·Nasopharyngeal Carcinoma Column·

Impact of pretherapy body mass index on prognosis of nasopharyngeal carcinoma

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[Abstract] Background and Objective: Given the limited information regarding the impact of BMI on treatment outcomes for nasopharyngeal carcinoma, we sought to examine the relationship between body mass index (BMI) and cancer control after radiotherapy. Methods: We compared clinic outcome information across BMI groups from 1,489 patients treated with radiotherapy between 1990 and 2003. Multivariate analysis was used to determine if BMI significantly predicted adverse recurrence. Results: In comparison with normal group, there were statistical difference in age, T staging, N staging, and clinical staging ($P<0.0001$). In survival analysis, in comparison with under-weight group, we could found the hazard ratio was less than one, in the risk of death, cancer recurrence and local recurrence. Meanwhile, the hazard ratio gradually declined when the body weight increased. In univariate survival analysis, under-weight patient had a significant decrease in overall survival, ($P<0.0001$). When Cox regression model was applied to multivariate analysis, we could found age, T staging, N staging, and BMI grades could be a significant independent prognosis factors($P<0.05$). Conclusion:Under-weight patients had a significant decrease in overall survival rate, distant metastasis failure-free survival, and local relapse-free survival. Pretherapy BMI grades could be a significant independent prognosis factors.

Key words: nasopharyngeal carcinoma (NPC); BMI; prognosis

Nasopharyngeal carcinoma (NPC) is one of the common malignant tumors in China, especially in the middle south of China. It is called the Cantonese Cancer. It was reported that the 5-year overall survival rate of NPC patients after conventional radiotherapy was just 30%-55% in the past. But with the development of imaging diagnostic techniques and radiotherapy equipments, the efficacy of radiotherapy on NPC has been significantly improved. Nowadays, the standard treatments for NPC are radiotherapy and radiochemotherapy, but the 5-year overall survival rate is still around 50%-60%.[1-4] NPC is sensitive to radiotherapy, with favorite short-term responses, but the distant metastasis rate is 21.8%,[5] meanwhile, the local recurrent rate is 19.8%.[6] Therefore, it is important to study the factors affecting recurrence and metastasis prediction and the prognosis of NPC.

Nowadays, obesity and underweight are threats to our health, which are related to the occurrence and development of many chronic diseases, such as cardiovascular disease, hypertension, diabetes and chronic obstructive pulmonary disease. The reports of the Chinese Diabetes Education Program indicated that obesity caused an increase in the risk of insulin resistance by 3 folds as well as an increase in the risk of cardiovascular disease and hypertension by 2 folds in the patients with type 2 diabetes.[7] Underweight is an independent factor of the development of chronic obstructive pulmonary disease.[8] Patients of low body weight often suffer from dyspnea, malnutrition, and the imbalance of energy metabolism, with abnormal pulmonary functions present as the decline of FEV1, FVC, and DLCO as well as the increase of RV/TLC.[9-12] Obesity and underweight are also associated with the development of many tumors, such as breast cancer, rectal cancer, and endometrial cancer.[13] But the relationship of obesity and underweight to NPC has not yet been clarified. Body mass index (BMI) is defined as the individual´ s body weight divided by the square of height. As a reliable index reflecting protein-energy malnutrition and obesity, BMI has been widely adopted to evaluate the obese degree and health status of individuals, with the major advantage of reducing the impact of height on body weight when judging obesity and underweight.

To investigate the impact of BMI on the prognosis of NPC, we analyzed the clinical data of 1,489 NPC patients treated with radiotherapy in our cancer center between 1990 and 2003.

Table 1 Clinical Features of nasopharyngeal carcinoma patients classed by BMI

Features	BMI classes				P
	<18.5 kg/m²	18.5~22.9 kg/m²	23~24.9 kg/m²	≥25 kg/m²	
No. of patients	201	776	274	238	
Median of BMI	17.6	20.8	24.1	26.4	
Median of age, years	46	45	48	46	
Sex, (%)					0.162
Make	73.1	78.9	78	81.9	
Female	26.9	21.1	22	18.1	
T stage, (%)					<0.0001
T1	13.1	16.4	17.6	13.9	
T2	25.1	32.1	34.9	42.4	
T3	33.7	33.2	31.6	28.6	
T4	28.1	18.3	15.8	15.1	
N stage, (%)					<0.0001
N0	29.6	26.4	27.6	30	
N1	34.2	37.5	31.7	36.1	
N2	30.2	29.1	30.6	27.5	
N3	6	7	10.1	6.4	
Clinical stage, (%)					<0.0001
I	5	5.7	4.8	7.1	
II	16.9	25.1	30.4	32.8	
III	46.3	44.5	39.6	39.1	
IV	31.8	24.7	25.3	21	

