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Preoperative Body Mass Index May Determine the Prognosis of Advanced Gastric Cancer

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ABSTRACT

Radical gastrectomy followed by adjuvant chemotherapy for advanced gastric cancer causes serious nutritional impairment. Our study evaluated the clinical impact of body mass index (BMI) on the long-term outcomes of advanced gastric cancer (stage II and III). We analyzed 211 cases of stage II and III gastric cancer between January 2005 and December 2010 at Chung-Ang University Hospital, Seoul, Korea. Patients were divided into four groups according to BMI: underweight, normal, overweight, and obese. In addition, we divided patients into two groups: BMI-High (BMI ≥ 23 kg/m²) vs. BMI-Low (BMI < 23 kg/m²). We assessed age, sex, tumor location, lymph node (LN) involvement, operation method, initial cancer stage, recurrence, and survival between the two groups. There was significant difference in overall survival (OS) between the underweight group and the other groups ($P = 0.005$). The survival of the BMI-High group was better than that of the BMI-Low group. The rate of cancer-related death in the BMI-High group was significantly lower than that in the BMI-Low group (cancer-related death: BMI-Low 27% vs. BMI-High 12.6%, $P = 0.022$). Our findings suggest that preoperative BMI may have an influence on the long-term outcomes of advanced gastric cancer after radical surgery and chemotherapy.

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Introduction

Gastric cancer is the fourth most common malignancy and the second leading cause of cancer death worldwide (1). According to global cancer statistics, the incidence and mortality rate of gastric cancer are higher in developing countries and in males (2). In Korea, despite a decline in incidence in recent decades, gastric cancer remains the second most common cancer and the third leading cause of cancer-related death (3). To date, clinical and basic research have demonstrated that *Helicobacter pylori* infection is a major risk factor involved in the pathogenesis of gastric cancer (4). Indeed, the Asia-Pacific consensus guidelines for *H. pylori* suggest that screening for and treatment of *H. pylori* infection in communities with high incidence of gastric cancer is an effective strategy for gastric cancer prevention (5).

The optimal treatment for gastric cancer is surgical resection. Additional treatment with perioperative chemotherapy and/or radiotherapy offers the best chance of long-term survival (6,7). Gastric bypass surgery, however, leads to gastrointestinal (GI) disorders and a

decreased quality of life. Furthermore, postgastrectomy conditions such as dumping syndrome and alkaline reflux gastritis may lead to a delay in nutritional recovery and cause weight loss or nutritional changes (8).

The patient's nutritional status should therefore be an important prognostic factor in gastric cancer patients after surgery. One useful method for assessing nutritional status is to evaluate the patient's weight (9), which can be confirmed via body mass index (BMI). BMI has been widely used as an indicator to express the degree of a patient's weight and nutritional status. According to a recent study in colorectal cancer, a high BMI (BMI ≥ 23 kg/m²) is not associated with an increased risk of cancer recurrence, rather a high BMI is associated with a favorable overall survival (OS) (10). However, the influence of BMI on the outcome of patients with gastric cancer is less clear. Some studies (11–13) have demonstrated that a high BMI correlated with improved outcome in patients with gastric cancer; however, others reported no association between BMI and outcome (14–17). There have only been a few studies showing associations between BMI and surgical outcomes

in advanced gastric cancer. Therefore, the aim of this study was to investigate the impact of preoperative nutritional status, especially BMI, on the long-term outcomes in patients with advanced gastric cancer.

Materials and methods

The clinical data of patients who underwent subtotal gastrectomy or total gastrectomy for primary gastric cancer between January 2005 and December 2010 at the Department of Surgery, Chung-Ang University Hospital, were retrospectively reviewed. All of the patients underwent curative surgical resection and cisplatin-based adjuvant chemotherapy. Data on height and body weight and other clinical variables including age, sex, laboratory findings such as preoperative hemoglobin and serum albumin level, and operation method of gastric resection were obtained from the database. Pathological variables including tumor location, tumor grade, Lauren type, presence of vascular or neural invasion, and number of collected lymph nodes (LN) were analyzed. Tumor, node, and metastasis (TNM) staging was performed in accordance with the 7th edition of the American Joint Committee on Cancer staging system (18).

