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ORIGINAL SCIENTIFIC REPORT

Overweight or Obesity is an Unfavorable Long-Term Prognostic Factor for Patients who Underwent Gastrectomy for Stage II/III Gastric Cancer

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Abstract

Background Obesity has been reported to be a prognostic factor for many diseases in epidemiological studies; however, the results of studies examining the relationship between obesity and gastric cancer (GC) prognosis are inconsistent.

Methods A total of 460 patients with Stage II and III GC who underwent open R0 gastrectomy were included. Age, sex, body mass index (BMI classified into < 18.5, 18.5–25, and ≥ 25 kg/m^2), stage, and postoperative adjuvant chemotherapy were analyzed to investigate the correlation with relapse-free survival (RFS).

Results Five-year RFS was 51% for the study patients. Five-year RFS values were 47.6%, 54.3%, and 40.1% for patients with BMI < 18.5, 18.5–25, and ≥ 25 kg/m^2, respectively. The forest plot for relapse risk according to BMI showed a U shape. Multivariate analysis for RFS showed significant differences in stage and BMI; the hazard ratio for recurrence in patients with BMI ≥ 25 kg/m^2 was 1.42 (95% confidence interval: 1.01–2.02, $p = 0.0423$) with reference to patients with BMI < 25 kg/m^2. BMI ≥ 25.0 was associated with longer operation times, more blood loss, fewer lymph nodes dissected, more frequent postoperative surgical site infection, and intra-abdominal abscesses.

Conclusions BMI ≥ 25 kg/m^2 is an unfavorable prognostic factor for patients who underwent gastrectomy for Stage II and III GC.

Introduction

The incidence of obesity is rising rapidly worldwide [1]. High body mass index (BMI) is an important risk factor for cardiovascular and kidney diseases, diabetes, and some cancers [2–4]. BMI has become a widely used variable in clinical practice, classifying specific comorbidities and differential clinicopathological characteristics [5]. The "obesity paradox" was first documented by Lavie et al. [6–8] regarding heart failure, indicating the paradoxically favorable outcomes of overweight and obese patients compared with non-overweight patients, which is in contrast to the common belief that a high BMI is associated with an increased risk of death in the general population. Although the mechanisms underlying the positive effects of BMI remain poorly understood, the "obesity paradox" has been addressed in some studies regarding surgical oncology [8, 9].

Gastric cancer (GC) is the third most common cause of cancer-related death worldwide [10]. Curative resection is the gold-standard treatment for non-metastatic GC. Recently, several studies have investigated the relationship between BMI and long-term outcome in GC patients [11–17]; however, the results are inconsistent. Therefore,

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the aim of this study was to investigate whether BMI is a prognostic factor for patients who underwent gastrectomy for GC.

Patients and methods

We reviewed a prospectively recorded database of patients with Stage II and III GC who underwent elective open R0 gastrectomy at our hospital from January 2005 to December 2014. A total of 460 patients were identified and included in this study. Patients who underwent chemotherapy before surgery or received R1 or R2 resection were excluded. The mean age was 67.8 ± 10.1 years (range 31–88); 71.3% of the patients were men. Postoperative adjuvant chemotherapy (PAC) was administered according to the Japanese gastric cancer treatment guideline [18] and was performed in patients with ECOG performance status 0 and 1, sufficient main organ function, and informed consent.

BMI was computed as weight in kilograms divided by height in meters squared. BMI at gastrectomy was used in the analyses and categorized to underweight, normal weight, and overweight or obesity for < 18.5, 18.5–25, and ≥ 25 kg/m^2 with reference to World Health Organization (WHO) categories [19].

The resected GCs were histopathologically classified according to the Japanese classification of gastric carcinoma [20]. All evidence of relapse was obtained from the patients' medical records. Follow-up information through October 2017 was compiled for all survivors. Relapse-free survival (RFS) was calculated as the time from the date of surgery to the date of identification of disease relapse.

We attempted to identify whether BMI is a prognostic factor independent of stage. Age, sex, BMI, tumor location, size, histology, depth of invasion (T), lymph node metastasis (N), stage, and PAC were analyzed to investigate the correlation with RFS.

