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Comparative Outcomes of Laparoscopic Gastrectomy and Open Gastrectomy for Scirrhous Gastric Cancer: A Multicenter Retrospective Cohort Study

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Objective: A multicenter retrospective cohort study was performed to compare the outcomes of laparoscopic gastrectomy (LG) versus open gastrectomy (OG) for scirrhous gastric cancer (GC) as a unique subtype also known as type 4 gastric cancer or linitis plastica.

Background: Although data on the efficacy and safety of LG as an alternative to OG are emerging, the applicability of LG to scirrhous GC remains unclear.

Methods: Patients with clinical type 4 GC undergoing gastrectomy at 13 hospitals from 2005 to 2015 were retrospectively reviewed. As the primary endpoint, we compared overall survival (OS) between the LG and OG groups. To adjust for confounding factors, we used multivariate Cox regression analysis for the main analyses and propensity-score matching for sensitivity analysis. Short-term outcomes and recurrence-free survival were also compared.

Results: A total of 288 patients (LG, 62; OG, 226) were included in the main analysis. Postoperative complications occurred in 25.8% and 30.1%, respectively (P = 0.44). No significant difference in recurrence-free survival was observed (P = 0.72). The 5-year OS rates were 32.4% and 31.6% in the LG and OG groups, respectively (P = 0.60). The hazard ratio (LG/OG) for OS was 0.98 (95% confidence interval [CI], 0.65–1.43) in the multivariate regression analysis. In the sensitivity analyses after propensity-score matching, the hazard ratio for OS was 0.92 (95% CI, 0.58–1.45).

Conclusions: Considering the hazard ratios and 95% CIs for OS, LG for scirrhous GC was not associated with worse survival than that for OG.

INTRODUCTION

The standard treatment for gastric cancer (GC) is multimodality therapy that includes resection.[1] Recently, the efficacy and safety of laparoscopic gastrectomy (LG) as an alternative to open gastrectomy (OG) has also been demonstrated; in many large-scale randomized controlled trials (RCTs), LG showed similar surgical and oncological outcomes.[2–8] In addition, there is evidence suggesting that LG is associated with faster postoperative recovery, shorter hospitalization, and a better quality of life.[2–5]

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Y.F. and K.O. designed the study, and Y.F. wrote the initial draft of the article. Y.F., T.N., S.T., S.H., K.H., and S.T. contributed to analysis and interpretation of data. T.N. and K.O. assisted in the preparation of the article. All other authors have contributed to data collection and interpretation, and critically reviewed the article. All authors approved the final version of the article and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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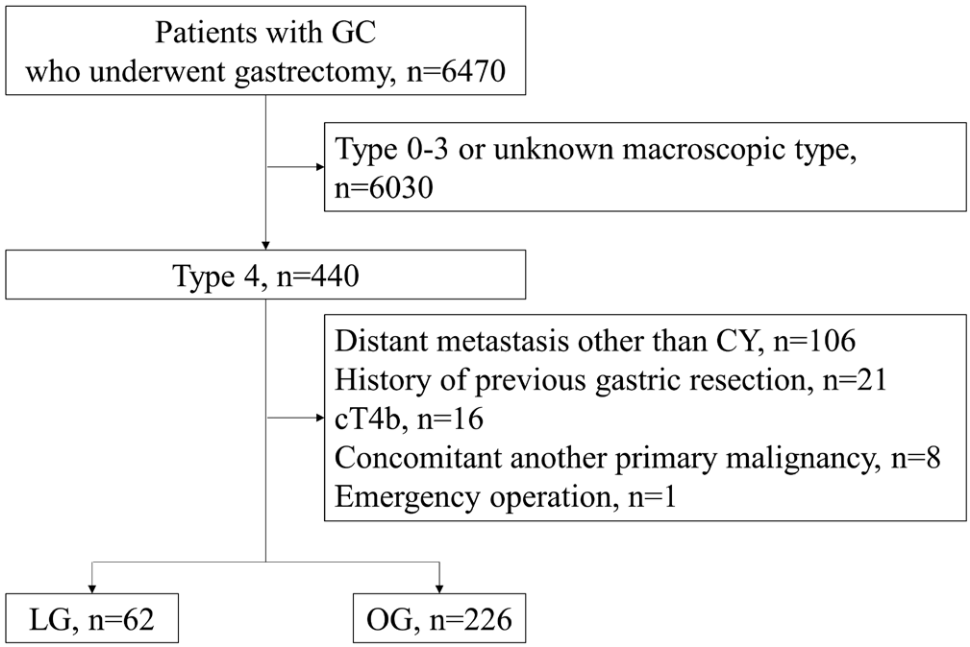

