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Original Article

Title: Relationship between laparoscopic total gastrectomy-associated postoperative complications and gastric cancer prognosis

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Author Contributions:

Study conception and design: Yuma Ebihara and Satoshi Hirano.

Acquisition of data: Yuma Ebihara.

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Original Article

Title: Relationship between laparoscopic total gastrectomy-associated postoperative complications and gastric cancer prognosis

Abstract

This study aimed to investigate the incidence and prognosis of postoperative complications after laparoscopic total gastrectomy (LTG) for gastric cancer (GC). We retrospectively enrolled 411 patients who underwent curative LTG for GC at seven institutions between January 2004 and December 2018. The patients were divided into two groups, complication group (CG) and non-complication group (non-CG), depending on the presence of serious postoperative complications (Clavien-Dindo grade III [≥CD IIIa] or higher complications). Short-term outcomes and prognoses were compared between two groups. Serious postoperative complications occurred in 65 (15.8%) patients. No significant difference was observed between the two groups in the median operative time, intraoperative blood loss, number of lymph nodes harvested, or pathological stage; however, the 5-year overall survival (OS; CG 66.4% vs. non-CG 76.8%; p = 0.001), disease-specific survival (DSS; CG 70.1% vs. non-CG 76.2%; p = 0.011), and disease-free survival (CG 70.9% vs. non-CG 80.9%; p = 0.001) were significantly different. The Cox multivariate analysis identified the serious postoperative complications as independent risk factors for 5-year OS (HR 2.143, 95% CI 1.165–3.944, p = 0.014) and DSS (HR 2.467, 95% CI 1.223–4.975, p = 0.011). A significant difference was detected in the median days until postoperative recurrence (CG 223 days vs. non-CG 469 days; p = 0.017) between the two groups. Serious postoperative complications after LTG negatively affected the GC prognosis. Efforts to decrease incidences of serious complications should be made that may help in better prognosis in patients with GC after LTG.

Keywords: laparoscopic total gastrectomy, gastric cancer, postoperative complications, prognosis, overall survival

Introduction

Gastric cancer (GC) is the fifth most common type of cancer and third leading cause of death worldwide [1, 2]. Surgical resection or gastrectomy is the most important treatment for GC, but the postoperative complications (incidence rates of 12.8–14.0% [3-5]) negatively affects the patients' quality of life (QOL), subsequent treatment(s), and long-term survival [6, 7]. Several studies have confirmed the association of postoperative complications after gastrectomy for GC and poor oncological prognosis [8-10]. In 1994, laparoscopy-assisted distal end gastrectomy for early GC was introduced [11]; with advances in equipments and surgical techniques, laparoscopic gastrectomy (LG) has gradually been considered more often. In comparison to open gastrectomy, LG is associated with features such as feasibility, decreased surgical trauma, and a faster recovery. Further, many studies showed non-inferiority of LG to open gastrectomy for GC [12-14]. The impact of postoperative complications after LG for patients with GC remains controversial. In particular, laparoscopic total gastrectomy (LTG) requires a high degree of skill for performing the gastrectomy with systematic lymphadenectomy and post-resection reconstructions; the procedures are difficult and complex even for the experienced laparoscopic surgeons [15,16]. Further, the rates of complications after LTG are also reportedly high (7.6–42.6%) [17-19], but information on the postoperative complications-related adverse events (such as non-cancer-related deaths) is lacking. This study aimed to investigate the relationship between postoperative complications and long-term survival in patients who underwent LTG for GC.

Methods

Patients

We retrospectively reviewed all the patients who underwent curative LTG for GC at seven institutions (Hokkaido University Hospital, Teine Keijinkai Hospital, Obihiro-Kosei General Hospital, Hokkaido Gastroenterology Hospital, Tonan Hospital, Kitami Red Cross Hospital, and Asahikawa City Hospital) between January 2004 and December 2018. All patients were diagnosed with GC using endoscopy, computed tomography (CT), or endoscopic ultrasound. The Japanese Classification of Gastric Carcinoma (JCGC) was used for tumor staging [20]. The primary indication for LTG was stage I GC based on the Japanese Society of Endoscopic Surgery (JSES) guidelines [21]; however, over time, we expanded the indication to include cases of advanced GC that could be curatively resected.