To investigate the relationship between BMI and prognosis, we analyzed the relation between BMI and blood data including C-reactive protein (CRP), serum albumin (Alb), neutrophil-to-lymphocyte ratio (N/L), modified Glasgow prognostic score (mGPS) [21], prognostic nutritional index (PNI; Onodera) [22], and controlling nutrition status (COUNT) score [23] as conventional prognostic scores. The mGPS consists of CRP and albumin as follows: patients with both an elevated CRP level (> 1.0 mg/dl) and hypoalbuminemia (< 3.5 g/dl) are given a score of 2; patients with only one of these biochemical abnormalities are given a score of 1; and patients with neither of these abnormalities receive a score of 0 [21]. PNI was calculated as follows: 10 × albumin value (g/dL) + 0.005 × lymphocyte of the peripheral blood, in which a higher value suggests good immune-nutritional status [22]. The COUNT score was calculated from three parameters, including serum albumin, total cholesterol concentration, and total peripheral lymphocytes count [23], in which a lower value indicates a favorable nutritional status.

The study protocol was approved by the ethics committee of our hospital, which waived the need for informed consent due to the retrospective nature of the study (Registration number: 2018-014).

Statistical analysis

Continuous variables were presented as the mean ± standard deviation or the median (IQR) and were compared using one-way analysis of variance or the Kruskal–Wallis test, as appropriate. Differences in categorical variables were compared using the Chi-square test or Fisher's exact test. The Kaplan–Meier method was used to estimate survival curves, while the log-rank test was employed to evaluate differences in survival between groups. Factors with p values < 0.05 in univariate analysis were included in a subsequent multivariate analysis using a Cox proportional hazard model, while T, N, and stage were integrated into one factor (stage), as they had a close relationship. Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated during the multivariate analysis. Statistical analyses were performed using StatView version 5.0 and JMP version 10.0 for Windows (SAS Institute Inc., Cary, NC, USA) at a significance level of $p < 0.05$.

Results

Patient demographics are presented in Table 1. Mean BMI was 22.0 ± 3.3 kg/m^2. The categories of BMI < 18.5, 18.5–25, and ≥ 25 kg/m^2 were assigned to 64 patients (14%), 320 patients (70%), and 76 patients (17%), respectively. Eight patients died from postoperative complications (in-hospital mortality: 1.7%). PAC was administered to 260 patients, with 41% and 68% in Stage II and III, respectively. S-1, Tegafur/Uracil, and S-1/cisplatin were mostly used for PAC. The median follow-up duration was 34.4 months (interquartile range, 12.0–63.0 months). The death from the disease (gastric cancer) in patients with high BMI (> 25) and low BMI (< 25) was 84.6% and 77.1%, respectively ($p = 0.4236$).

Five-year RFS for study patients was 51.1%. The univariate analysis showed that BMI, tumor size, T, N, and stage were significantly correlated with RFS (Table 2). The five-year RFS values were 67.3% and 39.6% for patients with Stage II and III GC, respectively. The five-year RFS of patients with BMI < 18.5, 18.5–25, ≥ 25 kg/m^2 were

Table 1 Patients demographics

Age, years	67.8 ± 10.1 (31–88)			
Sex (male/female)	328:132			
Body mass index (BMI), kg/m^2	22.0 ± 3.3 (14.2–35.1, IQR: 19.8–24.1)			
	Underweight	<18.5	64	(14%)
	Normal weight	18.5–25	320	(70%)
	Overweight	25–30	67	(15%)
	Obesity	≧30	9	(2%)
Tumor location	Upper third		104	(23%)
	Middle third		143	(31%)
	Lower third		213	(46%)
Size, mm	50 (40–74)			
	<50		190	(41%)
	≧50		270	(59%)
Histology	pap, tub		216	(47%)
	por, sig, muc		232	(50%)
	others		12	(3%)
Depth of invasion (T)	T1		17	(4%)
	T2		51	(11%)
	T3		218	(47%)
	T4a		150	(33%)
	T4b		24	(5%)
Lymph node metastasis (N)	N0		83	(18%)
	N1		117	(25%)
	N2		140	(30%)
	N3		120	(26%)
Stage	II		193	(42%)
	III		267	(58%)
Postoperative adjuvant chemotherapy	Stage II		79	(41%)
	Stage III		181	(68%)