FIGURE 1. Patient flow diagram. GC indicates gastric cancer; CY, peritoneal lavage cytology; LG, laparoscopic gastrectomy; OG, open gastrectomy.

However, the safety and efficacy of LG for scirrhous GC, which is a unique subtype also known as type 4 GC or linitis plastica, remains unclear.[9] Patients with scirrhous GC were rarely included in previous RCTs, which have typically targeted distal gastrectomy; most scirrhous GCs require total gastrectomy. In addition, there are generally fewer patients with scirrhous GC, and they have a worse prognosis than patients with other types of GC.[10,11] From a surgical point-of-view, some surgeons have been concerned that when treating advanced or large tumors, it is sometimes impossible not to inadvertently pinch or at least touch them by metal graspers, which may cause cancer cell spillage, with potential risk of peritoneal metastasis.[12] Therefore, clinical research is warranted to evaluate the safety and efficacy of LG in this distinct patient group.

However, no study evaluating the impact of LG on short- and long-term outcomes in patients with scirrhous GC has been published so far. This multicenter retrospective cohort study aimed to compare the outcomes of LG versus OG, with an emphasis on patients with scirrhous GC.

METHODS

Patients

We retrospectively reviewed patients with GC who underwent gastrectomy between January 2005 and December 2015 at 13 institutions participating in the Kyoto Esophageal and Gastric Surgery Study Group. The macroscopic tumor type was categorized in accordance with the Japanese classification for gastric carcinoma. Patients diagnosed with clinical type 4 GC were identified for potential study enrollment. Although the term "scirrhous" refers to the growth characteristics and histologic findings of cancer tissue, the terms scirrhous GC and type 4 GC are used to describe almost the same type of GC.[13] The characteristics of type 4 GC include the lack of marked ulceration or raised margins, thickening and induration of the gastric wall, and unclear tumor margins. Diffuse and infiltrative type tumors are classified as type 4 GC. Macroscopic type was diagnosed by a clinician based on the endoscopic examination and upper gastrointestinal series in accordance with the classification.[14] The following patients were excluded from the study (Figure 1): those who had (i) tumors with unknown macroscopic type, (ii) cT4b tumor, (iii) a history of previous gastric resection, (iv) any other primary malignancy, (v) distant metastasis, and (vi) received emergency operation. Patients with positive peritoneal cytology (CY) in the absence of other noncurative factors were included in the analysis because the prognosis of these patients was shown to be identical to that of patients with type 4 cancer with P0CY0.[11,15–17]

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committees of Kyoto University (R1850) and all the hospitals involved. We collected data from original medical records according to the predetermined definitions described below.

Perioperative Treatment and Surgery

Perioperative treatments and surgery were generally performed in accordance with the Japanese Gastric Cancer Treatment Guidelines.[1,17,18] Neoadjuvant chemotherapy (NAC) was offered preoperatively in a clinical trial or at the discretion of clinicians.[19]

OG is the standard treatment for advanced cancer according to the guidelines, and LG was selected at the discretion of the surgeons, institutions, and patients. Moreover, patients underwent LG when they participated in a clinical trial examining the efficacy of LG for advanced GC.[20] LG was mostly performed or supervised by surgeons qualified by the Japan Society for Endoscopic Surgery or board-certified with equivalent qualifications. All surgical procedures including OG were performed at designated cancer-care hospitals in Japan, which are relatively large-scale institutions with 358–1,121 beds. Our gastrectomy procedures have been standardized through trimonthly interinstitutional video conferences since 2005 and have been described in detail elsewhere.[21–25] In this study, patients were categorized into LG and OG groups based on the surgical approach at the time of starting resection (intent-to-treat approach). Lymphadenectomy was performed according to the Japanese guidelines, which recommend D2 lymphadenectomy for advanced or N+ tumors.[1,17,18] As the extent of lymphadenectomy differs between different versions of the guidelines, data pertaining to the extent of lymphadenectomy was collected in accordance with the latest guidelines.[1]

