Full Length Articles:

Impact of visceral adipose tissue on compliance of adjuvant chemotherapy and relapse-free survival after gastrectomy for gastric cancer: a propensity score matching analysis

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Abstract

Background and Aims: It has been reported that skeletal muscle mass loss during adjuvant chemotherapy and preoperative reduced skeletal muscle mass are associated with discontinuation of adjuvant chemotherapy. However, the relationship between visceral fat mass and compliance has not yet been investigated. In this study, we clarified the impact of low preoperative visceral fat mass on compliance and relapse-free survival (RFS) in gastric cancer patients.

Methods: This was a retrospective cohort study of consecutive patients with gastric cancer who underwent radical gastrectomy for pathological stages II and III, and who received postoperative S-1 adjuvant chemotherapy between April 2008 and April 2017. Treatment failure was defined as discontinuation of adjuvant chemotherapy within 1 year. Visceral fat mass was measured preoperatively at the umbilical level on computed tomography, which was divided by height ($m^{2)}$ to obtain the visceral adipose tissue index (VAI). Patients with a VAI below the median cut-off value were categorized as low-VAI, while those above the cut-off value were classified as high-VAI. We compared the treatment failure rate and RFS in the low-VAI and high-VAI groups after adjusting for group differences with propensity score matching. In addition, risk factors related to treatment failure and poor prognostic factors for RFS were analyzed in multivariate analyses that included all cases.

Results: Among all 263 patients, treatment failure and recurrence were observed in 44 patients (16.7%) and 90 patients (34.2%), respectively. The median follow-up period was 52 months. After propensity matching, there were 101 patients in both low -and high-VAI groups. Treatment failure rate was higher (P=0.037) and RFS was worse (P=0.025) in the low-VAI group. In multivariate analyses, low-VAI was an independent risk factor

associated with treatment failure (odds ratio (OR): 2.360, 95% CI: 1.120-5.000, P = 0.025), and was a poor prognostic factor for RFS (hazards ratio (HR):1.652, 95% CI: 1.057-2.582, P＝0.028).

Conclusions: Preoperative low visceral fat mass was an independent risk factor for poor compliance with adjuvant chemotherapy and a poor prognostic factor for RFS after radical gastrectomy in gastric cancer patients. Preoperative evaluation using body composition may be useful for post-treatment and prognosis prediction.

Keywords：Adjuvant chemotherapy; compliance; gastric cancer; relapse-free survival; visceral adipose tissue.

Abbreviations:

VAI: visceral adipose tissue index

SMI: skeletal muscle mass index

RFS: relapse-free survival

OS: overall survival

PSM: propensity score matching

BWL: body weight loss

CD: Clavien-Dindo classification

1. Introduction

In Asia, postoperative adjuvant chemotherapy for patients with gastric cancer with pathological stages II and III, has been shown to be useful in randomized control trials. The ACTS-GC trial in Japan demonstrated that treatment for 1 year with S-1 significantly improved relapse-free survival (RFS) and overall survival (OS) compared to surgery alone [1, 2]. Postoperative adjuvant chemotherapy with S-1 has been used as standard treatment. The OPAS-1 trial, which was a non-inferiority study, compared treatment with S-1 for a duration of 1 year versus 6 months. It was discontinued due to many recurrences in the group that was treated for a shorter period of time [3]. Therefore, it is necessary to continue S-1 adjuvant chemotherapy for one year to improve the long-term prognosis, and it is important to identify the risk factors related to compliance with adjuvant chemotherapy.

It has been reported that if the body weight loss rate within 1 month after gastrectomy is 15% or more, compliance with adjuvant chemotherapy worsens [4], which leads to poor OS [5—7]. Recent studies that have focused on postoperative changes in body composition, have shown that skeletal muscle mass loss is a risk factor for poor compliance [8], which worsens the OS [9—12]. Therefore, it is necessary that we should consider a strategy to prevent body weight loss after gastrectomy in order to improve compliance with adjuvant chemotherapy.

