Pretreatment body mass index as an independent prognostic factor in patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy: Findings from a randomised trial

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KEYWORDS
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Abstract  Objective: To investigate the relationship between the pretreatment body mass index (BMI) and the clinical outcomes in patients with locoregionally advanced nasopharyngeal carcinoma treated with combination of chemotherapy and radiotherapy.

Methods: From August 2002 to April 2005, 400 patients with stage III or stage IVa nasopharyngeal carcinoma were recruited for a randomised clinical trial of induction chemotherapy combined with radiotherapy or concurrent chemoradiotherapy. The patients were divided into four groups of underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–22.9 kg/m²), overweight (BMI 23.0–27.4 kg/m²) or obese (BMI ≥ 27.5 kg/m²) according to the World Health Organization classifications for Asian populations. The differences in the long-term survival, of these four BMI groups were analysed.

Results: The 5-year failure-free survival rates for the underweight, normal weight, overweight and obese groups were 44%, 61%, 68% and 73%, respectively (p = 0.014), and the 5-year overall survival rates were 51%, 68%, 80% and 72% (p = 0.001), respectively. BMI was a strongly favoured prognostic factor of overall survival and failure-free survival in a Cox regression model.

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Conclusions: Pretreatment body mass index was a simple, reliable independent prognostic factor for patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy.

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1. Introduction

Nasopharyngeal carcinoma (NPC) is endemic in southern China where undifferentiated nasopharyngeal carcinoma occurs more frequent. During the past 10 years, radiotherapy combined with chemotherapy has become the standard of care. Meta-analyses highlight the need for adjunct chemotherapy with radiotherapy: a significant benefit was found for overall survival (6% at 5 years) and event-free survival (10% at 5 years) with the addition of chemotherapy.  

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in metres (kg/m²). In this study, we calculated BMI of the patients according to the World Health Organization (WHO) classifications for Asian population which is more suitable for Chinese patients. Two reports that many prognostic factors such as tumour-node-metastasis (TNM) staging and Karnofsky performance status may influence the survival in cancer patients. The relationship between body mass index (BMI) and the prognosis of cancer is not consistent. According to some published studies, a high BMI was associated with a favourable prognosis for various tumour types, including cervical cancer, head and neck cancer, oesophageal cancer, clear cell renal cell carcinoma, colon cancer and endometrial cancer. However, the results of some studies showed that patients with a higher BMI had a worse prognosis for breast cancer, prostate cancer and ovarian cancer. The relationship between BMI and NPC remains unclear.

2. Materials and methods

2.1. Patients

Patients enrolled in this analysis were drawn from a randomised trial that compared the efficacy of induction chemotherapy and concurrent chemoradiotherapy (IC + CCRT) with that of induction chemotherapy and radiotherapy (IC + RT) for patients with locoregionally advanced nasopharyngeal carcinoma conducted between August 2002 and April 2005 in our institute. The details were described by Huang. In brief, the study had an enrolment of 408 patients, and eight patients were excluded due to pathological type of WHO I in two patients in the IC + RT group and distant metastasis before the initiation of treatment in six patients, three each in IC + RT and IC + CCRT groups. Patients were treated with a uniform conventional 2-dimensional technique in line with the treatment policy for NPC at Sun Yat-sen University Cancer Center. Conventional radiation therapy was used in all patients by 2 Gy per fraction with five daily fractions per week to a total dose of 68–78 Gy. For the IC + CCRT group, two cycles of Fluorouridine (FuDR) + carboplatin (FuDR, 750 mg/m², d1–5; carboplatin, area under the curve [AUC] = 6) were administered. Patients received RT 1 week after they finished their chemotherapy. Patients in this group also received carboplatin (AUC = 6) on days 7, 28 and 49 of RT. For the IC + RT group, two cycles of FuDR + carboplatin (FuDR, 750 mg/m², d1–5; carboplatin, AUC = 6) were administered. Patients received RT 1 week after they finished their second cycle of chemotherapy.