Adjuvant chemotherapy with S-1 was administered for patients with Stage II/ III cancer during the 12 months after surgery. Patients were usually followed for 5 years after surgery and were subjecting to blood tests and chest/abdominal computed tomography scan every 3 to 6 months as per the guidelines.[1]

Outcomes

The primary outcome was overall survival (OS), defined as the number of days of survival after initial treatment. Patients who could not be traced or who were still alive were censored at the date of the last contact.

The secondary outcomes were as follows: (1) operative time, (2) intraoperative bleeding, (3) intraoperative transfusion, (4) the number of harvested lymph nodes, (5) residual tumor, (6) postoperative complications with a severity ≥grade 2 according to the Clavien–Dindo classification,[26] (7) length of hospitalization after surgery, (8) initiation of adjuvant chemotherapy, (9) recurrence sites, and (10) recurrence-free survival (RFS). RFS was defined as the number of days from initial treatment to relapse or death from any cause. Patients with macroscopic residual tumors were dealt with as those who had the event at the date of surgery. Patients who were still alive without recurrence were censored at the date of the last contact.

Data Collection for Risk Adjustment

Preoperative variables that were reported to impact on short- and long-term outcomes in patients with GC were identified by a systematic search for previous studies on this topic. The following preoperative variables to be used for risk adjustment were decided through several research meetings before data collection. After that, preoperative data on age, sex, hemoglobin, serum albumin, body mass index (BMI), history of upper abdominal surgery, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), invasion into adjacent organs, and histology on biopsy were collected from the institutions involved according to previous studies.[27–32] The T and N classification were used in accordance with the Japanese classification of gastric carcinoma.[14] Data pertaining to the American Society of Anesthesiologists Performance Status (ASA-PS) as assessed preoperatively by the anesthesiologist were collected. Comorbidity was assessed according to the Charlson Comorbidity Index (CCI); however, GC, which was the disease under investigation, was not included in the index.[33] CCI was categorized into 2 categories in the multivariate analysis, ≤2 and ≥3, based on a previous study.[34] Tumor lesions were classified into 2 categories: whole (more than 2/3 of the stomach) and partial (not more than 2/3 of the stomach). Tumor stenosis was defined as the condition in which the gastroscope could not pass through the tumor region.

TABLE 1.

Patient Characteristics and Operative Features

Factor	Category	LG (n = 62)		OG (n = 226)		*P*
Year of operation	2005–2009	4	(6.5%)	103	(45.6%)	<0.01
	2010–2015	58	(93.5%)	123	(54.4%)	
Age*, years		69	(62–76)	68	(57–76)	0.42
Sex	Male	38	(61.3%)	130	(57.5%)	0.66
Body mass index*, kg/m²		21.5	(19.5–23.3)	21.0	(18.8–23.4)	0.33
ASA-PS	I-II	58	(93.5%)	208	(92.0%)	1.00
	III	4	(6.5%)	18	(8.0%)	
Charlson Comorbidity Index	Low	35	(56.5%)	146	(64.6%)	0.42
	Medium	22	(35.5%)	68	(30.1%)	
	High, very high	5	(8.1%)	12	(5.3%)	
Upper abdominal surgery history	+	11	(17.7%)	24	(10.6%)	0.13
Hemoglobin*, g/dL		12.7	(11–13.4)	12.4	(10.8–14.0)	0.94
Serum albumin*, g/dL		3.8	(3.6–4.2)	3.9	(3.4–4.2)	0.45
CEA*, ng/mL		2.3	(1.3–3.4)	2.1	(1.3–4.0)	0.91
CA19-9*, U/mL		11.9	(6.4–24.3)	11.2	(5.7–28.0)	0.90
Tumor stenosis	+	1	(1.6%)	25	(11.1%)	0.02
Tumor lesion	Partial	25	(40.3%)	113	(50.0%)	0.20
	Whole	37	(59.7%)	113	(50.0%)	
Esophageal invasion	+	5	(8.1%)	15	(6.6%)	0.78
Duodenum invasion	+	4	(6.5%)	16	(7.1%)	1.00
Histology in biopsy	Differentiated	7	(11.3%)	34	(15.0%)	0.79
	Undifferentiated	53	(85.5%)	183	(81.0%)	
	Others	2	(3.2%)	9	(4.0%)	
Neoadjuvant chemotherapy	+	13	(21.0%)	50	(22.1%)	1.00
cT	≤T2	5	(8.1%)	17	(7.5%)	0.79
	T3, T4a	57	(91.9%)	209	(92.5%)	
cN	–	24	(38.7%)	64	(28.3%)	0.12
	+	38	(61.3%)	162	(71.7%)	
CY	No test	8	(12.9%)	36	(15.9%)	0.55
	Negative	43	(69.4%)	161	(71.2%)	
	Positive	11	(17.7%)	29	(12.8%)	
Extent of resection	DG	10	(16.1%)	42	(18.6%)	0.72
	TG	52	(83.9%)	184	(81.4%)	
Lymph node dissection	D1	12	(19.4%)	36	(15.9%)	0.56
	D2	50	(80.6%)	190	(84.1%)	
Omentum resection	+	35	(56.5%)	166	(73.5%)	0.01
Combined resection	Gallbladder	4	(6.5%)	125	(55.3%)	<0.01
	Spleen	15	(24.2%)	89	(39.4%)	0.04
	Pancreas	1	(1.6%)	7	(3.1%)	1.00
	Other	5	(8.1%)	19	(8.4%)	1.00