Nevertheless, the impact of visceral fat mass on compliance with adjuvant chemotherapy for patients with gastric cancer has not yet been investigated. It is expected that an adequate nutritional status before surgery, as indicated by high visceral fat mass, may be better for postoperative treatment considering that body weight loss occurs after surgery. However, it has been reported that high visceral fat mass leads to an increase in

postoperative complications [13—17], which may affect postoperative compliance with adjuvant chemotherapy. Therefore, it is necessary to clarify the impact of preoperative visceral fat mass on compliance with adjuvant chemotherapy and RFS.

The purpose of this study was to investigate the impact of preoperative visceral adipose tissue on compliance with adjuvant chemotherapy, and postoperative recurrence after gastrectomy for patients with advanced gastric cancer. We hypothesized that preoperative high visceral fat mass would be a risk factor for poor compliance and a poor prognostic factor for RFS.

2. Materials and methods

2.1. Study design

This was a single-institution, retrospective cohort study conducted at Ishikawa Prefectural Central Hospital, which included consecutive patients who underwent radical gastrectomy for primary pathological stages II and III advanced gastric cancer, between April 2008 and April 2017, with S-1 adjuvant chemotherapy. The inclusion criteria were as follows: 1) pathological stages II and III, 2) radical gastrectomy, 3) postoperative S-1 adjuvant chemotherapy, and 4) preoperative visceral fat area and skeletal muscle mass on computed tomography (CT) images. We excluded patients 1) who were not eligible for S-1 according to Japanese gastric cancer treatment guidelines [18], 2) with residual gastric cancer, 3) with cancers of other organs, 4) with a performance status of 2 or higher, 5) who underwent different surgical procedures, 6) with adjuvant chemotherapy other than S-1, 7) who received neoadjuvant chemotherapy, and 8) who had insufficient data. The flow chart for this study is shown in Fig. 1. Patients who met the abovementioned criteria were divided into a low-visceral fat group and a high-visceral fat group.

Postoperative outcomes were compared between the two groups after adjusting for patient background with propensity score matching (PSM). In addition, the risk factors related to treatment failure of S-1 and the poor prognostic factors for RFS were analyzed in multivariate analyses that included all cases.

All experimental protocols described in this study were approved by the Institutional Ethical Review Committee of Ishikawa Prefectural Central Hospital (authorization number: 1588); met the ethical guidelines of the Japan Ministry of Health, Labour and Welfare for Medical and Health Research Involving Human Subjects; and conformed to the provisions of the Declaration of Helsinki. The opt-out recruitment method was applied to provide all patients an opportunity to decline to participate.

2.2. Adjuvant chemotherapy with S-1

We administered postoperative adjuvant chemotherapy with S-1 to patients with cancer stages II and III for a maximum period of one year according to the Japanese gastric cancer treatment guidelines [18]. The regimen was started at 80-120 mg/day and administered for 4 weeks, followed by 2 weeks of rest. If side effects were observed, we reduced the dose gradually according to the guidelines from 120 to 100 mg/day or from 100 to 80 mg/day. We decided to discontinue treatment when side effects could not be controlled with dose optimization, two or more steps of dose reduction, or a confirmed recurrence of disease during adjuvant chemotherapy. In this study, we defined treatment failure discontinuation of adjuvant chemotherapy within one year of having started it.

2.3. Follow-up

The patients were followed up at an outpatient clinic. Hematological tests were

performed at least every 2–3 weeks during S-1 treatment, and at least every 3 months for 5 years after completion of S-1 treatment. Patients underwent a CT scan every 6 months, and endoscopy every year, for 5 years after surgery. We administered no treatment other than adjuvant chemotherapy with S-1 until recurrence.

2.4. Body composition analysis

We measured the visceral fat area and skeletal muscle mass on plain CT images using the graphic analysis software Ziostation (ZIOSOFT, Tokyo, Japan) before surgery. The visceral fat area, defined as having a density of -150 to -50 Hounsfield units, was measured at the umbilical level, while skeletal muscle mass, defined as having a density of -29 to 150 Hounsfield units, was measured at the level of the third lumbar vertebra. The areas on a single CT image slice were divided by height in m^2 to obtain the visceral adipose tissue index (VAI) and skeletal muscle mass index (SMI) [15].