Data collection

Clinicopathological data, including age, sex, body mass index (BMI), American Society of Anesthesiologists physical status (ASA-PS), clinical stage, combined resection of other organs, lymph node dissection, and anastomosis method, were collected. Surgical outcomes, including operative time, estimated blood loss, postoperative complications, and length of postoperative hospital stay, were recorded. Patients were categorized either to a complication group (CG) or non-complication group (non-CG), depending on the presence of serious postoperative complications (≥CD IIIa: Clavien-Dindo grade III or higher complications) [22, 23]. All patients provided informed consent, and the Hokkaido University Hospital Institutional Review Board approved the data collection and analysis (No. 016-0151). This study was performed in accordance with the principles of the Declaration of Helsinki.

Surgical procedure

Gastric procedure type (resection and reconstruction) was determined based on the experience and preference of a surgeon who was accredited through the Endoscopic Surgical Skill Qualification System of the JSES [21]. In cases where the operating surgeon lacked this qualification, a qualified surgeon supervised the surgery. The extent of lymph node dissection was determined based on the JGCA guidelines [20]. Patients who underwent D2 lymph node dissection with splenectomy and D2–No.10 lymph node dissection were included in D1+. Patients were divided into three groups based on the Clavien-Dindo postoperative complication classification grade [22, 23].

Postoperative follow-up

All patients were observed every 3 months after surgery. Hematological analysis (including the tumor marker analysis for carcinoembryonic antigen and carbohydrate antigen 19–9) was performed at each visit. Abdominal CT scans were performed every 6 months or when clinical recurrence was suspected. Gastrointestinal endoscopy was performed at 1, 3, and 5 years postoperatively. Based on this surveillance, data on the 5-year overall survival (OS; time from surgery to death for any reason or follow-up interruption) and disease-specific survival (DSS; time from surgery to death from GC, including operative mortality or follow-up interruption), and disease-free survival (DFS; time from surgery to death from GC, the first recurrence of GC, or follow-up interruption) were collected.

Statistical analysis

Pearson's chi-square test and Fisher's exact probability test were performed for categorical variables. Mann−Whitney U tests were used to compare the clinicopathological characteristics for unpaired continuous variables between the two groups. Survival curves were estimated using the Kaplan−Meier method, and statistical differences were examined using the Wilcoxon test. A Cox proportional hazard regression model was used to determine the independent prognostic factors related to survival. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using the JMP® 15 software (SAS Institute Inc., Cary, NC, USA).

Results

Clinical features and surgical outcomes of the study population

A total of 459 patients were screened; after applying the exclusion criteria (neoadjuvant therapy, cStage IV, resection of other organs, and a total number of harvested lymph nodes ≤15), 411 patients were finally included in the analysis. In this study, for accurate prognostic analysis, we included more than 16 lymph nodes dissected using the exclusion criteria [24]. CG and non-CG groups had 65 and 346 patients, respectively (Fig. 1). Table 1 shows the clinical characteristics and surgical outcomes of the patients. Among total patients, 284 (69.1%) and 127 (30.9%) were males and females, respectively, with a median age of 68 years (range 25–88) and median BMI of 23.0 kg/m^2 (range 13.6–38.9). The ASA-PS was ≥II in 286 (69.6%) patients, clinical JCGC stage was ≥II in 187 (45.5%) patients, D2 lymphadenectomy was performed in 67 (16.3%) patients, median operation time was 330 (range, 123–762) min, median operative blood loss was 50 (range, 0–1940) mL, serious postoperative complications (≥CD IIIa) occurred in 65 patients (15.8%), and median postoperative hospital stay was 13 (range, 6–210) days.

Table 2 shows the clinicopathological characteristics of the study patients. No significant differences were observed in the age, BMI, ASA-PS, and clinical JCGC stage between the two groups. Female patients had significantly ($p = 0.018$) fewer complications than that of the male patients. Table 3 shows the surgical outcomes in patients of the two groups. The median operative time, blood loss, extent of lymph node dissection, method of esophagojejunostomy, and number of resected lymph nodes were not significantly different between the two groups; however, the median postoperative hospital stay was significantly ($p < 0.001$) longer in CG (34 days [range 8–210]) than that of the non-CG (12 days [range 6–43]). Further, the mortality was not observed in both the groups in 30 days postoperatively. Among the postoperative complications, esophagojejunostomy (EJS)-related complications (leakage or stenosis) were the most common (38.5 %) (Table 4).