*Median (inter quartile range).

ASA-PS indicates American Society of Anesthesiologists Performance Status; CA19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; CY, intraoperative peritoneal lavage cytology; DG, distal gastrectomy; LG, laparoscopic gastrectomy; OG, open gastrectomy; TG, total gastrectomy.

TABLE 2.
Short-term Outcomes

Factor	LG (n = 62)		OG (n = 226)		*P*
Operative time*, min	400	(325–471)	276	(230–330)	<0.01
Bleeding*, g	70	(25–253)	460	(249–741)	<0.01
Transfusion	0	(0.0%)	13	(5.8%)	0.08
Conversion	4	(6.5%)	–	–	–
Number of harvested lymph nodes*	44	(30–63)	43	(32–58)	0.97
Residual tumor					
Macroscopic residual tumor	2	(3.2%)	3	(1.3%)	0.29
Microscopic resections margin	9	(15.0%)	27	(11.9%)	0.52
Grades of complication†					
≥Grade2	16	(25.8%)	68	(30.1%)	0.44
Pancreatic fistula	6	(9.7%)	20	(8.8%)	0.81
Anastomotic leakage	4	(6.5%)	17	(7.5%)	1.00
Intraabdominal abscess	3	(4.8%)	17	(7.5%)	0.58
Wound infection	3	(4.8%)	17	(7.5%)	0.58
Pneumonia	2	(3.2%)	11	(4.9%)	0.74
Ileus, Obstruction	1	(1.6%)	7	(3.1%)	1.00
Cholecystitis	0	(0.0%)	1	(0.4%)	1.00
Others	1	(1.6%)	11	(4.9%)	0.47
≥Grade3	8	(12.9%)	35	(15.5%)	0.69
≥Grade3b	1	(1.6%)	11	(4.9%)	0.47
Grade5	0	(0.0%)	2	(0.9%)	1.00
Length of hospitalization*, day	14.5	(11–19)	16.0	(13–24)	0.01
Postoperative chemotherapy	49	(79.0%)	173	(76.5%)	0.86

*Median (inter quartile range).
†Clavien-Dindo classification.
LG indicates laparoscopic gastrectomy; OG, open gastrectomy.

Sample Size Calculation and Analysis of Primary Outcome

To estimate the optimal approximate sample size, our research team performed a questionnaire survey in each institution before data collection. According to the survey, the predicted ratio of patients who underwent OG and LG was 2:1. The expected median OS was approximately 900 days. In a previous RCT examining the oncological safety of LG for advanced GC, the noninferiority margin of hazard ratio (HR) was set at 1.46. Assuming an HR of 1.0, the sample size for the upper limit of the 95% confidence interval (CI) to be <1.46 was 279, while according to the survey, the expected number of eligible patients was 300.[8] Our research team expected that the oncological safety of LG would be evaluated, although this study was not a confirmatory clinical trial.