Cut-off values for VAI and SMI were separately estimated for men and women based on the median. The cut-off value for VAI was calculated as 35.43 cm^2/m^2 for men and 24.85 cm^2/m^2 for women. Patients with a VAI below the cut-off value were categorized as low-VAI, while those with a VAI above the cut-off value were classified as high-VAI. The cut-off value for SMI was calculated as 42.85 cm^2/m^2 for men and 35.15 cm^2/m^2 for women. Likewise, patients with an SMI below and above the cut-off value were categorized as low-SMI and high-SMI, respectively.

2.5. Outcomes

The primary outcome was treatment failure rate of S-1 adjuvant chemotherapy, while the secondary outcomes were RFS, postoperative complications, and postoperative body

weight loss (BWL). We defined treatment failure as discontinuation of S-1 within one year of starting it, because of adverse events, patient's refusal to continue treatment, recurrence, or death. RFS was defined as the period between surgery and either recurrence or death, whichever occurred first of the two. Postoperative complications were defined as Clavien-Dindo classification (CD) grade 2 or higher that occurred within 30 days after surgery. We calculated the total number of postoperative complications, and severe complications were defined as CD grade 3a or higher. BWL rate was calculated according to the formula: % BWL = (preoperative body weight – postoperative body weight) × 100 / preoperative body weight. It was worked out at 1 month, 6 months, and 1 year.

2.6. Statistical analyses

We performed PSM on the low-VAI and high-VAI groups, to adjust for differences in patient background and to reduce selection bias in a non-randomized study. The propensity score was estimated using a logistic regression model with the following covariates: surgical procedure, pathological stage, serosal invasion, diabetes, and SMI; body mass index (BMI) and VAI were excluded. The nearest-neighbour matching method was applied, and a one-to-one matching between the two groups was achieved. The caliper size was 0.20. After matching, postoperative outcomes were compared between the two groups. Patient characteristics and postoperative outcomes were compared using the Mann-Whitney U test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables. For RFS, the log-rank test was used for Kaplan-Meier survival analyses. Logistic regression analysis was used for univariate analyses to identify the risk factors related to treatment failure with P-values < 0.05, on which multivariate analysis was performed and odds ratios (ORs) were calculated for all cases. Similarly,

Cox proportional hazards regression was used for univariate analysis to identify the prognostic factors for RFS with P-values < 0.05, on which multivariate analysis was performed to calculate hazard ratios (HRs) for all cases. All statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is based on R (The R Foundation for Statistical Computing, Vienna, Austria) and R commander [19]. A P-value of less than 0.05 was considered statistically significant.

2.7. Clinicopathological variables and definitions

The variables analyzed were sex, age, BMI, surgical approach, surgical procedure, lymph node dissection, pathological stage, serosal invasion, lymph node metastasis, histological type, comorbidities, SMI, VAI, postoperative complications, and BWL. Chronic kidney disease was defined as an estimated glomerular filtration rate < 60 mL/min/1.73m^2, diabetes was defined as either having a history of treatment or preoperative HbA1c ≥ 6.5%, chronic obstructive pulmonary disease (COPD) was defined as FEV1.0% < 70% on spirometry, and congestive heart failure was defined as either having a history of treatment or ejection fraction < 50% on echocardiography.

3. Results

3.1 Patient characteristics

The flow chart of this study is shown in Fig. 1. A total of 263 patients who met the eligibility criteria were selected, and 132 (50.2%) and 131 (49.8%) patients were categorized into the high- and low-VAI groups, respectively. There were 101 patients in both groups after PSM. Patient characteristics are shown in Table 1. Before matching, the

low-VAI group had a lower BMI (P<0.001), a greater number of patients with serosal invasion (P=0.018), fewer patients with diabetes (P=0.026), a lower SMI (P=0.001), and lower VAI (P<0.001). After matching, there was no significant difference in factors other than BMI and VAI that were not adjusted.

3.2 Comparison of postoperative outcomes after matching

Comparisons of postoperative outcomes after matching are shown in Table 2. The failure rate of S-1 adjuvant chemotherapy was significantly higher in the low-VAI group (P=0.037). There was no significant difference in the incidence of postoperative complications between the two groups. BWL rates for 6 months and 1 year were significantly higher in the high-VAI group (P<0.001 and P<0.001, respectively).