47.6%, 54.3%, and 40.1%, respectively (Fig. 1), and the forest plot for HR of recurrence according to BMI showed a U shape (Fig. 2). The RFS of patients with BMI $\geq$ 25.0 kg/m^2 was significantly lower than that with BMI < 25.0 kg/m^2 (40.0% vs. 53.3%, $p = 0.0253$). The multivariate analysis for RFS showed that stage and BMI were significant independent factors (Table 2). The HR for relapse in patients with BMI $\geq$ 25.0 kg/m^2 were 1.42 (95%CI: 1.0–2.02, $p = 0.0423$) with reference to patients with BMI < 25.0 kg/m^2. The RFS of patients with BMI $\geq$ 25.0 kg/m^2 tended to be lower than that of patients with BMI < 25.0 kg/m^2 in Stage II and III (Fig. 3a, b). Five-year overall survival (OS) for study patients was 59.4%. The univariate analysis showed that age, BMI, tumor location, tumor size, histology, T, N, stage, and PAC were significantly correlated with OS (Table 3). Overall survival in patients with BMI > 25 tended to be worse than that in patients with BMI < 25 ($p = 0.076$).

To investigate the mechanism underlying the U-shaped risk of relapse according to BMI, clinical factors regarding age, sex, tumor, conventional prognostic factors, surgery, postoperative short-term outcome, and PAC were analyzed based on BMI (Table 4). Age, sex, tumor location, size, histology, lymph node metastasis, and stage were not different among the BMI categories, while depth of invasion was deepest in patients with BMI < 18.5 kg/m^2. For conventional prognostic factors, patients with BMI < 18.5 kg/m^2 had higher CRP ($p = 0.0589$), mGPS ($p = 0.0032$), CONUT score ($p = 0.0022$), lower serum albumin ($p < 0.0001$) and PNI ($p < 0.0001$). Although surgical procedures were not different among the BMI categories, patients with BMI $\geq$ 25.0 kg/m^2 had longer operation times ($p = 0.0610$), more blood loss ($p = 0.0003$), and fewer lymph nodes dissected ($p = 0.1894$). In addition, patients with BMI $\geq$ 25.0 kg/m^2 had frequent postoperative complications (Clavien–Dindo $\geq$ 3), surgical site

Table 2 Univariate and multivariate analyses of clinicopathological factors for relapse-free survival

	Univariate analysis			Multivariate analysis		
	n	5-yr survival (%)	*P*	Hazard ratio	(95% confidence interval)	*P*
Age, years						
<65	160	55.3				
≧65	300	48.8				
Sex						
Male	328	50.0	0.4768			
Female	132	53.6				
Body mass index (BMI), kg/m^2						
<18.5	64	47.6	0.0867			
18.5–25	320	54.3				
≧25	76	40.1				
<25	384	53.3	**0.0253**	1		
≧25	76	40.0		1.42	(1.01–2.02)	**0.0423**
Location						
Upper third	104	42.5	0.0606			
Middle third	143	60.0				
Lower third	213	48.9				
Size, mm						
<50	190	56.7	**0.0122**	1		
≧50	270	47.9		1.20	(0.89–1.62)	0.2219
Histology						
pap, tub	216	53.9	0.1879			
por, sig, muc	232	49.5				
others	12	38.1				
Depth of invasion (T)						
1	17	70.0				
2	51	63.1				
3	218	55.1	**0.0063**			
4a	150	40.8				
4b	24	38.9				
Lymph node metastasis (N)						
0	83	74.1	**<0.0001**			
1	117	55.1				
2	140	51.9				
3	120	31.5				
Stage						
II	193	67.3	**<0.0001**	1		
III	267	39.6		2.45	(1.77–3.39)	**<0.0001**
Postoperative adjuvant chemotherapy						
Done	260	50.7	0.6578			
Not done	200	52.7				

Bold values are statistically significant ($P < 0.05$)

infection and intra-abdominal abscesses. To sum up, BMI < 18.5 kg/m^2 was associated with deeper tumor invasion and lower immune-nutritional status, while BMI ≥ 25.0 kg/m^2 was associated with greater surgical stress, fewer lymph nodes dissected, and frequent postoperative infective complications. The five-year RFS of patients with and without postoperative infectious