BMI was calculated by the following formula: body weight (kilograms) divided by height (meters) squared. According to the World Health Organization (WHO) criteria, BMI classification was as follows: underweight (BMI < 18 kg/m²), normal weight (BMI = 18–24.9 kg/m²), overweight (BMI = 25–29.9 kg/m²), and obese (BMI ≥ 30 kg/m²) (19).

The OS was estimated in months from the time of surgery to death or the date of the last follow-up assessment. Disease-free survival (DFS) was estimated in months from the time of surgery to cancer-specific death (related to gastric cancer) or the date of the last follow-up assessment. Follow-up assessments were performed every 3 months for the first 5 years after surgery, and then every 6 months until the patient's death. Follow-up procedures included a medical history, physical examinations, routine blood tests, liver function tests, a chest radiograph, upper endoscopy, and an abdomen and pelvis computed tomography (CT) scan. Local recurrence or distant metastases were confirmed histologically or radiographically. The study protocol was approved by the institutional review board (IRB) of Chung-Ang University College of Medicine [IRB No. C2013005(965)].

Statistics

Statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL). When the data were analyzed, patients were categorized into four or two groups according to

BMI. For the 5-year OS and DFS, the patients were categorized into four groups according to BMI: underweight (BMI < 18.0 kg/m²), normal (18.0–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (>30.0 kg/m²). To compare the long-term outcomes after radical gastrectomy followed by adjuvant chemotherapy, the patients were categorized into two groups according to BMI: BMI-High (BMI ≥ 23 kg/m²) and BMI-Low (BMI < 23 kg/m²). Patient clinicopathological data are presented as the mean ± SD. Categorical data were compared by a χ^2 test with Yates correction or a Fisher's exact test, as indicated. DFS and OS were analyzed by the Kaplan–Meier method and compared with the log-rank test. To assess predictive factors associated with OS, we constructed three Cox proportional hazards regression models by adjusting different confounding factors, including age, sex, stage, BMI, and Charlson Comorbidity Index. A *P*-value <0.05 was considered to be statistically significant.

Results

Baseline demographics and clinical characteristics

A total of 529 patients with advanced gastric cancer were enrolled in this study. The final pathological stage groups were: 307 patients (58%) with stage I disease, 81 patients (15%) with stage II disease, 130 patients (25%) with stage III disease, and 11 patients (2%) with stage IV disease. Only those patients with stage II and stage III disease were included in the analysis of this study, therefore, 211 study subjects in total. All of these 211 patients had undergone total or subtotal gastrectomy and started oxaliplatin-based adjuvant chemotherapy 4 weeks later. The baseline demographic of the patients is summarized in Table 1.

Long-term outcomes according to BMI

A total of 211 patients were divided into four groups according to BMI: underweight (BMI < 18.0 kg/m²), normal (18.0–24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (>30.0 kg/m²). As shown in Fig. 1, the 5-year OS rate in the underweight group was significantly lower than those in the other groups (*P* = 0.005). However, the 5-year DFS rate in the underweight group was not significantly lower than those in the other groups (*P* = 0.285) (Fig. 2). As shown in Table 2, BMI was statistically significant for predicting OS.

Five-year survival between BMI-High and BMI-Low groups

To investigate the long-term outcomes after radical gastrectomy followed by adjuvant chemotherapy, we divided

Table 1. Baseline characteristics of the patients.

Characteristics	N = 211
Age, years (mean \pm SD)	61.20 \pm 11.99
Sex	
Male (%)	149 (70.6)
Female (%)	62 (29.4)
Body weight (kg)	61.63 \pm 10.82
BMI (kg/m ²)	23.15 \pm 3.27
Underweight	9 (4.3)
Normal	145 (68.7)
Overweight	50 (23.7)
Obese	7 (3.3)
Tumor location	
Upper third (%)	26 (12.3)
Middle third (%)	15 (7.1)
Lower third (%)	159 (75.4)
Diffuse (%)	11 (5.2)
Histology	
Well differentiated	6 (2.8)
Moderately differentiated	85 (40.3)
Poorly differentiated	120 (56.9)
Stage	
Stage II (%)	81 (38.4)
Stage III (%)	130 (61.6)
LN involvement	
Yes (%)	195 (92.4)
No (%)	16 (7.6)
Operation method	
Total gastrectomy (%)	63 (30.0)
Partial gastrectomy (%)	148 (70.0)
Charlson comorbidity index	0.53 \pm 0.97
0	144 (68.2)
1	37 (17.5)
2	23 (10.9)
3	3 (1.4)
4	1 (0.5)
5	2 (1.0)
6	1 (0.5)
Initial hemoglobin (g/dL)	11.93 \pm 2.73
Initial serum albumin (g/dL)	3.76 \pm 0.49
Follow-up duration (months)	36.23 \pm 23.49
Recurrence \leq 5 years (%)	9 (4.2)
Death \leq 5 years (%)	44 (20.9)

BMI, body mass index; LN, lymph node.