Materials and Methods

Materials. Using Statistic Analysis System, 1489 patients were randomly selected from all NPC patients treated in Sun Yat-sen University Cancer Center between January 1990 and December 2003. All patients had pathologically diagnosed NPC, and initially underwent the radical radiotherapy.

The male-female ratio was 3.2:1. The median age was 45. According to the standard for the Asian adults proposed by International Task Force on Obesity, Regional Office for the Western Pacific (World Health Organization), with BMI of 18.5-22.9 kg/m² defined as normal weight, BMI of < 18.5 kg/m² as underweight group, BMI of 23.0-24.9 kg/m² as overweight, and BMI of ≥25 kg/m² as obesity, the 1489 patients were divided into 4 groups: 201 in underweight group, 776 in normal weight group, 274 in overweight group, and 238 in obesity group. The differences in age, T stage, N stage, and clinical stage between abnormal weight groups and normal weight group were significant, but no significant difference in gender was found (P =0.162).

Treatment. All patients underwent radiotherapy alone or in combination with adjuvant chemotherapy.

Conventional radiotherapy was performed using ^{60}Co γ-ray or 6-8 MV high-dose x-ray with a linear accelerator. The irradiation was initially given to bilateral faciocervical portals plus anterior cervical tangential field, and plus anterior nasal field in some cases, with a dose of 36-40 Gy. Then, irradiation was given to bilateral faciocervical field avoiding spinal irradiation plus anterior cervical tangential field and bilateral posterior cervical triangle field with a dose of 50 Gy, and to bilateral anterior auricular field to a total dose of 66-78 Gy on the nasopharynx. The patients without cervical lymph node metastasis received irradiation to a dose of 46-50 Gy; those with lymph node metastasis received boost irradiation on the metastatic lesions to a total dose of 60-70 Gy.

PF regimen was mainly adopted for adjuvant chemotherapy: cisplatin (DDP, 80-100 mg/m²) on day 1, and 5-fluorouracil (5-FU, 500-1000 mg/m²) on days 2-5.

Observation end-point and follow-up. Overall survival (OS), recurrence-free survival (RFS) and

Table 2 Overall survival, recurrence-free survival and distant metastasis-free survival of patients grouped by BMI

	BMI classes				P
	<18.5 kg/m²	18.5~22.9 kg/m²	23~24.9 kg/m²	≥25 kg/m²	
Overall survival, (%)					<0.0001
RR	1	0.61	0.45	0.37	
95% CI		0.47–0.79	0.32–0.63	0.25–0.55	
Recurrence-free survival, (%)					<0.0001
RR	1	0.75	0.53	0.59	
95% CI		0.59–0.94	0.39–0.71	0.45–0.81	
Distant metastasis-free survival, (%)					<0.0001
RR	1	0.67	0.57	0.42	
95% CI		0.53–0.84	0.42–0.77	0.30–0.59	

distant metastasis-free survival (DMFS) were used as observation end-points. We defined the start of follow-up as the first date of radiotherapy.

The patients were followed up by clinical visits, telephone and mails for 5-250 months, with a median of 83 months. The 3- and 5-year follow-up rates were 97.2% and 94.9%.

Statistical analysis. SPSS16.0 software was used for statistical analysis. The correlation of BMI to clinical factors of NPC was analyzed by χ^2 test. Survival analysis was performed using Kaplan-Meier method and log-rank test. Multivariate prognosis analysis was performed using Cox proportional hazard model. A P value of < 0.05 was considered significant.

Results

The relative risks of OS, RFS and DMFS. Using the data of underweight group as controls, the relative risks of normal weight group, overweight group and obesity group were all below 1 (Table 2), which decreased with the increase of the weight. The OS, RFS and DMFS rates of the 3 groups were higher than those of underweight group, indicating that the patients with higher BMI had better prognosis.

