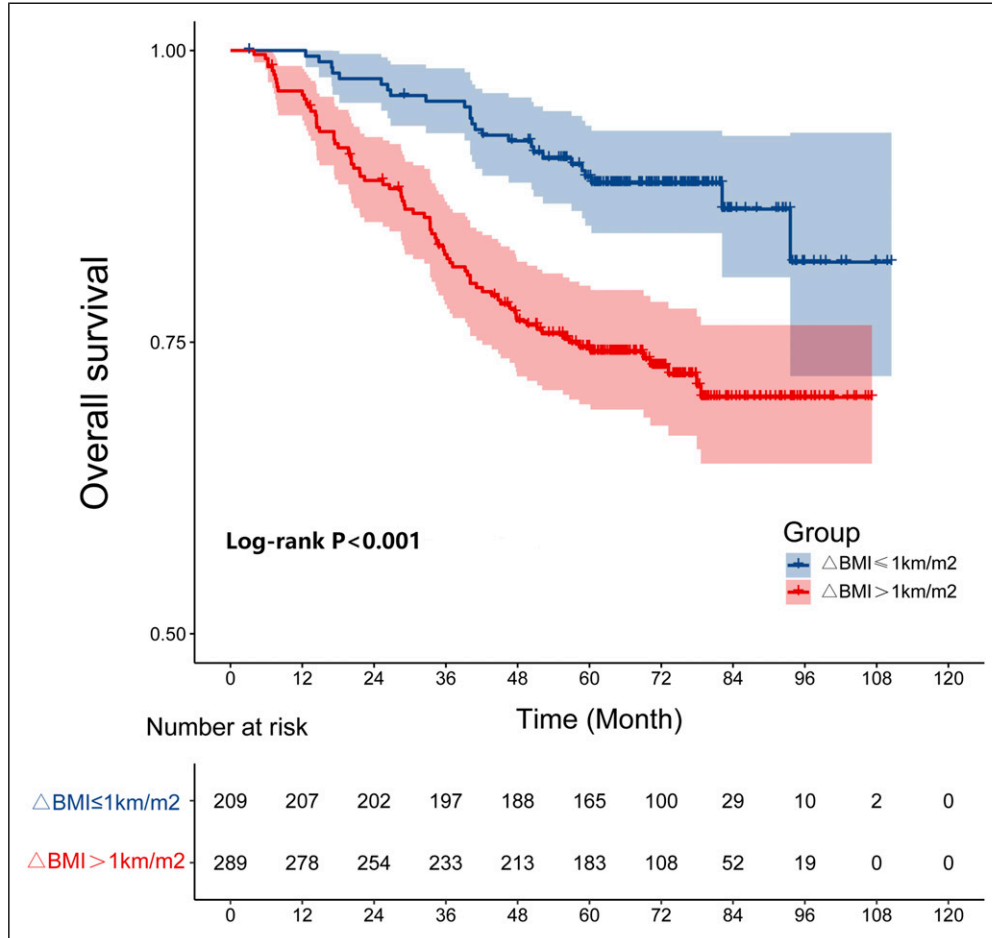


Figure 2. The cumulative overall survival curves by Δ BMI (≤ 1 and > 1 Kg/m²).

on the risk of L-FFR, D-FFR, DFS, or OS. One possible explanation was that the previous study was based on conventional two-dimensional radiotherapy. Therefore the conclusions may not be directly extrapolatable to patients receiving VMAT. VMAT can provide improved treatment outcomes and lower incidence of toxicity.²⁰ Less side effects of radiotherapy minimize the effect on nutrition status during the treatment course, thus decreasing the importance of pre-treatment BMI.

Moreover, we analyzed the prognostic relevance of Δ BMI in patients with NPC receiving VMAT. We further performed ROC curve analysis to determine the optimal Δ BMI cut-off point for the purpose of risk stratification. Cut-off point associated with optimal sensitivity and specificity should be used in clinical practice.²¹ Hence, we defined the critical cut-off point according to maximized Youden index and practicability of clinical application. A cut-off value of 1 kg/m² was chosen for predicting the treatment outcomes of NPC undergoing VMAT. Zeng et al²² also found that critical weight loss predicts poor prognosis in NPC patients. Li et al²³ found that weight loss had an adverse effect on the prognosis of NPC patients. However, the radiotherapy

techniques used in these studies were different. In the present study, we just focused on NPC patients treated with VMAT. Thus the study is predominantly different from the previous studies.

Based on the current study, Δ BMI had a significant prognostic value in NPC patients receiving VMAT. The potential reasons are as follows. Severe decrease in BMI during the treatment course is indicative of malnutrition, which increases the toxicity and reduces the patient's ability to tolerate treatment, including surgery, radiotherapy, and chemotherapy. Patients with malnutrition experience more treatment delays or interruptions and poor overall survival. In addition, the immune system is highly dependent on adequate nutrition. So malnutrition also impairs the immune status leading to poorer therapeutic effect.^{24,25} Moreover, Langius et al²⁶ reported that patients with severe weight loss had significantly lower numbers of T cells and iNKT cells. Unfortunately, it was demonstrated that a severe deficiency of peripheral blood iNKT cells in patients with head and neck cancer was significantly related to poor clinical outcome.²⁷ However, it is crucial to note that the result was related to the extent of decrease in BMI. Our study showed that 5-year D-FFR, DFS,

OS rates were significantly higher in patients with Δ BMI ≤ 1 kg/m².

Advances in the radiotherapy techniques have facilitated higher rates of local control. Distant metastasis has gradually become the major reason for treatment failure in NPC patients.²⁸ Therefore, identification of effective markers of distant metastasis is a key imperative for NPC patients in addition to the N-stage. Our research demonstrated that Δ BMI (RR = 2.306, $P = .002$) is a potential convenient prognostic factor for D-FFS.

Several factors associated with unfavorable prognosis of NPC have been identified, including larger primary tumor volume,²⁹ advanced N stage, lower hemoglobin (Hb) level,³⁰ conspicuous decrease in Hb level during treatment course,³¹ and overexpression of vascular endothelial growth factor (VEGF)³² or epidermal growth factor receptor (EGFR).³³ However, the prognostic relevance of BMI as a convenient marker has largely been ignored. Our research revealed that Δ BMI might be a simple and reliable prognostic factor in NPC patients receiving VMAT. Therefore we believe that active and optimal treatment should be considered for patients who show a conspicuous decrease in BMI in order to prevent continued decline of BMI. Xu et al³⁴ reported that percutaneous endoscopic gastrostomy can confer survival benefit in NPC patients treated with concurrent chemoradiotherapy. Meng et al³⁵ demonstrated that early nutritional intervention can improve outcomes of NPC patients. Nevertheless, the appropriate treatment approach and time-point for intervention in NPC patients who show a conspicuous decrease in BMI during VMAT is not clear.

Despite the positive findings, some limitations of our study should be acknowledged. The single-center scope of the study and the retrospective study design are the principal limitations of the study. Thus, due caution should be exercised while interpreting the findings. A prospective multi-center study is warranted to obtain more robust evidence.

Conclusion

Δ BMI is a potential predictor of survival outcomes in NPC patients receiving VMAT. Nutritional intervention including the placement of feeding tubes is highly recommended for NPC patients as clinically indicated. Concerted efforts should be made to investigate the appropriate treatment strategy for NPC patients who exhibit a conspicuous decrease in BMI while undergoing VMAT.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

The study protocol was approved by the ethics committee of our institution (YKT2020-O11-12). The participants were telephonically contacted to obtain verbal informed consent for retrospective analysis of the pertinent clinical information. Additionally, we de-identified all patient details.

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