3.3 Relapse-free survival according to VAI

The median follow-up period was 52 months. Of the 263 patients, recurrence was observed in 90 patients (34.2%). The RFS before matching all cases was significantly poorer in the low-VAI group than in the high-VAI group (HR: 1.771, 95% CI: 1.151—2.725, P=0.009) (Fig. 2). The RFS after matching was also significantly poorer in the low-VAI group (HR: 1.757, 95% CI: 1.072—2.879, P=0.025) (Fig. 3).

3.4 Risk factors associated with discontinuation of adjuvant chemotherapy

Of the 263 patients, treatment failure was observed in 44 patients (16.7%). The results of the analysis of risk factors for treatment failure in all patients, are shown in Table 3. In the univariate analysis, total gastrectomy (P=0.029), COPD (P=0.005), low-VAI (P=0.021), and BWL for 6 months ≥ 15% (P=0.007) were significant. Multivariate

analysis revealed that low-VAI (HR: 2.360, 95% CI: 1.120—5.000, P=0.025) and BWL for 6 months ≥ 15% (HR: 2.970, 95% CI: 1.400—6.280,P=0.004) were significant independent risk factors.

3.5 Prognostic factors for relapse-free survival

The results of the analysis of prognostic factors for RFS, in all patients, are shown in Table 4. In the univariate analysis, age > 70 years (P=0.003), total gastrectomy (P<0.001), open surgery (P<0.001), serosal invasion (P<0.001), lymph node metastasis (P=0.011), and low VAI (P=0.009) were statistically significant. Multivariate analysis showed that age > 70 years (HR: 1.820, 95% CI: 1.180—2.807, P=0.007), total gastrectomy (HR: 1.642, 95% CI: 1.062—2.540, P=0.026), open surgery (HR: 2.827, 95%CI: 1.712—4.669, P<0.001), N3 lymph node metastasis (HR: 2.875, 95% CI: 1.800—4.593, P<0.001), and low VAI (HR: 1.652, 95% CI: 1.057—2.582, P=0.028) were significant independent prognostic factors for RFS.

４．Discussion

This study showed that low VAI, that is, low visceral fat mass, is an independent risk factor for discontinuation of S-1 adjuvant chemotherapy and an independent poor prognostic factor for RFS in patients with advanced gastric cancer who received S-1 adjuvant chemotherapy after radical gastrectomy. We revealed that these results were present not only in the two groups after PSM, but also in the multivariate analysis that included all cases. This is the first report to show that low preoperative visceral fat mass may result in poor compliance with adjuvant chemotherapy, and may shorten the postoperative recurrence-free period.

The multivariate analysis showed that low-VAI and 15% or more BWL for 6 months were the independent risk factors associated with discontinuation of adjuvant chemotherapy. The failure rate of adjuvant chemotherapy according to VAI was 11.4% in the high-VAI group and 22.1% in the low-VAI group (P=0.021) before matching. Additionally, it was 10.9% in the high-VAI group and 22.8% in the low-VAI group after matching, which was significant (P=0.037). In contrast, BWL for 6 months were 14.49% in the high-VAI group and 10.07% in the low-VAI group, which were significantly different (P<0.001). Thus, the proportion of patients who had 15% or more BWL for 6 months was 42.7% in the high-VAI group and 29.5% in the low-VAI group (P=0.071). This difference in BWL was considered to be reflective of the difference in body size. Although previous reports have shown that a BWL ≥ 15% within 1 month is associated with poor compliance with adjuvant chemotherapy [4], BWL ≥ 15% was not a significant risk factor in this study. However, it was suggested that a larger BWL was associated with poor compliance with adjuvant chemotherapy regardless of the duration and cut-off value of BWL. Therefore, it is considered necessary to support patients who have preoperative low VAI and high VAI whose weight loss rate exceeds 15% within 6 months in order to maintain compliance with adjuvant chemotherapy.