Results of univariate prognosis analysis. The OS rate was significantly lower in underweight group than in the other 3 groups ($P < 0.001$), and significantly higher in obesity group than in normal weight group (P=0.006) (Fig. 1).

The DMFS rate was significantly lower in underweight group than in normal weight group (P=0.013), and significantly higher in overweight group

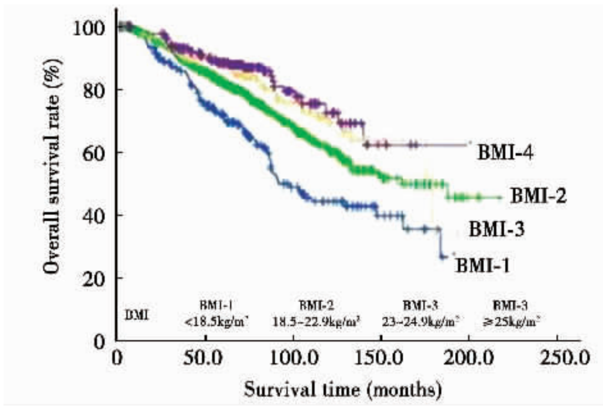

Figure 1 Kaplan-Meier overall survival curve grouped by BMI

Log-rank P values: under-weight versus normal, P<0.0001; under-weight vs. over-weight, P<0.0001; under-weight vs. obesity, P<0.0001; normal vs. over-weight, P=0.044; normal besity, P=0.006; over-weight vs. obesity, P=0.501.

than in normal weight group (P=0.007) and underweight group ($P < 0.001$) (Fig. 2).

The RFS rate was significantly lower in underweight group than in normal weight group (P=0.008), and significantly higher in overweight group than in normal weight group (P=0.03) and underweight group ($P < 0.001$) (Fig. 3).

Results of multivariate prognosis analysis. According to multivaritate analysis, patients age ($P < 0.001$), T stage (P=0.04), N stage ($P < 0.001$) and BMI ($P < 0.001$) were independent prognostic factors (Table 3).

Discussion

In our study, the NPC patients were grouped according to the BMI standard for Asian to analyze

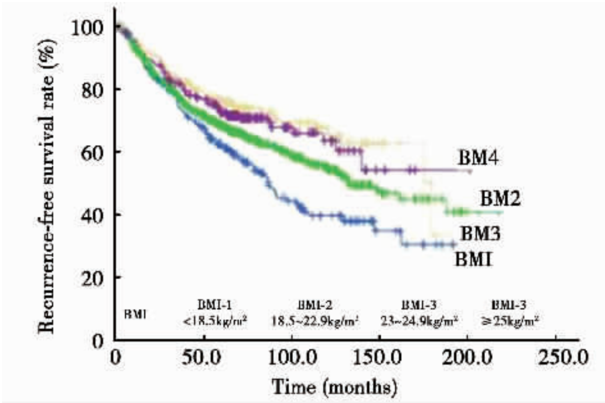

Figure 2 Kaplan-Meier recurrence-free survival curve grouped by BMI

Log-rank P values: under-weight versus normal, P=0.013; under-weight vs. over-weight, P<0.0001; under-weight vs. obesity, P=0.001; normal vs. over-weight, P=0.007; normal vs. obesity, P=0.077; over-weight vs. obesity, P=0.445.

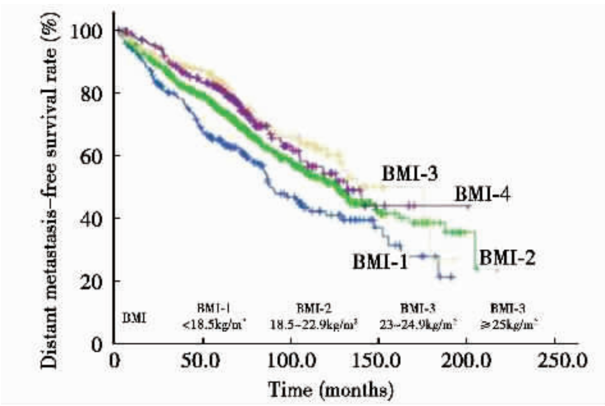

Figure 3 Kaplan—Meier distant metastasis-free survival curve grouped by BMI

Log-rank P values: under-weight versus normal, P=0.008; under-weight vs. over-weight, P<0.0001; under-weight vs. obesity, P=0.001; normal vs. over-weight, P=0.031; normal vs. obesity, P=0.124; over-weight vs. obesity, P=0.579.

the OS, RFS and DMFS. The differences in age, clinical stage, T stage, N stage and BMI, except for gender, among these groups were significant. In obesity group, more patients were at early stages; while in underweight group, more patients were at late stages. This situation is in accordance with the progression of the disease. Tumor is a kind of consumptive disease. More patients at advanced stage have low weight. The influences of age, clinical stage, T stage, N stage and BMI on the results should take into consideration.

