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1 Title: Outcomes of laparoscopic total gastrectomy in elderly patients: a propensity score matching
2 analysis

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6 Running head: Surgical outcomes of LTG in elderly patients aged over 80 years

8 **Abstract**

9 **Purpose**

10 This study evaluated the short-term outcomes and prognosis after laparoscopic total gastrectomy
11 (LTG) in elderly patients aged ≥ 80 years in a multicenter retrospective cohort study using propensity
12 score matching.

13 **Methods**

14 We retrospectively enrolled 440 patients who underwent curative LTG for gastric cancer at six
15 institutions between January 2004 and December 2018. Patients were categorized into an elderly
16 patient group (EG; age ≥ 80 years) and non-elderly patient group (non-EG; age < 80 years). Patients
17 were matched using the following propensity score covariates: sex, body mass index, American
18 Society of Anesthesiologists physical status, extent of lymph node dissection, and Japanese

Classification of Gastric Carcinoma stage. Short-term outcomes and prognoses were compared.

Results

We identified 37 propensity score-matched pairs. The median operative time was significantly shorter and postoperative stay was longer in the EG. In terms of postoperative outcomes, the rates of all complications were comparable. The median follow-up period of the EG and non-EG was 11.5 (1–106.4) months and 35.7 (1–110.0) months, respectively; there were significant differences in 5-year overall survival between the two groups (EG, 58.5% vs. non-EG, 91.5%; $P=0.031$). However, there were no significant differences in 5-year disease-specific survival (EG, 62.1% vs. non-EG, 91.5%; $P=0.068$) or 5-year disease-free survival (EG, 52.9% vs. non-EG, 60.8%; $P=0.132$).

Conclusions

LTG seems to be safe and feasible in elderly patients. LTG had a limited effect on morbidity, disease recurrence, and survival in elderly patients. Therefore, age should not prevent elderly patients from benefitting from LTG.

Keywords: laparoscopic total gastrectomy, gastric cancer, elderly patients, multicenter retrospective study

Declarations

- 1 Funding: Not applicable
- 2 Conflicts of interest/Competing interests: Not applicable
- 3 Availability of data and material (data transparency): The datasets during and/or analysed during the
- 4 current study available from the corresponding author on reasonable request.
- 5 Code availability: Not applicable
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- 12 Acquisition of data: Yuma Ebihara
- 13 Analysis and interpretation of data: Yuma Ebihara and Yo Kurashima
- 14 Drafting of manuscript: Yuma Ebihara.
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1 **Introduction**

2 The population of elderly people, especially those aged over 80 years in Japan, has been
3 dramatically increasing in number worldwide. The proportion of elderly patients with gastric cancer
4 (GC) undergoing surgery has also been increasing along with an increasing *Helicobacter pylori*
5 infection rate among the elderly [1]. Since the first laparoscopy-assisted distal gastrectomy for early
6 GC was performed in 1991 [2], the development of dedicated instruments and surgical techniques has
7 led to the use of laparoscopic distal gastrectomy (LDG) to treat GC [3]. However, laparoscopic total
8 gastrectomy (LTG) requires a high degree of skill in performing gastrectomy with systematic
9 lymphadenectomy, as well as postresection reconstruction; indeed, these procedures are difficult even
10 for experienced laparoscopic surgeons [4]. LTG has many advantages; however, it is associated with
11 a high incidence of postoperative complications (10–40%) [5-7]. Therefore, surgeons have some
12 difficulties in making decisions regarding the performance of LTG in elderly patients. Some authors
13 have reported the safety and effectiveness of LDG in elderly patients [8, 9]. However, few studies of
14 LTG in elderly patients, especially those aged ≥ 80 years, have been reported. Therefore, it is necessary
15 to study the safety, effectiveness, and prognosis of LTG in elderly patients.

16 In this study, we aimed to clarify surgical outcomes and prognosis in the elderly patient group (EG;
17 age ≥ 80 years) who underwent LTG with curative intent, compared with a non-elderly patient group
18 (non-EG; age < 80 years). A propensity score matching (PSM) method was used to compare the short-

term outcomes and prognosis between the EG and non-EG of LTG for GC in a multicenter setting.