We would like to assess the validity of our method for measuring and calculating visceral fat mass. BMI is commonly used to evaluate obesity, but it does not make a distinction between muscle, visceral fat, and subcutaneous fat. CT scans can differentiate these tissue types and are considered the gold standard for assessing visceral adipose tissue [20]. In the current study, we adopted the approach of Kobayashi et al. [21], who claimed that the abdominal visceral fat area on a single CT slice at the umbilical level correlates with total intra-abdominal visceral fat volume. As the SMI is a widely

recognized indicator of skeletal muscle mass [22—26], we attempted to use height in a similar way to evaluate visceral fat. The cut-off values of VAI and SMI were calculated in a similar way using the median; however, low VAI was involved in treatment failure, while low-SMI was not. This shows that preoperative visceral fat mass may be more useful for predicting compliance with adjuvant chemotherapy than skeletal muscle mass. To the best of our knowledge, no previous study has examined this type of visceral adipose tissue index in gastric cancer patients. We hope that a validation study for VAI cut-off values will be performed in future.

Among prognostic factors related to RFS, age over 70 years, total gastrectomy, open surgery, lymph node metastasis, and low-VAI were identified. In the background adjusted comparison, there was no difference in the parameters other than VAI in the low-VAI group and the high-VAI group. Thus, the reason why low VAI was a poor prognostic factor for RFS could be due to the difference in compliance with adjuvant chemotherapy. On the other hand, a BWL ≥ 15% for 6 months, which was a risk factor for discontinuation of adjuvant chemotherapy in multivariate analysis, was not an independent poor prognosis factor for RFS. BWL for 1 year tended to be higher in recurrent cases than in non-recurrent cases, but there was no significant difference of in BWL ≥ 15% for 6 months, which was 36.8% in recurrent cases and 33.7% in non-recurrent cases (P = 0.681). Although previous reports have reported that a BWL ≥ 15% within 1 month worsens RFS [6], it was not found to be a poor prognostic factor for RFS in this study. Since BWL is also affected by many factors other than treatment, such as preoperative physical size, postoperative nutritional intake, and tumor recurrence, a validation study is required for the period and cut-off value of BWL. The fact that open surgery was a poor prognostic factor may be due to a selection bias during treatment decision, whereby the

proportion of pathological stage III gastric cancer was 41.3% in the laparoscopic group and 63.8% in the open group (P <0.001). There was no difference in pathological stage between patients aged above and below 70 years. However, VAI was lower in patients over 70 years of age, with a greater proportion with low VAI, which was 58.3% in those aged > 70 years and 46.4% in those aged < 70 years (P = 0.086). This may have affected RFS.

The correlation of visceral fat and prognosis may be related to BWL observed after gastrectomy. Patients continue to lose body weight up to 6 months after surgery. Skeletal muscle mass decreases mainly in the acute phase and persists up to around 3 months, which is followed by a decrease in adipose tissue [27—31]. A decrease in skeletal muscle mass is especially prominent in the first week [30], and the following changes in body composition are thought to be a metabolic response to compensate for this loss of skeletal muscle mass. Harada et al. reported that a low visceral fat content on preoperative CT scans was associated with poor prognosis in patients with upper gastrointestinal cancer [32]. This was attributed to the fact that decreased visceral fat might reflect malnutrition and that visceral fat acts as an energy store that can be accessed in times of negative energy balance. This presents the benefit of BWL after gastrectomy. In addition, Park et al. found that a marked loss in visceral fat can also predict poor prognosis [33]. Visceral fat reflects nutritional status, which could explain why patients with preoperative decreases or marked losses after gastrectomy have less favorable outcomes.

There was no difference in the recurrence type between the low-VAI group and high-VAI group, which included lymph node metastasis (P=0.186), liver metastasis (P=0.341), lung metastasis (P=0.447), peritoneal metastasis (P=0.169), bone metastasis (P=0.122), and residual gastric cancer (P=1.000). Interestingly, recurrence within 1 year was

significantly higher in the low-VAI group (29.0%) than in the high-VAI group (16.9%) (P=0.027), and even when I excluded recurrent cases from treatment failure and performed a multivariate analysis, low-VAI was an independent risk factor of treatment failure (HR: 2.850, 95% CI: 1.130—7.210, P=0.027). Therefore, the treatment failure of the low-VAI group is not due to the difference in the number of recurrences.