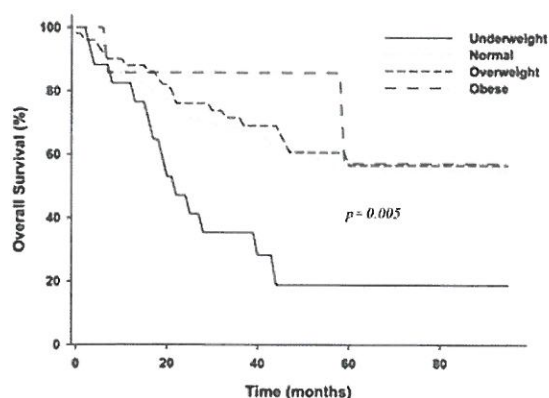


Figure 1. Five-year overall survival rate according to body mass index. The 5-year overall survival rate in the underweight group was significantly lower than the other three groups ($P = 0.005$).

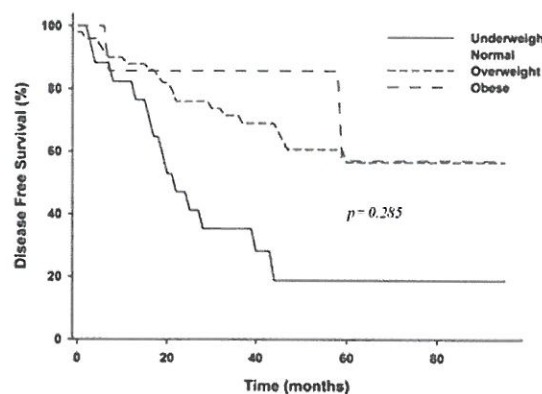


Figure 2. Five-year disease-free survival rate according to body mass index. There was no significant difference in the 5-year disease-free survival rate among the four groups ($P = 0.285$).

the enrolled patients into two groups on the basis of BMI value. One hundred and eleven patients (52.7%) were included in the BMI-High group ($BMI \geq 23 \text{ kg/m}^2$) and 100 patients (47.3%) were included in the BMI-Low group ($BMI < 23 \text{ kg/m}^2$). As shown in Table 3, there were no significant differences between the two groups in age, sex, tumor location, TNM stage, LN involvement, operation method, preoperative hemoglobin and serum albumin levels, follow-up duration, or recurrence. However, the survival of the BMI-High group was better than that of the BMI-Low group. For cancer-related deaths, the BMI-High group was significantly lower than BMI-Low group (cancer-related death: 27% vs. 12.6%, $P = 0.022$).

Discussion

This study investigated the impact of preoperative nutritional status, especially BMI, on the long-term outcomes of patients with advanced gastric cancer in the Korean population. As a result, our study found that a low BMI could contribute to a significant lower long-term survival rate. Indeed, low BMI is an indicator of a nutritionally depleted state and a preoperative poor nutritional status could result in a poor survival rate in advanced gastric cancer. Therefore, preoperative nutrition state is an

Table 2. HRs and their 95% CIs from the Cox model for predicting overall survival.

	HR	95% CI	P-value
Age	1.004	0.995–1.013	0.364
Sex	1.019	0.821–1.264	0.866
Stage	0.954	0.830–1.097	0.510
BMI	1.033	1.001–1.067	0.044
Charlson comorbidity index	1.072	0.951–1.208	0.255

HR, hazard ratio; CI, confidence interval; BMI, body mass index.

Table 3. Clinical characteristics according to BMI.