Prognosis

Table 5 shows the histological examination results of resected specimens; the pathological JCGC stage were similar ($p = 0.729$) in both the groups. The median follow-up periods for patients of the CG and non-CG were 36.7 (2–109.6 months) and 32.8 (1–139.2) months, respectively. During the follow-up period, postoperative recurrence was observed in 11 (16.9%) and 49 (14.7%) patients of the CG and non-CG, respectively, with no significance ($p = 0.569$). Further, the median days until recurrence was significantly ($p = 0.017$) shorter in CG (223 [range 60–1480] days) than that of the non-CG (469 [range 72–2289] days). For all the patients, the 5-year OS rate was 75.9%; 66.4 and 76.8% in the CG and non-CG, respectively. The Kaplan–Meier analysis for the OS indicated a significant ($p = 0.001$) difference between the two groups (Fig. 2a). The 5-year DSS and DFS rates were 80.3 and 75.3, 70.1 and 70.9, and 76.2 and 80.9% for all the patients, CG, and non-CG, respectively. The Kaplan–Meier analysis for DSS and DFS indicated significant (DSS, $p = 0.011$; DFS, $p = 0.001$) differences between the two groups (Fig. 2b,c).

Prognostic factors for OS, DSS and RFS

Table 6 shows the multivariate analysis conducted to assess the risk factors for OS, DSS, and DFS. In the OS, depth of tumor invasion (pT) and serious postoperative complications (≥CD IIIa) were identified as the independent prognostic factors (pT: hazard ratio [HR] 0.194, 95% confidence interval [CI] 0.094–0.397], $p < 0.001$; ≥CD IIIa: HR 2.143, 95% CI 1.165–3.944, $p = 0.014$). In DSS, pT, lymph node metastasis (pN), and serious postoperative complications (≥CD IIIa) were identified as the independent prognostic factors (≥CD IIIa: HR 2.467, 95% CI 1.223–4.975, $p = 0.011$; pT: HR 0.156, 95% CI 0.062–0.394, $p < 0.001$; pN: HR 2.289, 95% CI 1.088–4.814, $p = 0.029$). In DFS, age, sex, and pT were independent prognostic factors (age: HR 1.959, 95% CI 1.001–3.832, p = 0.004; sex: HR 2.033, 95% CI 1.193–3.463, p = 0.009; pT: HR 0.192, 95% CI 0.095–0.385, p <0.001).

Discussion

This is the first multicenter retrospective study that compared the serious postoperative complications and long-term outcomes associated with LTG for GC; we found that serious complications after LTG had a significant negative impact on the GC prognosis.

Severe postoperative complications increase the treatment costs, prolong the hospital stay, and have a negative effect on patients' QOL. The association of postoperative complications with the long-term survival has been suggested for malignant tumors, such as breast, colorectal, and periampullary cancers [25–28]. Higher local recurrence risk and worse long-term outcomes in patients with GC were also reported to be related to postoperative complications [29, 30]. Kubota et al. evaluated the prognostic significance of postoperative complications in patients with GC using the propensity score matching analysis and reported a significant and independent correlation between the infectious complications and decreased survival [29]. Tokunaga et al. also reported that postoperative intra-abdominal infectious complications (IaICs) in patients with GC predict a poor OS [8]. Hence, the presence of postoperative complications, especially infectious complications, in GC is significantly correlated with the disease recurrence and poor survival, and may be due to following reasons: (1) the inflammatory response, prolonged fasting conditions, and weight loss due to severe postoperative complications may result in immunosuppression. The cell-mediated immune response, particularly the cytotoxic T lymphocytes and natural killer cells, is compromised by systemic inflammation and surgical stress, promoting the immune escape of micrometastatic carcinoma cells [31, 32], (2) a large number of activated leukocytes and cytotoxic mediators such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha released from the inflammatory response due to infection-related postoperative complications could accelerate the proliferation and invasion ability of residual cancer cells, which promotes the development of tumor recurrence and metastasis [33, 34], and (3) chemotherapy cannot be adequately administered.