The limitations of this study include: 1) it is a single-center retrospective cohort study, 2) the possibility of selection bias by PSM, 3) absence of postoperative nutritional support, and 4) the race difference. To eliminate the selection bias due to PSM, we performed a multivariate analysis including a total of 263 cases before matching, and proved that the results of the two-group comparison were universal. Furthermore, the validity of the VAI cut-off values needs to be verified in additional studies, and a multi-center cohort study is required to show the universality of this study. In Japan, there are facilities that administer oral nutrition supplementation (ONS) to all patients regardless of their dietary intake in order to reduce postoperative body weight loss. In the present study, ONS was given only to patients with inadequate dietary intake and not to all patients. It is also necessary to take into account the differences in body size among race groups. Asians have a smaller BMI and are less obese than Europeans, and this may have affected the results. From the above, it is necessary to verify the results for each race group. To the best of our knowledge, this is the first report showing the relationship between visceral fat mass and compliance with adjuvant chemotherapy for gastric cancer patients, and this study is crucial in terms of the impact of preoperative visceral fat mass on postoperative treatment in patients with gastric cancer who exhibit postoperative body weight loss. Therefore, it is important to support patients with low VAI to maintain compliance with adjuvant chemotherapy. In the future, we would like to investigate

whether support system against side effects, including nutritional support, in the low-VAI group will lead to improved compliance with adjuvant chemotherapy and prolong RFS.

5. Conclusion

Preoperative low visceral fat mass was an independent risk factor for poor compliance with adjuvant chemotherapy and a poor prognostic factor for RFS after radical gastrectomy in patients with gastric cancer. Preoperative evaluation using body composition may be useful for postoperative and prognosis prediction.

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The authors declare no conflicts of interest.

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Ethics:

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Statement of informed consent:

Informed consent was obtained from all individual participants included in the study.

Author contribution:

All authors participated in the following:

• Substantial contributions to the study conception and design, data acquisition or analysis, and data interpretation;

• Drafting the manuscript or reviewing it critically for important intellectual content;

• Approval of the final version of the manuscript.

The main role of the authors was as follows:

1. Guarantor of the integrity of the entire study: Noriyuki Inaki.

2. Study conception and design: Ryota Matsui and Noriyuki Inaki.

3. Literature search: Ryota Matsui.

4. Clinical studies: All authors.

5. Data collection: Ryota Matsui and Toshikatsu Tsuji.

6. Statistical analysis: Ryota Matsui.

7. Manuscript preparation: Ryota Matsui and Noriyuki Inaki.

8. Manuscript review: All authors.

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Figure legend

Fig.1 Study design

Fig.2 Relapse-free survival curves according to visceral adipose tissue index (VAI) for all patients (P=0.006).

Fig.3 Relapse-free survival curves according to visceral adipose tissue index (VAI) after matching (P=0.037).

Table1. Patient characteristics before and after propensity score matching

	All patients			After matching		
	High-VAI group (N=132)	Low-VAI group (N=131)	P value	High-VAI group (N=101)	Low-VAI group (N=101)	P value
Sex male	93 (70.5%)	92 (70.2%)	1.000	71 (70.3%)	72 (71.3%)	1.000
Female	39 (29.5%)	39 (29.8%)		30 (29.7%)	29 (28.7%)	
Age, mean ± SD	65.05 ± 8.23	64.50 ± 11.93	0.664	64.38 ± 8.28	64.47 ± 11.90	0.951
Body mass index, mean ± SD	24.98 ± 3.10	21.11 ± 2.64	<0.001	24.39 ± 2.88	21.48 ± 2.61	<0.001
Surgical approach						
laparoscopic surgery	71 (53.8%)	60 (45.8%)	0.218	54 (53.5%)	42 (41.6%)	0.121
open surgery	61 (46.2%)	71 (54.2%)		47 (46.5%)	59 (58.4%)	
Surgical procedure						
distal gastrectomy	78 (59.1%)	67 (51.1%)		60 (59.4%)	55 (54.5%)	
proximal gastrectomy	3 (2.3%)	5 (3.8%)	0.440	2 (2.0%)	4 (4.0%)	0.646
total gastrectomy	51 (38.6%)	59 (45.0%)		39 (38.6%)	42 (41.6%)	
Lymph node dissection						
D1+	49 (37.1%)	41 (31.3%)	0.363	32 (31.7%)	31 (30.7%)	1.000
D2	83 (62.9%)	90 (68.7%)		69 (68.3%)	70 (69.3%)	
Pathological stage						
II	66 (50.0%)	60 (45.8%)	0.538	47 (46.5%)	46 (45.5%)	1.000
III	66 (50.0%)	71 (54.2%)		54 (53.5%)	55 (54.5%)	
Serosal invasion						
absent	105 (79.5%)	87 (66.4%)	0.018	77 (76.2%)	76 (75.2%)	1.000
present	27 (20.5%)	44 (33.6%)		24 (23.8%)	25 (24.8%)	
Lymph node metastasis						