In the present study, BMI was calculated as the patient’s weight on day 1 of chemotherapy (in kilograms) divided by the patient’s height squared (in metres). The patients were divided into four groups: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–22.9 kg/m²), overweight (BMI 23.0–27.4 kg/m²) or obese (BMI ≥ 27.5 kg/m²) according to the World Health Organization classifications for Asian populations.

2.2. Statistical analysis

All events were measured from the date of random assignment, and statistical tests were performed using SPSS V13.0 (SPSS Inc., Chicago, IL). The actuarial rates were calculated with the Kaplan–Meier method,
and the differences were compared with the log-rank test. The time to the first defining event was assessed for the following end-points: local-regional failure-free survival (LR-FFS-persistence/recurrence in the nasopharyngeal region and/or in the cervical region), distant failure-free survival (D-FFS-haematogenous metastasis), failure free survival (FFS-disease failure at any site) and overall survival (OS-all cause mortality). The survival rates were calculated using the Kaplan–Meier method and compared with the log-rank test. A 2-tailed \( P \) value of less than 0.05 was considered statistically significant.

The entire cohort was analysed using the Cox proportional hazards model for OS, FFS, LR-FFS and D-FFS. Potentially important prognostic factors considered in the modelling process were patient gender (1. male versus 2. female), age (continuous variable), Chinese 1992 T stage\(^{16} \) (1.T1, 2.T2, 3.T3, 4.T4), Chinese 1992 N stage (1.N0, 2.N1, 3.N2, 4.N3), radiotherapy dose (continuous variable), treatment arm (1.IC + CCRT versus 2.IC + RT) and BMI (continuous or categorical variable: 1.underweight, 2.normal weight, 3.overweight, 4.obese). BMI was evaluated as a continuous variable with the risk calculated per each unit change in BMI and in separate models as a categorical variable with the risk calculated for those with different BMI groups. The last follow-up visit was in August 2011, with a median follow-up period of 7.3 years.

3. Results

3.1. Baseline characteristics

As previously described by Huang,\(^{14} \) no significant differences were observed in failure-free survival, loco-regional control or distant control between IC + RT and IC + CCRT group. Compared with the IC + RT program, the IC + CCRT program used in the study did not improve the overall survival or failure-free survival in patients with locoregionally advanced nasopharyngeal carcinoma.

In the present study, the mean age was 43 years (range, 18–65 years) for the entire group. The mean BMI was 22.71 kg/m\(^2\) (range, 14.44–39.06 kg/m\(^2\)). The baseline characteristics of the 400 patients are shown in Table 1 according to the WHO BMI subgroups. A total of 41 patients (10.25%) were underweight, 184 (46%) had a normal BMI and 142 (35.5%) were overweight; only 33 (8.25%) were obese. The four BMI groups showed similar demographics, such as in the T and N stage, gender and radiotherapy dose. Aside from these factors, compared with underweight patients (mean age: 39.4 years, range 18–59 years), an increasing BMI was associated with a higher age (\( P = 0.000 \)). In overweight group, there were more patients received IC + CCRT (\( P = 0.037 \)).

3.2. Acute toxicities related with therapy by BMI category

We examined the influence of BMI on the rates of major treatment-related acute toxicity during the course of therapy (Table 2). The grades 3 and 4 thrombocytopenia occurred in four patients (9.8%) in the underweight group, which is significantly higher than that in the other groups (\( P = 0.029 \)). Aside from thrombocytopenia, no significant differences in treatment-related leukopenia, anaemia, liver and kidney dysfunction, neck dermatitis or mucositis were found among the four groups.