As for the primary outcome, the Cox proportional hazards model was used to reduce any confounding impact on outcomes and examine the association between OS and surgical approach. Surgical approach and factors with *P* values <0.1 in the univariate analysis were included in the multivariate analysis.

Sensitivity Analysis by Propensity-score Matching

As the sample size was not expected to be as large as stated above, conventional multivariate analyses were used for the primary endpoint. To ensure a better balance in patient background data between the groups and confirm the robustness of the results of the conventional multivariate analyses, we performed a sensitivity analysis using propensity-score matching (PSM). Individual propensity scores were calculated using a logistic regression model, including the following preoperative factors; year of operation, age, sex, BMI, ASA-PS, CCI, upper abdominal surgery history, hemoglobin, serum albumin, carcinoembryonic antigen, carbohydrate antigen 19-9 (CA19-9), tumor stenosis, tumor lesion, esophageal invasion, duodenal invasion, biopsy histology, NAC, clinical T (cT), clinical N (cN), CY, extent of resection, and lymph-node dissection. After nearest-neighbor 1-to-1 matching with a caliper width of 0.2 without replacement, the covariate balance was checked using the standardized mean difference (SMD). A SMD <0.2 was considered trivial. After matching, primary and secondary outcomes were compared between the 2 groups.

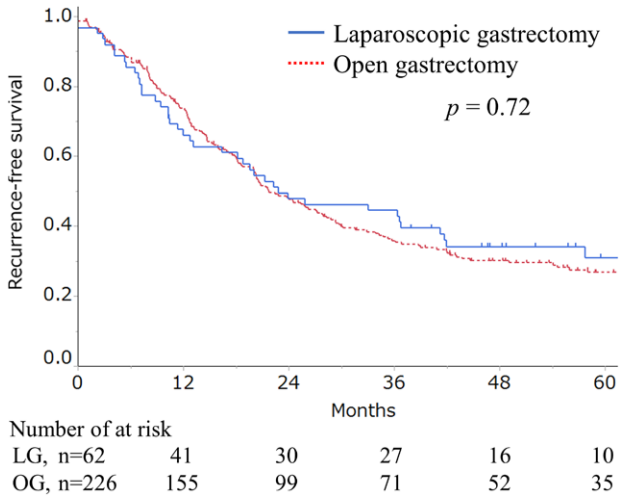

FIGURE 2. Recurrence-free survival curves using the Kaplan-Meier method and the number of at-risk patients. There was no significant difference in the recurrence-free survival between the 2 groups (*P* = 0.72).

Statistical Analysis

Continuous variables were expressed either as mean and standard deviation and compared using the *t* test or as median and range or interquartile range (IQR) and compared using the Mann–Whitney *U* test, as appropriate. Categorical data were expressed as frequencies and proportions and were compared using Fisher's exact test. Survival curves were estimated for each group using the Kaplan–Meier method and compared statistically using the log-rank test.

All probability (*P*) values were 2-sided, and *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed using JMP Statistical Software Version 14 (SAS-Institute Inc., Cary, NC).

RESULTS

Patient Flow and Characteristics

The patient flow is illustrated in Figure 1. A total of 6,470 patients who underwent gastrectomy for GC were reviewed, and 440 (6.8%) with type 4 cancer were identified. Of these, patients with distant metastasis, a history of previous gastric resection, cT4b tumor, concomitant another primary malignancy, or emergency operation were excluded. Accordingly, 288 patients were included in the analyses.

Patient characteristics and operative features are summarized in Table 1. LG and OG were performed in 62 and 226 patients, respectively. Patients who underwent surgery in the first half of the study period were likely to be involved in the OG group. Also, a larger proportion of patients with tumor stenosis were included in the OG group. Furthermore, the OG group had a higher proportion of patients undergoing resection of the omentum, gallbladder, and spleen than the LG group. There were no significant differences between the groups with regard to other factors.

Short-term Outcomes

Table 2 shows a comparison of the short-term outcomes between the groups. The operative time was significantly longer, and the amount of bleeding was lesser in the LG group.