absent	19 (14.4%)	22 (16.8%)	0.614	15 (14.9%)	15 (14.9%)	1.000
present	113 (85.6%)	109 (83.2%)		86 (85.1%)	86 (85.1%)	
Histological type						
differentiated	53 (40.2%)	45 (34.4%)	0.373	38 (37.6%)	39 (38.6%)	1.000
undifferentiated	79 (59.8%)	86 (65.6%)		63 (62.4%)	62 (61.4%)	
Comorbidity CKD	18 (13.6%)	17 (13.0%)	1.000	13 (12.9%)	15 (14.9%)	0.839
COPD	21 (15.9%)	26 (19.8%)	0.425	15 (14.9%)	19 (18.8%)	0.573
Diabetes	32 (24.2%)	17 (13.0%)	0.026	13 (12.9%)	17 (16.8%)	0.553
CHF	7 (5.3%)	3 (2.3%)	0.334	5 (5.0%)	1 (1.0%)	0.212
SMI (cm^2/m^2), median (range)	41.86 (21.05-68.43)	38.95 (20.81-58.74)	0.001	40.91 (21.05-67.76)	40.60 (22.89-58.74)	0.274
Low-SMI	53 (40.2%)	78 (59.5%)	0.002	49 (48.5%)	52 (51.5%)	0.778
VAI (cm^2/m^2), median (range)	50.64 (24.96-123.8)	18.18 (0.38-35.24)	<0.001	49.80 (24.96-102.1)	19.99 (1.67-34.73)	<0.001

VAI visceral adipose tissue index, *SD* standard deviation, *CKD* chronic kidney disease,

COPD chronic obstructive pulmonary disease, *CHF* chronic heart failure,

SMI skeletal muscle mass index

Table2. Comparison of postoperative outcomes after matching

	High-VAI group (N=101)	Low-VAI group (N=101)	P value
Failure of adjuvant chemotherapy	11 (10.9%)	23 (22.8%)	0.037
Postoperative complication			
Clavien-Dindo classification ≧2	19 (18.8%)	14 (13.9%)	0.447
Clavien-Dindo classification ≧3a	9 (8.9%)	5 (5.0%)	0.407
Postoperative body weight loss (%)			
for 1 month, median (range)	7.64 (0.0-23.76)	7.69 (0.0-22.03)	0.701
for 6 months, median (range)	14.49 (0.0-28.42)	10.07 (0.0-31.19)	<0.001
for 1 year, median (range)	16.31 (0.79-31.35)	9.43 (0.0-31.49)	<0.001

Table3. Results of univariate and multivariate analyses of risk factors associated with discontinuation of adjuvant chemotherapy

Variables		**Univariate analysis**			**Multivariate analysis**		
		OR	95%CI	P value	OR	95%CI	P value
Sex	female	1					
	Male	0.943	0.489-1.820	0.861			
Age (years)	＜70	1					
	≧70	1.440	0.768-2.710	0.254			
Surgical procedure	distal gastrectomy	1			1		
	total gastrectomy	1.990	1.070-3.700	0.029	1.500	0.728-3.080	0.272
Surgical approach	laparoscopic surgery	1					
	open surgery	1.710	0.917-3.180	0.092			
Lymph node dissection	D1+	1					
	D2	0.721	0.384-1.350	0.309			
Pathological stage	II	1					
	III	0.893	0.485-1.650	0.718			
Chronic kidney disease	absent	1					
	Present	0.522	0.176-1.550	0.240			
Diabetes	absent	1					
	Present	1.190	0.551-2.580	0.653			
COPD	absent	1			1		