Evans et al. [35] reported that laparoscopic surgery had little impact on the human immune function and induced a slight inflammatory reaction in elderly patients, which could effectively reduce the occurrence of cardiopulmonary complications. With the advancement of laparoscopic technology and accumulation of surgical experience, laparoscopic gastrectomy is attracting attention as an alternative surgical method for patients with GC, and the occurrence of trauma and postoperative complications is expected to decrease further in the future. Regarding the long-term oncological results in LTG for GC, the 2-year OS and DFS rates were comparable between LTG and open total gastrectomy in meta-analysis studies [36, 37]. These results demonstrated that the surgical method did not affect long-term survival rates. Further, Jia-Bin Wang et al. reported that laparoscopic gastrectomy for GC can improve the prognosis of patients with postoperative IaICs and is therefore recommended for patients at a high risk of IaICs [38]. At present, the prognostic benefit of reduced surgical invasiveness with laparoscopy is controversial. In the present study also, we observed significantly worse 5-year OS, DSS, and DFS in patients with complications after LTG for GC. Furthermore, previous studies have also reported that weight loss associated with gastrectomy for GC decreased the nutritional status, postoperative QOL, and compliance of S-1 adjuvant chemotherapy, and could have led to the poor survival [39, 40]. Indeed, body weight loss at 1 year after surgery was reported to be approximately 10 and 15% following distal and total gastrectomy, respectively [41-43]. Weight loss after total gastrectomy may occur through various mechanisms, such as the hyper catabolism associated with inflammatory reactions due to surgical stress, reduced food intake owing to loss of reservoir function, and reduction in blood ghrelin level [44]. Furthermore, the postoperative complications related to EJS forces prolong fasting, resulting in poor nutritional status and QOL. The EJS stenosis increases the risk of aspiration pneumonia as well [45]. In the present study, the EJS-related complications were also the most common; it is necessary to establish simple EJS techniques that show less frequent postoperative complications.

Several recent studies have suggested that male gender is a risk factor for postoperative complications in bowel surgery.[46] Furthermore, male gender has also been associated with shorter overall survival and disease-free survival after anastomotic leakage, suggesting that the male risk factor deserves more attention [47, 48]. Our results in the present study showed that male gender was associated with more serious postoperative complications male ($p = 0.018$). The gender difference may be explained by a combination of anatomical differences and the recently shown hormonal differences that influence the intestinal microcirculation [49]. Without a clear biological explanation for these findings and this finding should be interpreted with caution.

Randomized controlled studies have established that adjuvant chemotherapy following gastrectomy has survival advantages as compared to gastrectomy alone [50, 51]. Thus, adequate delivery and completion of chemotherapy are necessary to obtain a survival benefit after curative gastrectomy for GC. Li et al. reported that the completion of multimodality therapy could extenuate the adverse influence of complications on the long-term survival of patients with locally advanced GC [52]. In the present study, no significant differences were observed in the number of patients receiving adjuvant chemotherapy between the two groups, but the median days until recurrence was significantly shorter in CG than that of non-CG); these findings indicate that postoperative complications could accelerate the proliferation and invasion ability of residual cancer cells. Moreover, the prognosis may have been worse in patients who were unable to complete multimodality therapy due to serious postoperative complications after LTG. The European Society for Medical Oncology (ESMO) suggests radical gastrectomy with free margins and an adequate lymphadenectomy, and if indicated along with perioperative neoadjuvant chemotherapy, as the standard of care in patients with advanced GC [53, 54]. Several recent studies demonstrated no difference in postoperative complication ratesin gastric cancer patients who received neoadjuvant treatment compared with those undergoing operation first [55-57]. In Japan, no evidence of perioperative neoadjuvant therapy is reported for GC. For patients with high risk of postoperative complications, neoadjuvant approach may be more beneficial to improve the chemotherapeutic agent compliance.