In our study, Kaplan-Meier survival analysis showed that the OS rate was lower in underweight

Table 3 Multivariate analysis of overall survival using Cox regression model

	Factor	HR	95%CI	P
Step one	Age	1.02	1.01-1.03	<0.0001
	T stage	1.12	1.01-1.24	0.04
	N stage	1.46	1.3 -1.63	<0.0001
	Sex	0.96	0.75-1.24	0.76
	BMI classes	0.7	0.62-0.79	<0.0001
Step two	Age	1.02	1.01-1.03	<0.0001
	T stage	1.12	1.01-1.24	0.04
	N stage	1.46	1.3 -1.63	<0.0001
	BMI classes	0.7	0.62-0.79	<0.0001

group than in the other 3 groups, and was obviously higher in obesity group than in normal weight group, but no significant difference was found between overweight and obesity group. It was obvious that, among NPC patients, the OS rate was lower in underweight group than in the other 3 groups. The PFS rate was lower in underweight group than in the other 3 groups, and was obviously higher in overweight group than in normal weight group. The OS rate of obesity group was higher than that of overweight group although without significant difference, but the PFS rate of obesity group was lower than that of overweight group and similar to that of normal weight group. These results showed that the OS rate of NPC patients decreased with the increase of BMI, but the trend was unobvious between overweight and obesity groups; meanwhile, the RFS rate was still lower in underweight group than in the other 3 groups, but slightly lower in obesity group than in overweight group. The DMFS rate was lower in underweight group than in normal weight and overweight groups, and was obviously higher in obesity group than in normal weight group.

Cox univariate prognosis analysis showed that BMI was an independent prognostic factor in OS, RFS and DMFS.

NPC is the most common malignant tumor in the head and neck. It was found that patients age, gender, clinical stage, T stage, N stage, skull base invasion, cranial nerve invasion, paranasal sinuses invasion, cervical lymph node metastases, brachytherapy, fraction of external radiotherapy, and chemotherapy are affecters of OS, RFS and DMFS.[14]

Obesity and underweight are important health problems around the world,[15-17] which has caused great concern. Many studies have shown that the weight is associated with the progression of various tumors, such as rectal cancer, breast cancer, endometrial cancer and prostate cancer. Obesity is an important risk factor to the occurrence and progression of rectal cancer as confirmed by retrospective analyses[18-21] and prospective analyses.[22-23] However, the effects of obesity and underweight on the prognosis of NPC has not been revealed.

BMI is a reliable index reflecting protein-energy malnutrition and obesity, therefore, protein-energy malnutrition may be an unfavorable independent prognostic factor of NPC. It is shown that high-fat and high-cholesterol diet will promote the occurrence and progression of colon cancer and breast cancer. On the other hand, the lack of protein can also lead to the occurrence and progression of some cancers. Animal experiments showed that high-protein diet or complementary of some certain amino acids in food may inhibit the occurrence of tumors. Using methyl-benzyl-nitrosamine to induce esophageal cancer in rats, those in high-protein group have a long latency with well differentiation of tumor cells. In high incidence areas of esophageal cancer, people intake less protein. High -protein diet will improve the immunity and nutritional status of tumor patients. According to our results, nutritional intervention may improve the prognosis of NPC patients.

As shown in our results, the OS, RFS and DMFS rates of the patients with low BMI are lower than those of the ones with normal BMI; BMI may be an independent prognostic factor of NPC. Therefore, pretreatment BMI is an important index for assessment of general status of NPC patients, and may guide the treatment of NPC.

However, we have not identified a quantitative cut-off value of nutrition that predict poor prognosis of NPC patients. If we have, the cut-off value can be used as a reference for nutritional intervention to maintain well nutrition status and improve prognosis of the patients. What is more, the impact of dynamic change of body weight on the prognosis of the NPC has not be clarified in this study.

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