	BMI-L (<23 kg/m ²) (n = 100)	BMI-H (≥ 23 kg/m ²) (n = 111)	P-value
Age, years (mean \pm SD)	61.27 \pm 13.31	61.14 \pm 10.73	0.935
Sex			0.675
Male (%)	72 (72.0)	77 (69.4)	
Female (%)	28 (28.0)	34 (30.6)	
Tumor location			0.523
Cardia (%)	6 (6.0)	4 (3.6)	
Non-cardia (%)	94 (94.0)	107 (96.4)	
Stage			0.337
II (%)	35 (35.0)	46 (41.4)	
III (%)	65 (65.0)	65 (58.6)	
LN involvement			0.828
Yes (%)	92 (92.0)	103 (92.8)	
No (%)	8 (8.0)	8 (7.2)	
Operation method			0.344
Total gastrectomy (%)	33 (33.0)	30 (27.0)	
Partial gastrectomy (%)	67 (67.0)	81 (73.0)	
Initial hemoglobin (g/dL)	11.65 \pm 2.59	12.18 \pm 2.83	0.161
Initial serum albumin (g/dL)	3.70 \pm 0.53	3.81 \pm 0.45	0.104
Follow-up duration (months)	38.58 \pm 24.88	44.58 \pm 23.76	0.075
Recurrence \leq 5 years (%)	5 (5.0)	4 (3.6)	0.738
Death \leq 5 years			0.022
Cancer-related (%)	27 (27.0)	14 (12.6)	
Others (%)	2 (2.0)	1 (0.9)	

BMI, body mass index; BMI-H, body mass index-high; BMI-L, body mass index-low.

important indicator for long-term outcome in advanced gastric cancer.

Although the overall incidence of gastric cancer has steadily declined due to decrease of *H. pylori* infection and changes in life style over the past years, gastric cancer remains the second leading cause of cancer death (20,21). A worldwide consensus on the standard management of gastric cancer has not been established (2); however, surgery still remains the major, potentially curative treatment method. Standard radical total or subtotal gastrectomy with lymphadenectomy is performed, considering the tumor location, the size of the tumor, and its invasion to the adjacent organs. However, with increasing cancer stage, the risk of cancer recurrence is increased and the survival rate is decreased. Therefore, adjuvant chemotherapy has helped to reduce recurrence or disease progression after curative surgery. According to a recent large meta-analysis (Global Advanced/Adjuvant Stomach Research International Collaboration [GASTRIC] group), postoperative adjuvant chemotherapy increased OS rates in gastric cancer, compared with surgery alone (22). In Japan, Sakuramoto et al. also reported a positive result from adjuvant chemotherapy for East Asian patients who had undergone gastrectomy with extended LN dissection for locally advanced gastric cancer (23).

The treatment of gastric cancer can, however, cause changes to GI function and decrease a patient's quality of life, particularly in perioperative/postoperative periods. Nitenberg and Raynard reported that patients treated for upper GI and colorectal cancers are particularly at risk of

malnutrition because of the catabolic effects of the cancer; the side effects of nausea, vomiting, anorexia, diarrhea, and dysphagia; and the side effects of adjuvant treatments, which can also reduce nutrient intake when nutritional status is already compromised (24). In addition, Isabel et al. reported that malnourished patients with GI cancer, as with all malnourished surgical patients, have increased rates of complications and mortality and longer hospital admissions than healthy patients (25). Pichard et al. showed that malnourished patients made up 37% and 55.6% of patients who were hospitalized for 1–2 days and for over 12 days, respectively. The odds ratios (OR) demonstrated a significant relationship between nutritional status and hospital stay [men (OR: 5.6; 95% CI: 3.1, 10.4), women (OR: 4.4; 2.3, 8.7)] than in those with a length of hospital stay over 1–2 days [men (OR: 3.3; 95% CI: 2.2, 5.0), women (OR: 2.2; 95% CI: 1.6, 3.1)], confirming that preoperative malnutrition was significantly associated with longer hospital stays and a trend to a greater risk of complications (26).

Malnutrition has, therefore, been shown to be closely associated with postoperative outcomes of morbidity and mortality. Moreover, nutritional status can be judged as an important long-term prognostic factor in GI cancer patients after surgery. Sinicrope et al. reported that underweight patients had significantly poorer OS ($P = 0.0258$) than normal weight patients with colon cancer (27). This study suggests that weight loss is a marker of nutritional status and an indicator of advanced disease and, as a result, malnutrition may affect long-term outcome. In gastric cancer, however, little is known about abnormal BMI on the long-term outcomes, especially survival after gastrectomy and/or adjuvant chemotherapy.