This study had several limitations. First, this was a retrospective, observational, and non-experimental study. Additionally, we included patients who underwent either laparo-assisted total gastrectomy (LATG) or totally laparoscopic total gastrectomy (TLTG); different results may have been obtained in an analysis with exclusion of patients who underwent LATG. Second, this study was conducted over a rather long period between 2004 and 2018, which may have resulted in historical biases in terms of the treatment strategies and perioperative management, affecting the short-term and prognostic outcomes after LTG. The detailed chemotherapy regimens administered after relapse and their impact were not known. Third, the surgical procedures and indication for GC were subjectively determined based on the experience of each surgeon. Fourth, shorter median follow-up time and underestimation of the survival differences between the two groups were possible. A well-designed randomized control trial is required to validate our findings.

Conclusions

Occurrence of serious postoperative complications after LTG showed a negative impact on the OS of the patients with GC. Strategies that decrease the complications after LTG are required for contributing towards better prognosis of patients with GC after LTG.

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Figure legends

Fig. 1 Study enrolments

LTG, laparoscopic total gastrectomy; NAC, Neoadjuvant therapy; CD, Clavien-Dindo.

*In this study, for accurate prognostic analysis, we included the number of lymph nodes dissected to >16 in the exclusion criteria.

Fig. 2 Prognosis of patients who underwent laparoscopic total gastrectomy for gastric cancer according to age

(a) Overall, (b) disease-specific, and (c) disease-free survival

Table 1. Clinical features and surgical outcomes of the study population

Variable	Overall (n=411)
Gender (M/F)	284/127
Age (year) (median, range)	68 (25-88)
BMI† (kg/m^2) (median, range)	23.0 (13.6-38.9)
ASA-PS* (≥II) (patients,%)	286 (69.6%)
Clinical JCGC stage** (≥II) (patients,%)	187 (45.5%)
Lymph node dissection (≥D2) (patients,%)	67 (16.3%)
Operation time (min) (median, range)	330 (123-762)
Blood loss (ml) (median, range)	50 (0-1940)
Postoperative complication (CD§, ≥IIIa) (patients,%)	65 (15.8%)
Postoperative hospital stays (days) (median, range)	13 (6-210)

†Body mass index, *The American Society of Anesthesiologist's physical status, **According to the Japanese classification of gastric carcinoma: 3rd English edition, §ClavienDindo, classification

Table 2. Patient's characteristics of two groups

	Overall (n=411)		
	CG (n=65)	non-CG (n=346)	p value
Age (year) (median, range)	70 (25-85)	67 (33-88)	0.264
Sex (%)			0.018
Male	53 (81.5)	231 (66.8)	
Female	12 (18.5)	115 (33.2)	
BMI†(kg/m^2), median (range)	23.0 (14.0-30.9)	22.9 (13.6-38.9)	0.992
ASA-PS* (%)			0.755
1-2	61 (93.9)	328 (94.8)	
3-4	4 (6.1)	18 (5.2)	
Clinical JCGC stage** (%)			0.729
I	35 (53.9)	189 (54.6)	
II	18 (27.7)	82 (23.7)	
III	12 (18.4)	75 (21.7)	

†BMI, Body mass index, *The American Society of Anaesthesiologist's physical status, **According to the Japanese classification of gastric carcinoma: 3rd English edition.

Table 3. Surgical outcomes of two groups

	Overall (n=411)		
	CG (n=65)	non-CG (n=346)	p value
Operative time (min), median (range)	350 (123-648)	330 (171-762)	0.172
Blood loss (mL), median (range)	63.5 (0-1940)	50.0 (0-1160)	0.128
Extent of lymph node dissection			0.607
D1/D1+ (%)	53 (81.5)	291 (84.1)	
D2 (%)	12 (18.5)	55 (15.9)	
Esophagojejunostomy (Linear stapler/Circular stapler/Unknown)	36/29/0	218/124/4	0.302
Number of harvested lymph nodes, median (range)	41 (17-105)	41 (16-114)	0.208
Postoperative hospital stay (day), median (range)	34 (8-210)	12 (6-43)	<0.001
Mortality (within 30 days)	0	0	

Table 4. Postoperative complications in the complication group (CG)

Postoperative complications	CG (n=65)
EJS† leakage	13
EJS† stenosis	12
Duodenal stump leakage	10
Pancreatic fistula	5
Pneumonia	1
Abdominal abscess	7
Postoperative bleeding	6
Ileus	6
Others	5