3.3. Survival results by BMI category and multivariate analysis for different end-points

For the entire group, the actuarial 5-year OS, FFS, LR-FFS and D-FFS rates were 51%, 44%, 72% and 59%, respectively. As shown in Fig. 1, the 5-year OS rates in underweight, normal weight, overweight and obese group were 51%, 68%, 80% and 72%, respectively. The difference was statistically significant (\( P = 0.001 \)) (Fig. 1). Fig. 2 depicted the 5-year FFS rates, which were 44%, 61%, 68%, 73% (\( P = 0.014 \)) for the four groups, respectively. The 5-year LR-FFS rates were 72%, 91%, 84% and 87% (\( P = 0.045 \)), respectively, and the 5-year D-FFS rates were 59%, 65%, 77% and 82% (\( P = 0.037 \)), respectively (Table 3).

In a multivariate analysis, whether BMI was calculated as a categorical variable or as a continuous variable, the results showed that age, N stage and BMI were independent factors for OS. As a categorical variable, the HR of the BMI for OS was 0.633 (95% CI 0.506–0.792; \( P = 0.000 \)). As a continuous variable, the BMI was still an independent factor for OS, with \( HR = 0.890 \) (95% CI 0.844–0.939; \( P = 0.000 \)) (Tables 4 and 5).

In a multivariate analysis for FFS, we found similar results. Gender, N stage and BMI were independent factors associated with FFS. BMI was an independent factor for FFS, whether it was calculated as a categorical variable (HR 0.700, 95% CI 0.563–0.870; \( P = 0.001 \)) or as a continuous variable (HR 0.904, 95% CI 0.859–0.952; \( P = 0.000 \)) (Tables 6 and 7).

For D-FFS, multivariate analysis results showed that both the N stage and the BMI were independent factors associated with D-FFS. As a categorical variable, BMI was an independent factor for D-FFS (HR 0.690, 95% CI 0.536–0.887; \( P = 0.004 \)) (Table 8).

Multivariate analysis for LR-FFS identified that both gender and RT dose were independent factors associated with LR-FFS. BMI was not an independent factor for LR-FFS (HR 0.783, 95% CI 0.551–1.113; \( P = 0.173 \)) (Table 9).
4. Discussion

In the present study, using data from a large, randomised trial of patients with locoregionally advanced nasopharyngeal carcinoma, we have found that a higher pretreatment BMI was associated with increased failure free survival. The findings of this study have demonstrated that pretreatment BMI was a significant independent prognostic factor for patients with nasopharyngeal carcinoma. In our study, compared with low-BMI patients, high-BMI patients had a better FFS. We speculated about the possible reasons for this phenomenon.

First of all, underweight patients may have a worse survival because cachexia may be a reflection of both an advanced stage and an aggressive type of tumour. A number of published studies have demonstrated that cancer cachexia syndrome is associated with a decreased response to therapy and increased morbidity. Malnutrition impairs the immune status and reduces the patient’s ability to tolerate oncological therapies, including surgery, chemotherapy and radiotherapy. In our study, we did not find significant differences between the pretreatment BMI and the NPC stage distribution, furthermore, the body habits (reflect inadequate oral intake/poor quality diet and/or increased energy) more than cachexia were likely reason for the low body weight. The tumour stages of the different BMI groups were well balanced. In this instance, pretreatment BMI adjusted for both the T stage and the N stage was still