A previous study demonstrated that BMI was closely related with long-term survival in the gastric cancer patient. Dhar et al. reported that high BMI patients had a 1.85 times increased risk of cancer recurrence than low BMI patients. Consequently, BMI became an independent prognostic factor and researchers defined BMI-Low and BMI-High groups by using a cut-off value of BMI 25 kg/m² (28). On the other hand, Kulig et al. reported that high BMI is not a prognostic factor in patients with gastric cancer. The researchers described the median survival of overweight patients with BMI ≥ 25 kg/m² as significantly higher than the median survival of those patients with BMI < 25 kg/m² (29). In addition, Tokunaga et al. analyzed the correlation between BMI and long-term survival in Japan, and they found that the 5-year survival rate in the BMI-High group was significantly higher than that in the BMI-Low group (30).

In this study, we measured patient's nutritional status by BMI and compared their long-term survival, especially 5-year OS and DFS. We focused on advanced

gastric cancer, especially stage II and stage III. As a result, the 5-year OS rate in the underweight group was significantly lower than that of the other BMI groups. According to our data, BMI by itself was not a significant factor in normal BMI patients. However, BMI was an important factor for long-term survival in underweight patients. Despite a similar DFS rate, the 5-year OS rate in underweight patients was significantly lower than that in other weight groups. This implies that the main cause of death in these underweight patients was related to noncancer events and that the high mortality risk may originate from aggravation of comorbidities. Moreover, these findings suggest that a patient's initial BMI and overall nutritional status may play an important role in noncancer-related death in underweight patients.

Furthermore, we analyzed the long-term survival difference between BMI-High and BMI-Low groups. According to the Korea National Health and Nutrition Survey, high rates of diabetes, hypertension, and dyslipidemia were noted in low BMI categories compared with the Western population (31). In addition, WHO expert consultation concluded that the proportion of Asian people with a high risk of type 2 diabetes and cardiovascular disease is substantial at BMIs lower than the existing WHO cut-off point for overweight ($>25 \text{ kg/m}^2$) (32). As a result, we divided subjects into BMI-Low and BMI-High groups by using a BMI cut-off value of 23 kg/m^2 . We found that long-term survival of the BMI-High group was better than that of the BMI-Low group. Cancer-related death in the BMI-High group was significantly lower than that of the BMI-Low group ($P = 0.002$). As a result, we can consider low BMI to be an indicator of malnutrition status.

Resection of the stomach reduces reservoir function, may lead to an early feeling of fullness, and lead to reduced food intake. Therefore, postoperative patients can face a reducing nutritional status. Furthermore, chemotherapy also contributes to a host of GI effects, including nausea, vomiting, and diarrhea, all of which are likely to further deplete the nutritional status of postoperative patients (7). As a result, the nutritional status is likely to deteriorate after treatment and this malnutrition status can contribute to a significant reduction in long-term survival in advanced gastric cancer patients.

Albumin is commonly considered a good marker of nutritional status. Moreover, some studies have demonstrated that the low serum albumin prognostic tool to detect malnutrition correlates with longer hospital stays, increased medical complications, and increased mortality (33, 34). Additionally, the quality of life of the cancer patients may depend on their nutritional status. Low hemoglobin levels were associated with fatigue, decreased ability to work, and poor performance statuses, and these

anemia-related symptoms could have negative effects on immune function and quality of life (35). However, there was no association between albumin, hemoglobin, and long-term outcome in this study.

This study has some limitations. First, there is a possibility of a selection bias arising from its retrospective design and restriction to a single institution. Second, we assessed nutritional status only by BMI and laboratory findings (hemoglobin and albumin). No other measures such as percentage weight loss, triceps skinfold thickness, and mid-arm circumference were used. To overcome these limitations, randomized studies with prospective design, as well as various measurements of the nutritional status, are required.

In conclusion, BMI is a simple and effective predictor for long-term survival in patients with advanced (stage II and stage III) gastric cancer, especially those who underwent surgery and adjuvant chemotherapy. Therefore, providing adequate nutritional support for these high-risk patients (underweight or low BMI), before gastrectomy and adjuvant chemotherapy treatment for advanced gastric cancer, may have a positive effect on their clinical outcome.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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