Open conversion was required for 4 patients in the LG group. The reasons for conversion were bulky tumor (1 case), adhesion (1 case), and positive resection margin (2 cases). Negative margins could not be achieved in either patient even after conversion to open surgery because of the avoidance of

TABLE 3.

Recurrence Sites

	LG (n = 62)		OG (n = 226)		*P*
Recurrence	42	(67.7%)	153	(67.7%)	1.00
Peritoneum	36	(58.1%)	136	(60.2%)	0.77
Liver	3	(4.8%)	6	(2.7%)	0.41
Lung	1	(1.6%)	4	(1.8%)	1.00
Bone	2	(3.2%)	6	(2.7%)	0.68
Lymph nodes	5	(8.1%)	21	(9.3%)	1.00
Locoregional	8	(12.9%)	16	(7.1%)	0.19
Others	1	(1.6%)	10	(4.4%)	0.47

LG indicates laparoscopic gastrectomy; OG, open gastrectomy.

pancreaticoduodenectomy or thoracotomy. No differences were observed in the number of harvested lymph nodes or the incidence of residual tumor between the groups.

In addition, the incidence of postoperative complications and those with a severity of grade 3 or greater was lower in the LG group but not significantly (25.8% vs 30.1%, $P = 0.44$, 1.6% vs 4.9%, $P = 0.47$). There was no mortality in the LG group, whereas there were 2 in-hospital deaths in the OG group. The length of hospitalization after surgery was significantly shorter in the LG group (14.5 days vs 16.0 days, $P = 0.01$).

Long-term Outcomes

The median observation period (IQR) was 50 months (39–78) in the LG group and 55 months (30–75) in the OG group. The 5-year RFS was 31.1% and 27.0% in the LG and OG groups, respectively. There was no statistical difference in the RFS curves between the 2 groups (Figure 2, $P = 0.72$). No differences were observed in the recurrence sites, including peritoneal recurrence (Table 3).

OS curves are displayed in Figure 3. The 5-year OS rates were 32.4% in the LG group and 31.6% in the OG group. There was no statistical difference in the OS curves between the 2 groups ($P = 0.60$). In the multivariate regression analysis adjusting for variables with P values < 0.1 in the univariate analysis (Table 4), the adjusted HR of LG compared with OG was 0.98 (95% CI, 0.65–1.43; $P = 0.90$). Age, BMI, CCI, CA19-9, stenosis, cN, and extent of resection were identified as independent prognostic predictors.

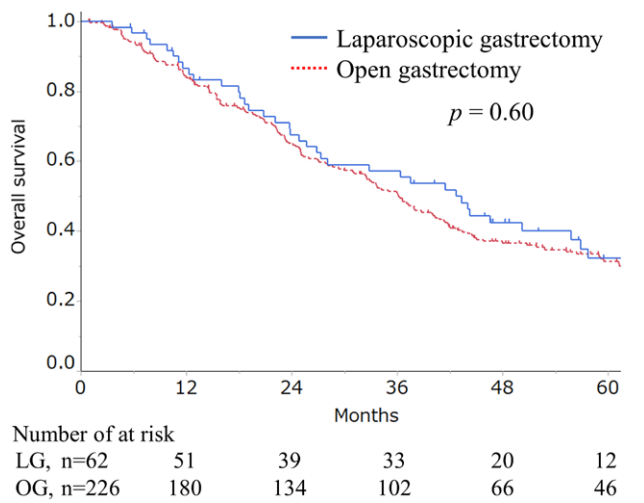

FIGURE 3. Overall survival curves using the Kaplan-Meier method and the number of at-risk patients. There was no significant difference in the overall survival between the 2 groups ($P = 0.60$).

Sensitivity Analyses by Propensity-score Matching

Patient characteristics and operative features after matching are summarized in Supplementary Table 1, http://links.lww.com/AOSO/A27. A total of 114 patients were included in the sensitivity analysis, and the 2 groups were well balanced by PSM.

Supplementary Table 2, http://links.lww.com/AOSO/A28 shows the comparison of short-term outcomes between the groups. The operative time was longer, and the amount of bleeding was less in the LG group. The number of transfusions tended to be fewer and the length of hospitalization tended to be shorter in the LG group, but not significantly so.