	Present	2.620	1.320-5.170	0.005	1.880	0.812-4.350	0.141
Chronic heart failure	absent	1					
	Present	0.503	0.062-4.070	0.520			
Body mass index (kg/m^2)	≧18.5	1					
	＜18.5	1.360	0.520-3.570	0.528			
Body mass index (kg/m^2)	＜25.0	1					
	≧25.0	0.655	0.300-1.430	0.287			
SMI (cm^2/m^2)	High-SMI	1					
	Low-SMI	1.260	0.656-2.410	0.492			
VAI (cm^2/m^2)	High-VAI	1			1		
	Low-VAI	2.220	1.130-4.370	0.021	2.360	1.120-5.000	0.025
Postoperative complication							
	absent	1					
	Clavien-Dindo ≧2	1.730	0.842-3.550	0.136			
	Clavien-Dindo ≧3a	1.170	0.373-3.660	0.789			
Body weight loss for 1 month	＜15 (%)	1					
	≧15 (%)	2.450	0.873-6.900	0.089			
Body weight loss for 6 months	＜15 (%)	1			1		
	≧15 (%)	2.420	1.270-4.620	0.007	2.970	1.400-6.280	0.004

OR odds ratio, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease,

SMI skeletal muscle mass index, *VAI* visceral adipose tissue index

Table4. Results of univariate and multivariate analyses of prognostic factors for relapse-free survival

Variables		**Univariate analysis**			**Multivariate analysis**		
		HR	95%CI	P value	HR	95%CI	P value
Sex	female	1					
	Male	1.597	0.988-2.581	0.056			
Age (years)	＜70	1			1		
	≧70	1.874	1.236-2.842	0.003	1.820	1.180-2.807	0.007
Surgical procedure	distal gastrectomy	1			1		
	total gastrectomy	2.117	1.398-3.208	<0.001	1.642	1.062-2.540	0.026
Surgical approach	laparoscopic surgery	1			1		
	open surgery	3.836	2.403-6.123	<0.001	2.827	1.712-4.669	<0.001
Lymph nodes dissection	D1+	1					
	D2	1.139	0.730-1.779	0.566			
Serosal invasion	absent	1			1		
	Present	2.424	1.600-3.672	<0.001	1.311	0.820-2.095	0.258
Lymph node metastasis	absent	1					
	present	2.734	1.262-5.921	0.011			
	N2	2.298	1.447-3.650	<0.001			
	N3	3.658	2.413-5.545	<0.001	2.875	1.800-4.593	<0.001
Histological type	differentiated	1					
	Undifferentiated	1.353	0.867-2.113	0.184			

Chronic kidney disease	absent	1					
	Present	1.336	0.768-2.325	0.306			
Diabetes	absent	1					
	Present	0.879	0.497-1.553	0.657			
COPD	absent	1					
	Present	1.566	0.968-2.531	0.067			
Chronic heart failure	absent	1					
	Present	0.274	0.038-1.964	0.198			
Body mass index (kg/m^2)	≧18.5	1					
	＜18.5	0.730	0.338-1.579	0.424			
Body mass index (kg/m^2)	＜25.0	1					
	≧25.0	0.762	0.455-1.276	0.302			
SMI (cm^2/m^2)	High-SMI	1					
	Low-SMI	1.422	0.931-2.173	0.104			
VAI (cm^2/m^2)	High-VAI	1			1		
	Low-VAI	1.771	1.151-2.725	0.009	1.652	1.057-2.582	0.028
Postoperative complication	absent	1					
	Clavien-Dindo ≧2	0.667	0.364-1.225	0.192			
	Clavien-Dindo ≧3a	1.105	0.511-2.389	0.800			
Body weight loss for 1 month	＜15 (%)	1					
	≧15 (%)	1.615	0.810-3.219	0.173			

Body weight loss for 6 months	＜15 (%)	1			
	≧15 (%)	1.162	0.749-1.802	0.503	

HR hazard ratio, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *SMI* skeletal muscle mass index, *VAI* visceral adipose tissue index