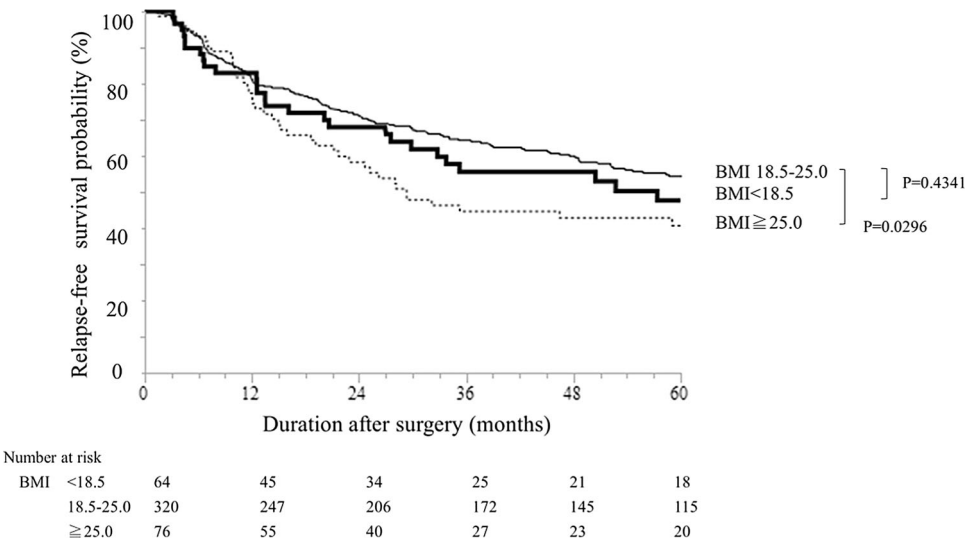

Fig. 1 Relapse-free survival curves for patients with Stage II and III gastric cancer according to BMI

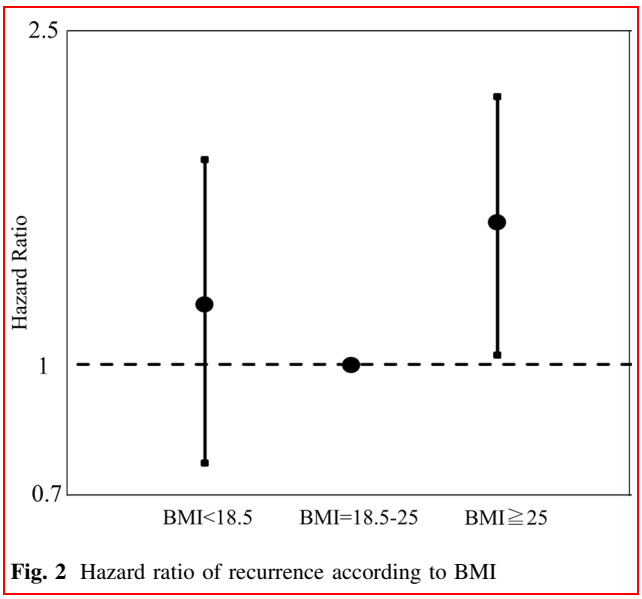

Fig. 2 Hazard ratio of recurrence according to BMI

complications was 37.1% and 53.5%, respectively ($p = 0.0016$).

We analyzed the association between BMI and relapse sites (Table 5). The relapse of lymph node was more frequent in patients with BMI > 25, compared with BMI < 25 (32% vs. 16%).

Discussion

This study investigated the relation between BMI and RFS of patients who underwent R0-gastrectomy for Stage II and III GC. The results indicated that overweight or obesity was an unfavorable prognostic factor independent of stage. BMI ≥ 25 kg/m^2 was associated with greater surgical stress, fewer lymph nodes dissected, and frequent postoperative infective complications.

The "obesity paradox" has been proposed in heart diseases as well as in malignant diseases [6–9]. Several studies have reported that obesity was associated with a better prognosis in uterine cancer and renal cell carcinoma [24, 25]. There have been many studies investigating the impact of BMI on the long-term outcomes of GC patients who underwent gastrectomy. Tokunaga reported that survival following curative gastrectomy is better in overweight than non-overweight Japanese patients, especially for early-stage GC [26]. Chen HN et al. reported that high-BMI GC patients had a significantly better overall survival (OS) compared with their normal counterparts in China [27]. They hypothesized that patients with a high BMI may be better able to withstand cancer-induced consumption and stress compared with patients with a low BMI.