This is the first multicenter retrospective study to compare EG and non-EG in LTG using the PSM method.

Material and Methods

Patients

We retrospectively reviewed patients who underwent LTG for GC at six institutions (Hokkaido University Hospital, Teine Keijinkai Hospital, Obihiro-Kosei General Hospital, Hokkaido Gastroenterology Hospital, Tonan Hospital, and Asahikawa City Hospital) between January 2004 and December 2018. All patients who underwent curative LTG were included in the analysis. 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 [10]. The primary indication for LTG was stage I GC based on the Japanese Society of Endoscopic Surgery (JSES) guidelines [11]; 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, time to recurrence, and prognosis were collected. Surgical outcomes, including operative time, estimated blood loss, postoperative complications, and length of postoperative hospital stay were recorded.

Patients were categorized into an elderly patient group (EG; age ≥ 80 years) and non-elderly patient group (non-EG; age < 80 years). 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

The gastric procedure type (resection and reconstruction) was determined based on the experience and preference of a surgeon accredited through the endoscopic surgical skill qualification system of the JSES [11]. In cases where the operating surgeon did not possess this qualification, a qualified surgeon supervised the surgery. The extent of lymph node dissection was determined according to the JGCA guidelines [10]. Patients who underwent D2 lymph node dissection and patients who underwent D2–No.10 lymph node dissection were included in D1+. Patients were divided into three groups based on the Clavien–Dindo (CD) postoperative complication classification grade [12, 13].

Postoperative follow-up

All patients were observed every 3 months after surgery. Hematological analysis (including tumor marker analysis for carcinoembryonic antigen and carbohydrate antigen 19-9) was performed at each visit. Abdominal computed tomography 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), disease-specific survival (DSS), and disease-free survival (DFS) were collected. OS was defined as the time from surgery to death for any reason or interruption of follow-up. DSS was defined as the time from surgery to death from GC, including operative mortality or interruption of follow-up. DFS was defined as the time from surgery to death from GC, the first recurrence of GC, or the interruption of follow-up.

Statistical analysis

PSM was performed using a logistic regression model to mitigate the selection bias in the present study. The parameters used for PSM were age, sex, BMI, American Society of Anesthesiologists physical status, splenectomy, clinical stage, surgical method, and lymph node dissection. We matched the logit of the propensity score within 0.2 standard deviations of the value based on the recommendations by Austin [14]. Categorical variables were analyzed using the chi-squared test before propensity score matching and the McNemar and Wilcoxon signed-rank tests after PSM. Continuous variables were examined using the unpaired t-test before PSM and the paired t-test or

Wilcoxon signed-rank test after propensity score matching. Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Statistical significance was set at $P < 0.05$. Statistical analysis was performed using the JMP® 15 software (SAS Institute Inc., Cary, NC, USA).

Results

Patients' backgrounds

Table 1 shows the clinical characteristics and surgical outcomes of the study population. A total of 440 patients were included, comprising 305 men (69.3%) and 135 women (30.7%), with a median age of 67 years (range 25–88) and median BMI of 22.9 kg/m² (range 13.6–38.9). The American Society of Anesthesiologist's physical status (ASA-PS) was $\geq$ II in 318 patients (72.3%), clinical JCGC stage was $\geq$ II in 135 patients (30.7%), D2 lymphadenectomy was performed in 68 patients (15.5%), the median operation time was 329 (range, 123–762) minutes, the median operative blood loss was 50 (range, 0–1940) mL, postoperative complications CD $\geq$ IIIa occurred in 66 patients (15.0%), and the median postoperative hospital stay was 14 (range, 6–210) days. After applying our exclusion criteria (neoadjuvant therapy, cStage IV, resection of other organs, and total number of harvested lymph nodes $\leq$ 15), 395 patients were included in the subgroup we evaluated for PSM. In this study, for accurate prognostic analysis, we included more than 16 lymph nodes dissected using the exclusion criteria [15].