†Esophagojejunostomy

Table 5. Pathological results and recurrence site of two groups

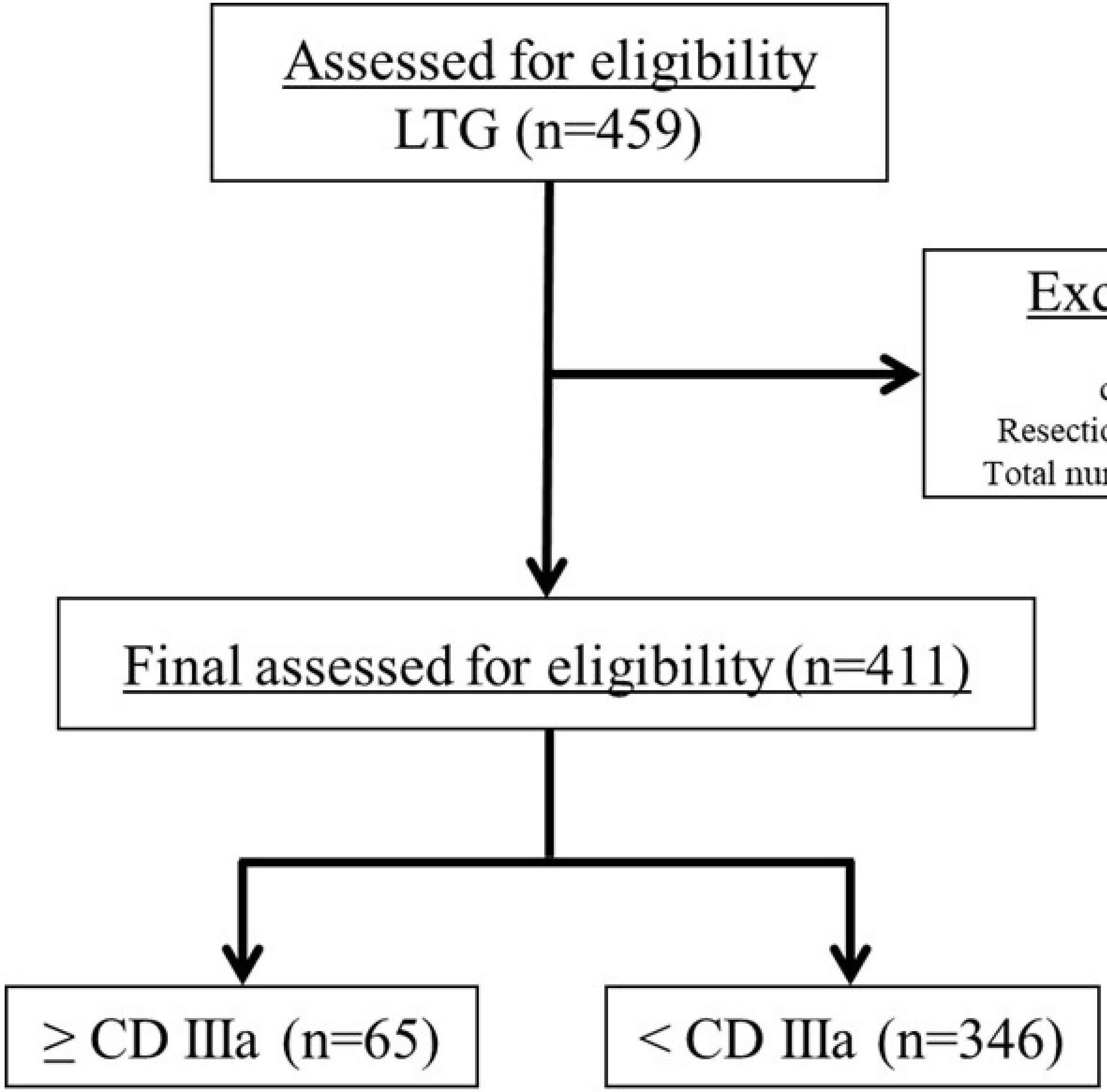
	Overall (n=411)		
	CG (n=65)	non-CG (n=346)	p value
Pathological JCGC stage* (%)			0.729
I	35 (53.9)	189 (54.6)	
II	18 (27.7)	82 (23.7)	
III	12 (18.4)	75 (21.7)	
Adjuvant chemotherapy	15 (23.1)	100 (28.9)	0.337
Recurrence (Y/N)	11/54	49/296	0.569
Recurrence site			
LN (Regional/Para Ao/Distant)	0/1/0	4/5/2	
Peritoneum dissemination	4	18	
Liver metastasis	5	12	
Lung metastasis	0	5	
Brain metastasis	0	1	
Bone metastasis	1	1	
Port site recurrence	0	1	
Days until recurrence (day), median (range)	223 (60-1480)	469 (72-2289)	0.017