Table 1
Baseline Characteristics by BMI group.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BMI group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Underweight</td>
<td>Normal weight</td>
</tr>
<tr>
<td>Case (%)</td>
<td>41 (10.3%)</td>
<td>184 (46.0%)</td>
</tr>
<tr>
<td>Median follow-up (y)</td>
<td>7.6 (2.0–8.8)</td>
<td>7.3 (0.5–9.2)</td>
</tr>
<tr>
<td>Weight (kg) [mean(range)]</td>
<td>46.2 (36.5–55.0)</td>
<td>55.6 (40.0–68.5)</td>
</tr>
<tr>
<td>Mean BMI [mean(range)]</td>
<td>17.3 (14.4–18.37)</td>
<td>20.88 (18.55–22.99)</td>
</tr>
<tr>
<td>Age (y) [mean(range)]</td>
<td>39.4 (18–59)</td>
<td>41.6 (18–65)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>29 (70.7%)</td>
<td>12 (29.3%)</td>
</tr>
<tr>
<td></td>
<td>119 (83.8%)</td>
<td>23 (16.2%)</td>
</tr>
<tr>
<td>T stage</td>
<td>T1–2</td>
<td>T3–4</td>
</tr>
<tr>
<td></td>
<td>6 (14.6%)</td>
<td>35 (85.4%)</td>
</tr>
<tr>
<td></td>
<td>18 (9.8%)</td>
<td>111 (6.3%)</td>
</tr>
<tr>
<td></td>
<td>27 (19.0%)</td>
<td>115 (81.0%)</td>
</tr>
<tr>
<td>N stage</td>
<td>N0–1</td>
<td>N2–3</td>
</tr>
<tr>
<td></td>
<td>20 (48.8%)</td>
<td>21 (51.2%)</td>
</tr>
<tr>
<td></td>
<td>100 (54.3%)</td>
<td>84 (45.7%)</td>
</tr>
<tr>
<td></td>
<td>66 (46.5%)</td>
<td>76 (53.5%)</td>
</tr>
<tr>
<td>RT dose (Gy) [mean(range)]</td>
<td>72 (68–78)</td>
<td>72 (68–78)</td>
</tr>
<tr>
<td>Weight loss (kg) [mean(range)]</td>
<td>2.4 (–1.0 to 7.0)</td>
<td>3.4 (–4.0 to 11.0)</td>
</tr>
<tr>
<td></td>
<td>1.8 (0–3.5)</td>
<td>3.2 (–4.0 to 10.0)</td>
</tr>
<tr>
<td></td>
<td>2.3 (–1 to 7)</td>
<td>3.3 (–4 to 11)</td>
</tr>
<tr>
<td>Treatment arm</td>
<td>IC + CCRT</td>
<td>IC + RT</td>
</tr>
<tr>
<td></td>
<td>29 (70.7%)</td>
<td>12 (29.3%)</td>
</tr>
<tr>
<td></td>
<td>89 (48.4%)</td>
<td>95 (51.6%)</td>
</tr>
<tr>
<td></td>
<td>58 (31.5%)</td>
<td>77 (54.2%)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI = body mass index; RT Dose = radiotherapy dose; IC + CCRT = induction chemotherapy plus concurrent chemoradiotherapy and IC + RT = induction chemotherapy plus radiotherapy.

Table 2
Grade 3 or 4 acute toxicities by body mass index (BMI) group.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BMI group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Underweight</td>
<td>Normal weight</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5 (12.2%)</td>
<td>20 (10.9%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1 (2.4%)</td>
<td>7 (3.8%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (9.8%)</td>
<td>6 (3.3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1 (2.4%)</td>
<td>12 (6.5%)</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>0</td>
<td>6 (3.3%)</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arbitrary grade 3 or 4 toxicity</td>
<td>10 (24.3%)</td>
<td>58 (31.5%)</td>
</tr>
</tbody>
</table>

* Statistics cannot be performed.
an independent prognostic factor for nasopharyngeal carcinoma in a Cox regression model.

Secondly, weight loss was commonly observed during chemotherapy and radiotherapy in NPC patients. The most likely causes of weight loss were treatment-related side-effects, such as decreased appetite, nausea, vomiting and radiotherapy-induced mucositis. The average weight loss was $4.29 \pm 3.54$ kg for patients.
receiving chemoradiotherapy in this study, which debilitated the patients' nutritional status. Therefore, patients with a higher pretreatment BMI who had higher nutritional stocks could withstand weight loss during chemoradiotherapy.
Multiple factor analysis indicated that older patients had a poor prognosis. In the present study, a higher pre-treatment BMI was associated with a favourable prognosis although the mean age of the patients in the higher BMI group was greater than that in the lower BMI group. Cox regression analysis demonstrated that, after adjusting for age, gender, T stage, N stage, radiotherapy dose and treatment modality, the pretreatment BMI was still an independent prognostic factor for nasopharyngeal carcinoma. In the present study, larger proportion (70.7%) of underweight group received IC + CCRT regimen than other three groups (48.4%, 45.8% and 54.5%, respectively) \((P = 0.037)\). As reported in our previous study, \(IC + RT\) and \(IC + CCRT\) modality had no significant difference. So unbalance distribution of treatment modality would not affect the survival among different BMI groups.