In contrast, Kulig J reported that overweight was not an independent prognostic factor for long-term survival in a Western population with GC [28]. Lin YS et al. reported no significant difference in OS among Taiwanese patients with BMI < 25, 25–30, and > 30 kg/m^2 [29]. Wong et al. examined 186 patients in the USA and concluded that increased BMI does not adversely impact OS or disease-free survival [30]. Ejaz et al. investigated 775 patients from multiple institutions in the USA and reported that BMI did not impact perioperative morbidity, RFS, or OS in patients undergoing gastrectomy for GC [31]. Meanwhile, there are a few studies reporting worse long-term outcomes associated with high BMI. Wu et al. reported in a meta-analysis that a BMI of 25 kg/m^2 was correlated with increased surgical difficulty, complications, and poor long-term survival [32]. They hypothesized that the excess accumulation of visceral fat might impair patient survival as a result of

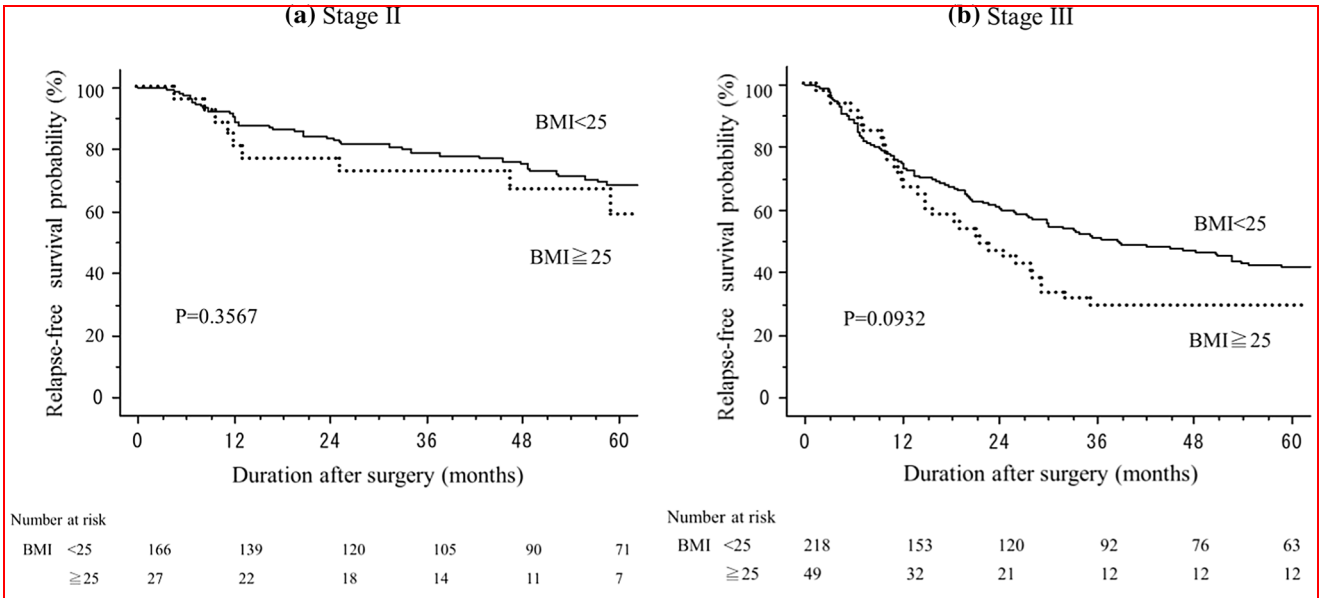

Fig. 3 Relapse-free survival curves for patients with Stage II and III gastric cancer according to BMI. **a** Stage II, **b** Stage III

increased comorbidities and complications. Our results were in line with those of Wu XS. The inconsistent results among the studies investigating the association between BMI and long-term outcome in patients who underwent gastrectomy for GC might be attributed to several factors including study population, patient selection criteria, surgical procedure, and sample size. Among these factors, patient selection criteria are especially important, because tumor stage is closely associated with BMI. Generally, the more advanced stage GC the patients have, the less their BMI. The inclusion of patients with Stage IV, therefore, would be biased by tumor progression. Furthermore, the inclusion of patients with Stage I would lead to less meaningful results, because the prognosis of early GS is generally favorable.