RFS and OS curves are shown in Supplementary Figures 1, http://links.lww.com/AOSO/A30, and 2, http://links.lww.com/AOSO/A31. No significant differences in the RFS and OS curves between the groups were observed ($P = 0.73$ and 0.71, respectively). Recurrence sites were similar between the groups (Supplementary Table 3, http://links.lww.com/AOSO/A29). The HR for RFS and OS were 0.92 (95% CI, 0.59–1.45, $P = 0.73$) and 0.92 (95% CI, 0.58–1.45, $P = 0.72$), respectively.

DISCUSSION

Although it is well known that recurrences are very common in patients with scirrhous GC even after curative surgery, in the present study, the RFS curves and recurrence sites were similar between the 2 groups. Kim et al reported that the most frequent recurrence site was the peritoneum (65.7%), which was in line with the present study.[35] Although some surgeons are concerned about the potential risk of cancer cell spillage in LG, our results indicate that LG does not confer an increased risk of peritoneal recurrence compared with OG.[12] In addition to a safe surgical technique, control of peritoneal recurrence is essential to improve the prognosis of scirrhous GC. Further research is warranted to determine the best regimen and the duration of neoadjuvant and adjuvant chemotherapy. In addition, robust clinical trials of early postoperative intraperitoneal chemotherapy may provide insights for controlling residual microscopic disease.[36,37]

The reported incidence of positive resection margin in patients with scirrhous GC ranges between 8.9% and 19.2%[10,35,38]; in the present study, too, the incidence was high in both groups. Although open conversion was required due to positive margin in 2 patients in the LG group, negative margin was not achieved even after the conversion. In addition, we performed a post hoc sensitivity analysis for OS after assigning patients converted to open to the OG group; however, the adjusted HR was almost unchanged (HR 0.95; 95% CI, 0.63–1.40). These results suggest that surgical margin in scirrhous GC is a common issue in both procedures; hence, the application of LG is unlikely to increase the incidence of positive resection margin.

Due caution should be exercised while interpreting our results. In this study, LG was not associated with worse survival than OG; however, it should be noted that LG in this study was performed or supervised by experienced laparoscopic surgeons at relatively high-volume centers. It is well known that LG has a steep learning curve and is affected by tactile and movement limitations due to the use of forceps.[39,40] Considering that LG is not yet a common approach, particularly for total gastrectomy for advanced cancer,[41,42] our results may not be generalizable to all settings. Since 2005, our Kyoto Esophageal and Gastric Surgery Study Group have regularly conducted a multi-institutional video conference where both experienced surgeons as well as surgical residents participate and evaluate unedited videos of each other to help refine the laparoscopic techniques. We believe such continuing education initiatives are essential for facilities that intend to adopt LG for scirrhous type GC. From another perspective, such a technically demanding procedure is better performed by high-volume experienced surgeons or hospitals as the case-volume is reported to be inversely associated with adverse surgical outcomes of gastrectomy.[43,44] We expect that

TABLE 4.