In total, 37 patients in the elderly group (EG; age ≥ 80 years) were individually matched to 37 patients in the non-elderly group (non-EG; age < 80 years) (Fig. 1). The clinicopathological characteristics of the 395 patients who underwent curative LTG and 74 propensity score-matched patients are shown in Table 2. In the propensity score-matched patients, as determined by the study design, sex, BMI, ASA-PS, extent of lymph node dissection, and clinical JCGC stage distributions between the EG and non-EG groups were comparable.

Surgical outcomes

The surgical outcomes and postoperative complications of the 395 patients who underwent curative LTG and propensity score-matched patients are shown in Table 3. In the propensity score-matched group of patients, there was no significant difference in blood loss, number of harvested lymph nodes and the method of esophagojejunostomy. Furthermore, there was no difference in the rate of postoperative complications between the two groups (Table 4). The median operative time was significantly shorter in the EG than in the non-EG (EG vs. non-EG; 260 minutes [range 171–525] vs. 335 minutes [range 172–553], respectively, $P = 0.003$). The median postoperative hospital stay was significantly longer in the EG than in the non-EG (EG vs. non-EG; 16 days [range 8–82] vs. 12 days [range 7–65], respectively, $P = 0.008$).

Prognosis

The results of histological examinations of resected specimens were similar in both groups;

therefore, the pathological stages according to the JCGC were similar ($P=0.726$). The median follow-up periods of the EG and non-EG groups were 11.5 (1–106.4 months) and 35.7 (1–110.0) months, respectively. The number of patients who received adequate adjuvant chemotherapy according to the JGCA guidelines [8] was significantly lower in the EG than in the non-EG (EG vs. non-EG; 4 patients [21.1%] vs. 16 patients [84.2%], respectively, $P=0.047$). During the follow-up period, postoperative recurrence was observed in eight patients (21.6%) in the EG and nine patients (24.3%) in the non-EG, with no statistical significance ($P=0.782$). There was no difference in the recurrence site or length of recurrence between the two groups (Table 5). The 5-year OS rates were 79.1% in all patients, were 58.5% and 91.5% in the EG and non-EG groups, respectively. The Kaplan–Meier analysis for OS indicated that there was a significant difference between the two groups ($P=0.031$). The 5-year DSS and DFS rates were 80.7% and 56.9% in all patients, and were 62.1% and 52.9% in the EG, and 91.5% and 60.8% in the non-EG, respectively. The Kaplan–Meier analysis for DSS and DFS indicated that there was no significant difference ($P=0.068$ and $P=0.132$, respectively) (Fig. 2). In the 5-year DSS, the Wilcoxon test showed a significant difference between the two groups ($P=0.031$) because the curves of the two groups overlapped at 12 months after surgery.

Discussion

This is the first multicenter retrospective study comparing the surgical outcomes and prognosis of

1 elderly patients aged ≥ 80 years and < 80 years who underwent LTG using PSM. This study aimed to
2 evaluate the short-term outcome and prognosis after LTG in elderly patients with gastric cancer after
3 LTG. After adjustment using PSM, we found no significant differences in the incidence of
4 postoperative complications and recurrence rates between the non-elderly and elderly patients.

5 The average age of patients with gastric cancer undergoing gastrectomy has been increasing in
6 recent years [8]. The natural life expectancy of elderly patients is obviously shorter than that of
7 younger patients, and elderly patients usually have various comorbidities, such as cardiovascular
8 disease [16, 17] and decreased respiratory function, leading to limited use of the procedure. In addition,
9 postoperative complications in elderly patients, such as delirium and sarcopenia, are also problems
10 [18]. In general, elderly patients often have physiological difficulties associated with aging, such as
11 decreased organ function, various complications, and mental imbalance. Surgeons are sometimes
12 hesitant to perform standard gastrectomy with lymphadenectomy in such patients because of the high
13 incidence of age-related morbidity and mortality. In addition, surgeons need to overcome perioperative
14 issues specific to elderly patients, such as postoperative delirium, sarcopenia, and frailty [18-20]. In
15 this study, many patients in the EG group did not receive adjuvant chemotherapy according to the
16 JGCA guidelines [10] due to a high preoperative complication rate. As a result, the time to relapse was
17 shorter. There was no difference in postoperative complications ($CD \geq II$) between the groups. In
18 addition, no deaths were observed in the hospital.