Patients with high BMI tend to have a great deal of visceral fat, which increases surgical complexity. Several studies reported that high BMI was associated with postoperative complications including anastomotic leakage, cardiopulmonary disease, and intra-abdominal abscess [33–35]. Similarly, some studies reported that excessive visceral fat could negatively affect postoperative short-term outcomes such as infectious complications and pancreatic fistula [36–38]. Patients with a high BMI were more likely to exhibit insulin resistance and poor glycemic control, both of which might be risk factors for delayed wound recovery and infection [39, 40]. Thus, we suggest that the high-BMI patients are at greater risk for postoperative infective complications due to technical difficulties and metabolic disturbances. In addition, there is growing evidence of adverse long-term outcomes associated with postoperative infective complications; a possible explanation is that cell-mediated immunity is compromised by surgical stress, and excessive catecholamine and prostaglandin responses adversely affect the immune system, contributing to metastatic progression and worse survival outcome [41–43].

The current study showed BMI $\geq$ 25 kg/m^2 was associated with fewer lymph nodes dissected, the number frequently being less than 15. This can lead to "stage migration" [44]. Biondi et al. reported that the retrieval of fewer than 16 lymph nodes in GC surgery may cause inaccurate staging and inadequate treatment, thus affecting survival [45]. D2 dissection might be difficult in obese patients. Incomplete lymph node dissection could result in residual metastatic nodes, which could be responsible for lower RFS. This hypothesis was supported our investigation analyzing relapse sites.

When comparing RFS of patients with Stage II and III GC, the association between BMI and RFS was more evident in Stage III (Fig. 3). We hypothesize two possible reasons; First, patients with BMI > 25 included patients with more advanced stage due to stage migration. Second, unfavorable prognostic factors including larger surgical stress, less number of lymph node dissected, and frequent postoperative infective complication had less deleterious effect on the disease relapse in relative early-stage GC.

We acknowledge our study has some limitations. First, this was a retrospective uncontrolled study in a single Japanese institution. The cohort with high BMI was small

Table 3 Univariate and multivariate analyses of clinicopathological factors for overall survival

		Univariate analysis		Multivariate analysis		
	n	5-year survival (%)	*P*	Hazard ratio	(95% confidence interval)	*P*
Age, years				1		
<65	160	69.9	**0.0048**			
≧65	300	53.5		1.24	(0.88–1.75)	0.2155
Sex						
Male	328	57.1	0.2755			
Female	132	64.9				
Body mass index (BMI), kg/m^2						
<18.5	64	50.1	**0.0416**	1.42	(0.92–2.12)	0.1096
18.5–25	320	62.5		1		
≧25	76	53.8		1.39	(0.94–2.00)	0.0945
<25	384	60.6	0.076			
≧25	76	53.8				
Location						
Upper third	104	46.7		1.94	(1.31–2.88)	**0.0009**
Middle third	143	65.0	**0.0035**	1		
Lower third	213	62.3		1.16	(0.81–1.69)	0.4225
Size, mm						
<50	190	64.8	**0.0145**	1		
≧50	270	55.6		1.08	(0.793–1.49)	0.6203
Histology						
pap, tub	216	58.6		1.03	(0.75–1.42)	0.8380
por, sig, muc	232	61.6	**0.0364**	1		
Others	12	33.3		2.73	(1.20–5.41)	**0.0195**
Depth of invasion (T)						
1	17	77.3				
2	51	69.3				
3	218	63.3	**0.0009**			
4a	150	52.0				
4b	24	37.1				
Lymph node metastasis (N)						
0	83	79.7	**0.0002**			
1	117	58.8				
2	140	60.0				
3	120	45.7				
Stage						
II	193	72.1	**<0.0001**	1		
III	267	50.4		2.63	(1.85–3.77)	**<0.0001**
Postoperative adjuvant chemotherapy						
Done	260	63.9	**0.0049**	1		
Not done	200	53.8		1.92	(1.38–2.67)	**<0.0001**