In our study, multivariate analysis results showed that BMI was an independent prognostic factor associated with OS, FFS and D-FFS. BMI had no influence on the risk of locoregional recurrences. Compared with low-BMI patients, high-BMI patients had better D-FFS. This indicates that BMI had an impact on distant control and then influenced both the FFS and the OS. Whether BMI was calculated as a categorical variable or as a continuous variable, multivariate analysis results showed that BMI was a stable independent factor for OS and FFS. These results strongly indicate the prognostic value of pretreatment BMI in patients with loco-regionally advanced NPC. The results obtained in the present study differ from those for other cancer types. In hormone-related tumours, such as breast cancer and prostate cancer, a high BMI was associated with an increased risk of cancer metastasis and death. The inner mechanisms of BMI and distant control are still unclear, and further laboratory research is warranted.

Currently, with the advance of radiotherapy techniques, excellent local control rates can be achieved after primary treatment for NPC. Distant metastasis represents a major cause of treatment failure, particularly in patients presenting with advanced primary disease. Our results indicate that BMI may be a simple and reliable independent prognostic factor for D-FFS.

In our study, obese patients had a better FFS but a worse OS compared with overweight patients. The underlying reason for this was that more patients in the obese patients died from an obesity-related disease, such as diabetes mellitus or cardiovascular disease. In the obesity group, 9.1% (3/33) patients died from these diseases. However, in the overweight group, only 4.2% (6/142) patients died from obesity-related disease (Table 10) \((\chi^2 = 1.299, P = 0.254)\). Obesity as a risk factor for mortality due to cancer has been widely discussed elsewhere.

In the current study of nasopharyngeal carcinoma, grades 3 and 4 acute toxicities were not frequently found. No significant differences in treatment-related leukopenia, anaemia, liver and kidney dysfunction, neck dermatitis or mucositis were found among the four groups, except thrombocytopenia. Underweight patients experienced a higher rate of thrombocytopenia compared with other three group individuals. However, the rates of thrombocytopenia were similar in the other three groups, so, we believed that BMI had not truly affected thrombocytopenia.

Based on the published data, several variables including a local advanced tumour, an advanced N stage, male sex, a low haemoglobin level, vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) overexpression may contribute to a nasopharyngeal carcinoma progression resulting in an unfavourable prognosis. However, as a simple index, BMI has been ignored for quite some time. Our data suggest that BMI is a simple and reliable factor that can predict the NPC prognosis and that it should be used as a factor in selecting the optimal treatment option for patients. A patient’s pretreatment BMI should be considered in the future during clinical decision-making. The appropriate treatment approach for low BMI patients remains unclear and should be further investigated.

There are some limitations to our study. NPC is a unique disease characterised by an unbalanced endemic distribution. Our report reflects findings in patients referred to a single cancer centre in an endemic area. It is uncertain whether the same conclusion could be extrapolated to a low incidence area. Therefore, our
findings should be interpreted with caution until they are validated in a large multi-institutional pooled analysis. Secondly, the present study was based on conventional two-dimensional radiotherapy, and whether the conclusions of the present study can be expanded to patients receiving intensity-modulated radiation therapy (IMRT) is still unknown. Further research is needed to explore the value of pretreatment BMI in locoregionally advanced NPC treated with IMRT.

In conclusion, pretreatment BMI was an independent prognostic factor for patients with locoregionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy. How BMI influences the prognosis of NPC and its internal mechanism is uncertain and should be further investigated in the future.

Conflict of interest statement

None declared.

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