Laparoscopic surgery with minimal destruction of the body wall might be a beneficial approach for the elderly because people with reduced organ function are more susceptible to surgical invasion. Studies on long-term prognosis suggest an association between postoperative complications and long-term survival in several malignancies, including breast cancer, colorectal cancer, and peripancreatic cancer [21-24]. Furthermore, several reports have indicated that postoperative complications are associated with the prognosis of patients with GC [25, 26]. In our previous multicenter retrospective study on the long-term prognosis of laparoscopic surgery for GC, postoperative complications were also shown to be associated with survival [27]. Therefore, ensuring the safety of LTG may be important for the short- and long-term outcomes of patients with GC. The same was true in the present study for the occurrence of severe complications of CD grade $\geq$ III after LTG (EG vs. non-EG; 16.2 vs. 10.8%, respectively, $P=0.495$). There was no difference in long-term prognosis (DSS and DFS) between the two groups ($P=0.068$ and $P=0.132$, respectively), which may be due in part to the similarity of complications. In order to keep the postoperative complication rate low in elderly patients, surgeons must balance the complication rate with trefraioe oncological survival rate. The six affiliated hospitals that participated in this study are high-volume centers in our prefecture, and each facility has a JSES-certified laparoscopic surgeon who performed the procedure as a surgeon or teaching assistant in this study. The difference in the median postoperative hospital stay between the two groups was attributed to differences in the criteria for discharge among the affiliated hospitals. In addition, the median

postoperative hospital stay was 14 days, because the fast-track protocol was not applied in the early stages of the introduction of the LTG.

However, the number of patients who received adequate adjuvant chemotherapy according to the JGCA guidelines [10] was significantly lower in the EG than in the non-EG ($P=0.047$). The reasons why adjuvant chemotherapy was not administered in the EG are as follows. Adjuvant chemotherapy was not indicated due to poor postoperative general condition, and physicians refrained from adjuvant chemotherapy at their discretion. However, postoperative recurrence was observed in eight patients (21.6%) in the EG and nine patients (24.3%) in the non-EG, which was not significantly different ($P=0.782$). There was no difference in the recurrence site or length of recurrence between the two groups, and there was no effect of adjuvant chemotherapy on OS, DSS, or DFS (hazard ratio [HR] = 1.187, 95% confidence interval [CI]: 0.149–9.395; HR = 2.088, 95% CI: 0.242–17.963; and HR = 2.653, 95% CI: 0.936–7.519, respectively). Although prior randomized controlled studies indicated that postoperative adjuvant treatment in patients who underwent D2 gastrectomy could improve the 5-year DFS and OS, the subgroup analyses showed that the survival benefits decreased with increasing age. Furthermore, the ACTSGC study showed no statistically significant effects of postoperative chemotherapy on DFS or OS in patients older than 70 years (DFS: HR = 0.779, 95% CI: 0.527–1.151; OS: HR = 0.706, 95% CI: 0.490–1.017) [28]. Similar results for OS were observed in the CLASSIC study for patients older than 65 years (HR = 0.70, 95% CI: 0.4–1.12) [29]. These results might be due

1 to the considerably higher incidence of comorbidities, higher risk of complications, and shorter life
2 expectancy in elderly patients [30]. Nevertheless, when considering these conflicting results, whether
3 adjuvant chemotherapy should be administered to elderly patients with GC after D2 gastrectomy
4 remains a dilemma for physicians. In accordance with the consensus guidelines of the European
5 Society for Medical Oncology (ESMO), radical gastrectomy with free margins and an adequate
6 lymphadenectomy, and if indicated along with perioperative neoadjuvant chemotherapy, is the
7 standard of care in patients with advanced gastric cancer [31,32]. In Japan, there is still no evidence
8 of perioperative neoadjuvant therapy for gastric cancer. In the future, we look forward to the inclusion
9 of appropriate chemotherapy for elderly patients in the guidelines.