Bold values are statistically significant ($P < 0.05$)

compared with studies in Western countries; thus, the results may be less applicable to Western populations. Second, patients who received PAC were included and comprised 57% of the entire cohort. The percentage of patients who received PAC was relatively low, particularly among patients with Stage II GC. PAC modifies the disease course (RFS). Although there was not a significant difference in the number of patients with PAC between

Table 4 Relationship between clinical factors and BMI

	BMI						*p*
	<18.5 (*n* = 64)		18.5–25.0 (*n* = 320)		≧25.0 (*n* = 76)		
Background							
Age (years)	68 (62–76)		69 (62–75)		68 (62–74)		0.7961
<75	41	(64%)	229	(72%)	59	(78%)	0.2079
≧75	23	(36%)	91	(28%)	17	(22%)	
Sex							
Male	44	(69%)	230	(72%)	54	(71%)	0.8793
Female	20	(31%)	90	(28%)	22	(29%)	
Tumor							
Location							
Upper third	10	(16%)	76	(24%)	18	(24%)	
Middle third	24	(38%)	101	(32%)	18	(24%)	0.3245
Lower third	30	(47%)	143	(45%)	40	(53%)	
Tumor size, nm	60 (40–80)		50 (40–70)		53 (40–75)		0.2033
Histology							
pap, tub	31	(48%)	142	(44%)	43	(57%)	
por, sig, muc	30	(47%)	170	(53%)	32	(42%)	0.2471
others	3	(5%)	8	(3%)	1	(1%)	
Depth of invasion (T)							
T1	2	(3%)	11	(3%)	4	(5%)	
T2	7	(11%)	37	(12%)	7	(9%)	
T3	21	(33%)	158	(49%)	41	(54%)	**0.0270**
T4a	25	(39%)	101	(32%)	22	(29%)	
T4b	9	(14%)	13	(4%)	2	(3%)	
Lymph node metastasis (N)							
N0	12	(19%)	62	(19%)	9	(12%)	
N1	18	(28%)	83	(26%)	16	(21%)	0.1089
N2	20	(31%)	86	(27%)	34	(45%)	
N3	14	(22%)	89	(28%)	17	(22%)	
Number of lymph node metastasis		3 (1–6)	3 (1–7)		4 (2–6)		0.3528
Stage							
II	24	(38%)	142	(44%)	27	(36%)	
III	40	(63%)	178	(56%)	49	(64%)	0.2752
Conventional prognostic factors							
CRP (*n* = 300) (mg/dL)	0.3 (0.1–1.225)		0.1 (0.1–0.4)		0.1 (0.1–0.3)		0.0589
Alb (g/dL)	3.3 (2.8–3.8)		3.8 (3.3–4.2)		3.9 (3.4–4.2)		**<0.0001**
N/L	3.0 (1.9–4.7)		2.5 (1.9–3.6)		2.4 (1.7–3.7)		0.1661
Modified Glasgow prognostic score (CRP, Alb)							
0	19	(30%)	126	(39%)	33	(43%)	
1	19	(30%)	53	(17%)	16	(21%)	**0.0032**
2	12	(19%)	20	(6%)	2	(3%)	
PNI (Onodera) (Alb, Lymphocyte)	42 (35–46)		46 (41–50)		47 (40–51)		**<0.0001**
CONUT score (Alb, T-cho, Lymphocyte)	3 (1.5–7.5)		2 (0–4)		1 (1–4)		**0.0022**
<5	39	(61%)	244	(76%)	58	(76%)	
≧5	22	(34%)	53	(17%)	15	(20%)	**0.0062**