Univariate and Multivariate Analyses for Overall Survival

		Univariate Analyses			Multivariate Analyses		
Variables	**Category**	**Crude HR**	**95% CI**	***P***	**Adjusted HR**	**95% CI**	***P***
Surgical approach	LG/OG	0.91	0.63–1.28	0.59	0.98	0.65–1.43	0.90
Charlson Comorbidity Index	High, very high/low, medium	3.09	1.65–5.28	<0.01	3.16	1.59–5.82	<0.01
CA19-9, U/mL	≥37/<37	1.94	1.33–2.78	<0.01	2.11	1.40–3.10	<0.01
Tumor stenosis	±	1.72	1.07–2.63	0.03	3.15	1.77–5.42	<0.01
Extent of resection	TG/DG	1.53	1.04–2.33	0.03	2.45	1.39–4.43	<0.01
Age	80–65/<65	1.13	0.82–1.54	0.46	0.94	0.67–1.32	0.72
	≥80/<65	2.37	1.54–3.57	<0.01	1.99	1.18–3.30	0.01
cN	±	1.63	1.19–2.26	<0.01	1.52	1.07–2.19	0.02
Body mass index, kg/m²	<18.5/18.5–25	1.38	0.95–1.95	0.09	0.84	0.49–1.37	0.51
	≥25/18.5–25	0.75	0.45–1.18	0.22	1.56	1.05–2.28	0.03
CY	±	1.79	1.18–2.61	0.01	1.51	0.94–2.35	0.08
cT	≥T3/≤T2	3.07	1.61–6.80	<0.01	1.67	0.84–3.81	0.15
Tumor lesion	Whole/partial	1.34	1.01–1.79	0.04	1.29	0.90–1.88	0.16
Lymph node dissection	D1/D2	1.49	0.98–2.18	0.06	1.27	0.75–2.10	0.37
Esophageal invasion	±	2.06	1.20–3.30	0.01	1.29	0.70–2.23	0.39
ASA-PS	III/I, II	2.34	1.26–3.98	0.01	1.16	0.57–2.16	0.66
Neoadjuvant chemotherapy	±	1.28	0.92–1.77	0.14			
CEA, ng/mL	≥5/<5	1.33	0.90–1.90	0.15			
Serum albumin, g/dL	<3.5/≥3.5	1.27	0.91–1.74	0.15			
Histology in biopsy	Undifferentiated, others/differentiated	1.35	0.89–2.15	0.16			
Upper abdominal surgery history	±	1.20	0.75–1.81	0.43			
Hemoglobin, g/dL	<10/≥10	1.15	0.74–1.88	0.56			
Sex	Male/female	0.96	0.72–1.28	0.78			
Year of operation	2005–2009/2010–2015	1.03	0.77–1.38	0.84			
Duodenum invasion	±	1.02	0.52–1.79	0.95			

95% CI indicates 95% confidence interval; ASA-PS, American Society of Anesthesiologists Performance Status; CA19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; CY, intraoperative peritoneal lavage cytology; DG, distal gastrectomy; HR, hazard ratio; LG, laparoscopic gastrectomy; OG, open gastrectomy; TG, total gastrectomy.

future advances in surgical instruments and navigation systems may help realize safer minimally invasive surgery for scirrhous type GC in any clinical setting.[45]

In the RCT comparing long-term outcomes between laparoscopic and open distal gastrectomy in patients with locally advanced GC, the noninferiority of laparoscopic to open surgery was not clearly evident in the analyses after exclusion of patients with pathologic stage I tumors, although the noninferiority was identified in the primary analyses.[8] As OG has been the standard surgical approach for advanced GC, LG should be indicated for scirrhous GC after sufficient discussion among surgical staff members, patients, and their family.

There were important limitations in this study. First, the macroscopic type was not diagnosed by a central reviewer, and patients with tumors of unclear macroscopic types were excluded. Although it may be difficult to standardize the diagnostic criteria for macroscopic type, consensus meetings to define type 4 GC should be held in the future. Second, although we calculated OS and RFS as the number of days after initial treatment, this may have introduced an element of bias depending on whether patients were treated with upfront surgery or received neoadjuvant therapy. However, patients may have a short and standardized interval to initial treatment, and the proportion of patients who received neoadjuvant therapy and surgery was similar in the 2 groups. This calculation method, which has been commonly used in previous studies, may be acceptable.[46–48] Finally, there is a possibility that OG was selected for cases of surgery that were expected to be technically demanding. However, the predefined variables known to impact on not only long-term but also short-term outcomes were collected. The differences for these factors were evaluated between the groups and risk adjustment was performed using the multivariate model and the PSM method. To the best of our knowledge, this is the first large-scale multicenter study to examine the safety and efficacy of LG focusing on patients with scirrhous GC. We believe that the narrow 95% CI from this large multicenter study is very useful for surgeons and patients to discuss and select the appropriate surgical approach for this relatively rare type of cancer with poor prognosis on the condition that laparoscopic surgical proficiency is available. In addition, this study showed that an age of 80 years or higher, high BMI, advanced CCI, high CA19-9, stenosis, cN+, and total gastrectomy were independent strong prognostic factors for OS rather than surgical approach in patients with scirrhous GC.

In conclusion, LG was not associated with worse survival than OG. LG is a reasonable approach for scirrhous GC when performed by experienced surgeons with meticulous care to avoid cancer cell spillage and positive resection margin.

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