10 This study has several limitations. This was a retrospective, observational, and non-experimental
11 study. In the present study, most LTGs were performed by laparoscopic surgery experts as operators
12 or teaching assistants. In this study, 69.3% of the patients had stage I gastric cancer and only 15.5%
13 underwent D2 lymph node resection. In addition, 72.3% of all patients were ASA 1 or 2 and in
14 relatively good general condition, and there was a selection bias. The two study groups have
15 significantly different median postoperative follow-up periods (EG 11.5 months vs. non-EG 35.7
16 months). In this study, the number of cases was small because each institution was strict about the
17 indications for LTG. This may influence outcomes in term of OS, DSS, and DFS. A well-designed
18 randomized controlled trial is required to validate our findings. Selection bias was a limitation because

1 the cohort consisted of surgical patients for whom the surgeon decided the surgical indication
2 according to performance status, especially in EG. This study was conducted over a rather long period
3 between 2004 and 2018, which could have been associated with historical biases in terms of treatment
4 strategy and perioperative management, which might dictate the short-term and prognostic outcomes
5 after gastrectomy.

7 **Conclusions**

8 LTG seems to be safe and feasible for elderly patients. LTG has had a limited effect on morbidity,
9 disease recurrence, and survival in elderly patients. Therefore, age should not prevent elderly patients
10 from benefitting from LTG. We believe that guidelines are needed to determine the appropriate extent
11 of lymph node dissection and adjuvant chemotherapy for elderly patients.

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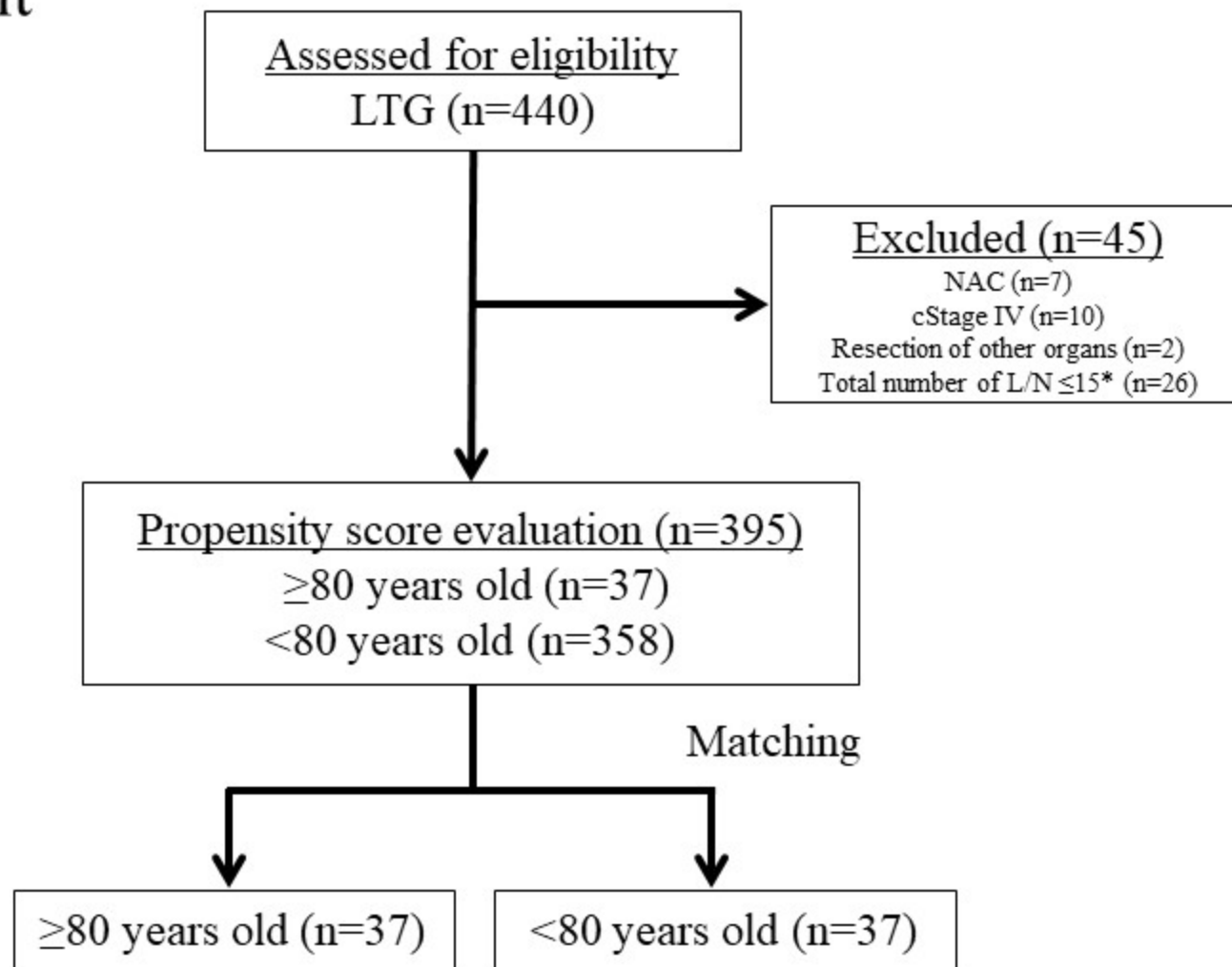
Figure legends