Table 4 continued

	BMI						*p*
	<18.5 (*n* = 64)		18.5–25.0 (*n* = 320)		≧25.0 (*n* = 76)		
Surgery							
Surgical procedure							
Distal gastrectomy	39	(61%)	190	(59%)	45	(59%)	
Total gastrectomy	24	(38%)	129	(40%)	28	(37%)	0.1062
Others	1	(2%)	1	(0%)	3	(4%)	
Operation time (min)	206 (163–260)		229 (183–284)		239 (182–294)		0.0610
<4 h	44	(69%)	167	(52%)	39	(51%)	
≧4 h	20	(31%)	153	(48%)	37	(49%)	**0.0443**
Blood loss (ml)	222 (123–400)		300 (145–520)		420 (250–610)		**0.0003**
<500 ml	53	(83%)	234	(73%)	47	(62%)	**0.0200**
≧500 ml	11	(17%)	86	(27%)	29	(38%)	
Blood transfusion							
Yes	4	(6%)	24	(8%)	10	(13%)	0.2445
No	60	(94%)	296	(93%)	66	(87%)	
Number of lymph node dissected	32 (21–40)			29 (20–39)		27 (17–37)	0.1894
<15	5	(8%)	40	(13%)	14	(18%)	0.1841
≧15	59	(92%)	280	(88%)	14 62	(82%)	
Postoperative short-term outcome							
In-hospital mortality	1	(2%)	5	(2%)	3	(4%)	0.3173
Postoperative complications, Clavien–Dindo ≧3	11	(17%)	59	(18%)	17	(22%)	0.6828
Pulmonary complications	3	(5%)	7	(2%)	3	(4%)	0.3389
Anastomotic leakage	2	(3%)	18	(6%)	5	(7%)	0.6919
Surgical site infection	8	(13%)	35	(11%)	14	(18%)	0.2050
Intra-abdominal abscess	2	(3%)	13	(4%)	12	(16%)	**0.0012**
Pancreatic fistula	5	(8%)	15	(5%)	3	(4%)	0.5332
Ileus	0	(0%)	4	(1%)	3	(4%)	0.1505
Cardiovascular complications	0	(0%)	4	(1%)	1	(1%)	1.0000
Postoperative hospital stay, days	15 (12–20.5)		14 (11–20.75)		15 (11.25–19)		0.8087
Postoperative adjuvant chemotherapy							
Done	30	(47%)	185	(58%)	45	(59%)	0.3316
Not done	34	(53%)	135	(42%)	31	(41%)	
Long-term outcome							
5-Year relapse-free survival	47.6%		54.3%		40.0%		0.0614
5-Year overall survival	50.1%		62.5%		53.8%		**0.0413**

Bold values are statistically significant ($P < 0.05$)

BMI < 25 and ≥ 25 kg/m^2, the intensity and adverse effects of PAC can be an important confounder. In subgroup analysis of RFS, however, unfavorable RFS in patients with BMI ≥ 25 kg/m^2 was more pronounced in patients with PAC (data not shown). In this study, PAC was not associated with RFS. Because the indication of PAC was determined by attending physicians, PAC might have been performed more frequently in patients with higher relapse risk. That may have led decreased benefit of adjuvant chemotherapy, compared with patients with lower relapse risk. Third, visceral fat was not evaluated. The visceral fat area that is usually calculated by computed

Table 5 The association between BMI and relapse sites

Relapse site	BMI				*P*
	<25 (n = 161)		≧25.0 (n = 41)		
Peritoneum	50	(31%)	5	(12%)	0.0651
Lymph node	26	(16%)	13	(32%)	
Liver	19	(12%)	7	(17%)	
Bone	3	(2%)	1	(2%)	
Lung	1	(1%)	1	(2%)	
Others or duplicated	62	(39%)	14	(34%)	

tomography can be more useful than BMI to investigate the relationship among surgical stress, operation quality, and postoperative complications [36–38]. However, BMI is easier to calculate and to understand because of worldwide standardization compared with visceral fat measurement. Fourth, the number of study patients was not large, partly because patients with Stage I and IV were excluded. Relapse of patients with Stage I was infrequent. The inclusion of patients with Stage IV can be biased by tumor progression. Therefore, we excluded Stage I and IV patients from the study.

Despite these limitations, the results of the present study are clinically relevant in the surgical management of GC patients. Surgical procedures with reduced stress, which can be performed using laparoscopy, meticulous lymph node dissection, and elaborate postoperative management, are a possible strategy for improving the RFS of overweight or obese patients.

Conclusion

Overweight or obesity was a significant unfavorable prognostic factor for patients who underwent R0-gastrectomy for Stage II/III GC. Greater surgical stress, fewer lymph nodes dissected, and frequent postoperative infective complications might contribute to unfavorable prognosis of patients with BMI $\geq$ 25 kg/m^2.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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