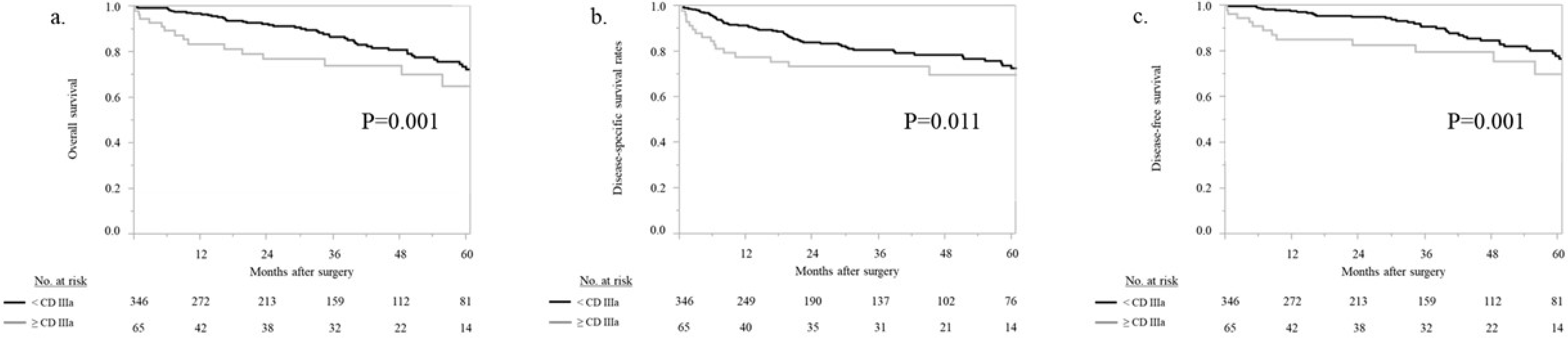
*According to the Japanese classification of gastric carcinoma: 3rd English edition.

Table 6. Multivariate Cox regression analyses for overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS)

	OS		DSS		DFS	
	HR（95%CI）	p value	HR（95%CI）	p value	HR（95%CI）	p value
Age (year) (≧80 / <80)					1.959 (1.001-3.832)	0.004
Sex (M / F)					2.033 (1.193-3.463)	0.009
Postoperative complication (CD[§] ≥ IIIa / CD < IIIa)	2.143 (1.165-3.944)	0.014	2.467 (1.223-4.975)	0.011		
pT (1 / 2,3)	0.194 (0.094-0.397)	<0.0001	0.156 (0.062-0.394)	<0.0001	0.192 (0.095-0.385)	<0.0001
pN (Y / N)			2.289 (1.088-4.814)	0.029		

[§]Clavien-Dindo, classification


Assessed for eligibility
LTG (n=459)
Excluded (n=48)
NAC (n=7)
cStage IV (n=10)
Resection of other organs (n=3)
Total number of L/N ≤15* (n=28)
Final assessed for eligibility (n=411)
≥ CD IIIa (n=65)
< CD IIIa (n=346)


a.
Overall survival
P=0.001
Months after surgery
No. at risk
< CD IIIa 346 272 213 159 112 81
≥ CD IIIa 65 42 38 32 22 14
b.
Disease-specific survival rates
P=0.011
Months after surgery
No. at risk
< CD IIIa 346 249 190 137 102 76
≥ CD IIIa 65 40 35 31 21 14
c.
Disease-free survival
P=0.001
Months after surgery
No. at risk
< CD IIIa 346 272 213 159 112 81
≥ CD IIIa 65 42 38 32 22 14