Fig. 1 Study enrollment. LTG: laparoscopic total gastrectomy; NAC: Neoadjuvant therapy

* In this study, for accurate prognostic analysis, we included the number of lymph nodes dissected to more than 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

Enrollment



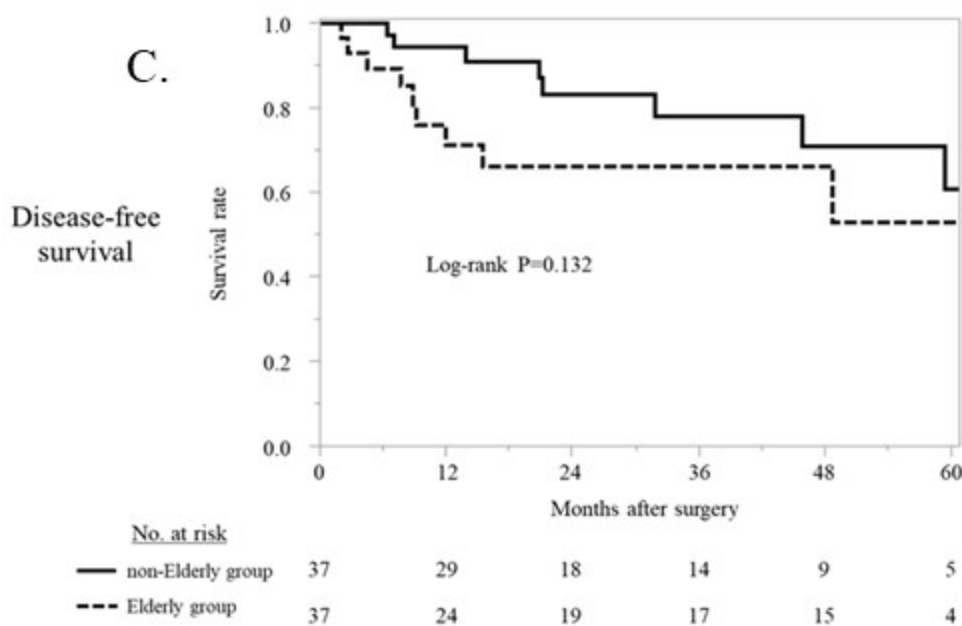
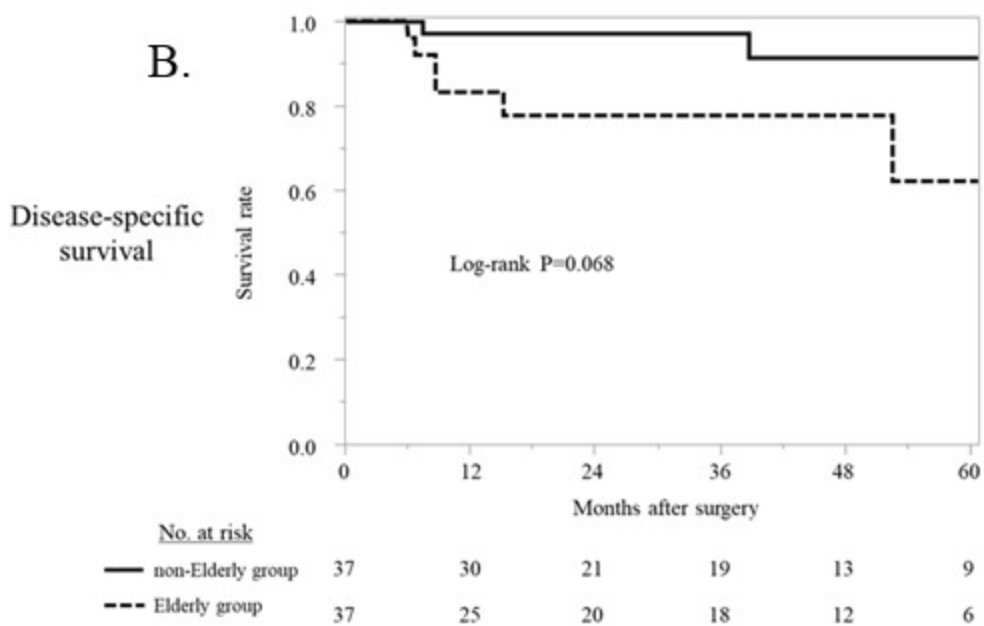
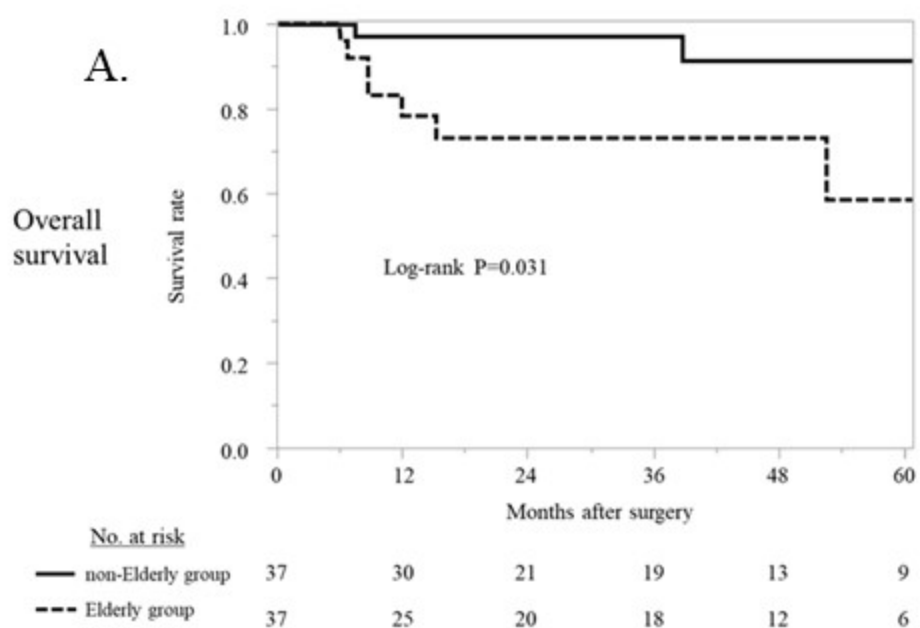


Table 1. Clinical features and surgical outcomes of the study population

Variable	Overall (n=440)
Gender (M/F)	305/135
Age (year) (median, range)	67 (25-88)
BMI [†] (kg/m ²) (median, range)	22.9 (13.6-38.9)
ASA-PS* (≤II) (patients,%)	318 (72.3%)
Clinical JCGC stage** (≥II) (patients,%)	135 (30.7%)
Lymph node dissection (≥D2) (patients,%)	68 (15.5%)
Operation time (min) (median, range)	329 (123-762)
Blood loss (ml) (median, range)	50 (0-1940)
Postoperative complication (CD [§] , ≥IIIa) (patients,%)	66 (15.0%)
Postoperative hospital stays (days) (median, range)	14 (6-210)
[†] Body mass index, *The American Society of Anesthesiologist's physical status, **According to the Japanese classification of gastric carcinoma: 3rd English edition, [§] Clavien-Dindo, classification	

Table 2. Patient's characteristics who underwent LTG before and after propensity score matching

	Unmatched patients (n=395)			Propensity-matched patients (n=74)		
	EG (n=37)	non-EG (n=358)	<i>p</i> value	EG (n=37)	non-EG (n=37)	<i>p</i> value
	Number	Number		Number	Number	
Sex (%)			0.585			0.619
Male	24 (64.9)	248 (69.3)		13 (35.1)	11 (29.7)	
Female	13 (35.1)	110 (30.7)		24 (64.9)	26 (70.3)	
BMI [†] (kg/m ²), median (range)	22.8 (13.6-38.9)	23.1 (15.0-30.9)	0.951	23.1 (15.6-33.4)	22.2 (14.9-34.3)	0.317
ASA-PS* (%)			0.014			0.740
1-2	32 (86.5)	343 (95.8)		32 (86.5)	34 (91.9)	
3-4	5 (13.5)	15 (4.2)		5 (13.5)	3 (8.1)	
Clinical JCGC stage** (%)			0.570			0.848
I	22 (59.5)	251 (75.2)		22 (59.5)	22 (59.5)	
II	11 (29.7)	75 (16.8)		11 (29.7)	9 (24.3)	
III	4 (10.8)	32 (8.0)		4 (10.8)	5 (13.5)	

[†] 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 and postoperative course in patients who underwent curative LTG before and after propensity score matching

	Unmatched patients (n=395)			Propensity-matched patients (n=74)		
	EG (n=37)	non-EG (n=358)	<i>p</i> value	EG (n=37)	non-EG (n=37)	<i>p</i> value
	Number	Number		Number	Number	
Operative time (min), median (range)	260 (171-525)	330 (123-762)	<0.001	260 (171-525)	335 (172-553)	0.003
Blood loss (ml), median (range)	102.5 (0-909)	50 (0-1940)	0.103	10 (0-909)	40 (0-850)	0.645
Extent of lymph node dissection			<0.001			1.000
D1/D1+ (%)	37 (100.0)	296 (82.7)		37 (100.0)	37 (100.0)	
D2 (%)	0	62 (17.3)		0	0	
Number of harvested lymph nodes, median (range)	29 (17-90)	41 (16-114)	0.028	29 (17-90)	37 (18-90)	0.645
Postoperative complication (%)						
CD ≥ II	9 (24.3)	79 (22.1)	0.756	9 (24.3)	5 (13.5)	0.233
CD ≥ III	6 (16.2)	55 (15.4)	0.892	6 (16.2)	4 (10.8)	0.495
Postoperative hospital stay (day), median (range)	16 (8-82)	13 (6-210)	0.034	16 (8-82)	12 (7-65)	0.008
Mortality (within 30 days)	0	2		0	0	

Table 4. Patient's characteristics who underwent LTG before and after propensity score matching

	Unmatched patients (n=395)			Propensity-matched patients (n=74)		
	EG (n=37)	non-EG (n=358)	<i>p</i> value	EG (n=37)	non-EG (n=37)	<i>p</i> value
	Number	Number		Number	Number	
Pathological JCGC stage* (%)			0.332			0.726
I	17(45.9)	204(57.0)		17(45.9)	16(43.3)	
II	9(24.3)	83(23.2)		9(24.4)	7(18.9)	
III	4(10.8)	32(8.0)		11(29.7)	14(37.8)	
Adjuvant chemotherapy	4	104		4	16	
Recurrence (Y/N)	8/29	49/309	0.191	8/29	9/28	0.782
Recurrence site						
LN (Regional/Para Ao/Distant)	1/0/0	2/5/2		1/0/0	0/1/1	
Peritoneum dissemination	4	17		4	1	
Liver metastasis	3	14		3	3	
Lung metastasis	0	6		0	1	
Brain metastasis	0	1		0	1	
Bone metastasis	0	1		0	0	
Port site recurrence	0	1		0	0	
Length of recurrence (day), median (range)	249.5 (60-1480)	452 (72-2289)	0.081	249.5 (60-1480)	713 (22-3079)	0.068

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