



Short-Term Outcomes from a Randomized Screening Phase II Non-inferiority Trial Comparing Omentectomy and Omentum Preservation for Locally Advanced Gastric Cancer: the TOP-G Trial

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Accepted: 24 January 2021 / Published online: 10 February 2021
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Abstract

Background Omentectomy is considered an essential part of curative gastrectomy for locally advanced gastric cancer (GC), albeit without solid evidence. We conducted a randomized phase II trial (the TOP-G trial) comparing omentectomy and omentum preservation for gastric cancer. This report describes the short-term findings regarding the trial's secondary endpoints.

Methods The trial protocol was submitted to the University Hospital Medical Information Network Clinical Trials Registry (<http://www.umin.ac.jp/ctr/>; UMIN000005421). The key eligibility criteria were histologically confirmed cT2–4a and N0–2 gastric adenocarcinoma. Short-term surgical outcomes, including morbidity and mortality, were compared between the omentectomy group (group A, control arm) and the omentum-preserving surgery group (group B, test arm). All procedures were performed via an open approach. Based on a non-inferiority margin of 7%, statistical power of 0.7, and type I error of 0.2, the sample size was set to 250 patients.

Results A total of 251 patients were eligible and randomized (group A: 125 patients, group B: 126 patients) between April 2011 and October 2018. After excluding patients who had peritoneal metastasis or laparotomy history, safety outcomes were analyzed for 247 patients. Group A had a significantly longer median operation time (225 min vs. 204 min, $p = 0.022$) and tended to have greater median blood loss (260 mL vs. 210 mL $p = 0.073$). The incidences of morbidity were similar and $< 10\%$ in both groups (8% vs. 9%, $p = 1.000$). There was no mortality in either group.

Conclusions Operative risk was generally similar between omentectomy and omentum-preserving surgery for locally advanced gastric cancer.

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Introduction

Gastric cancer (GC) is a leading cause of cancer-related death [1], and surgical treatment is key to curing localized GC. Radical surgery for gastrointestinal cancer has two theoretical goals: en bloc resection of the mesothelium, including the vessels and regional lymph nodes, and complete resection of the localized tumor. However, the stomach has unique mesothelial characteristics. For example, the stomach rotates during its embryological formation, the greater curvature becomes prolonged with the visceral mesothelium, and the omentum and bursa omentalis are formed. The omentum consists of three parts. The first part is the membranes close to the stomach's greater curvature, including the right and left epiploic vessels and lymph nodes. The second part is the membranes adjacent to the first part that hang over the transverse colon, which are filled with fat tissues and blood/lymphatic vessels. This second part is often narrowly referred to as the omentum. The third part is the membrane covering the bursa omentalis. All three parts should theoretically be resected to achieve en bloc resection and cure GC. This is because the omentum is a common site of peritoneal metastasis, and animal models have indicated that cancer cells implanted into the abdominal cavity aggregate to openings that connect the omental lymphatic system to the peritoneal cavity [2, 3]. Furthermore, omental micrometastasis can occasionally be detected in patients with GC using special staining or reverse transcription polymerase chain reaction [3, 4]. Therefore, if peritoneal metastasis is localized to the omentum as micrometastasis in some patients, it may be important to resect all three

parts of the omentum. The control of peritoneal metastasis is important for survival in advanced gastric cancer treatment [5, 6].

Based on these concepts, surgeons have completely resected the omentum in locally advanced GC cases [7]. However, a recent large phase III trial (JCOG1001) confirmed that bursectomy, which involves complete resection of the membrane covering the bursa omentalis (i.e., the third omentum part), did not improve survival relative to non-bursectomy [8]. Thus, en bloc resection of the entire gastric mesothelium was not considered necessary. Nevertheless, resection of the first omentum part (near the greater curvature) is essential for dissecting lymph nodes closed to the stomach, although it remains unclear whether the second part should be resected (the membranes that hang over the transverse colon). For the purpose of this report, we define resection of the second part as “omentectomy” and preservation of the second part as “omentum preservation.” It is unlikely that peritoneal metastasis would be limited to the second omentum part, as peritoneal metastasis is a systemic disease. Furthermore, some retrospective studies have demonstrated that omentectomy increased the operation time, blood loss, and surgical morbidity, relative to preservation of the second omentum part [9–12], although retrospective studies involve significant bias. Moreover, accurate estimation of risks and benefits is essential for calculating the sample size for a large phase III study to compare omentectomy and omentum-preserving surgery for GC. Therefore, we conducted a multicenter screening randomized phase II trial (the TOP-G trial) to compare omentectomy and omentum preservation [13]. This report describes the short-term findings regarding the trial's secondary endpoints.

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Materials and methods

Ethical considerations

The study protocol was approved by the institutional review boards at all participating institutions. The study procedures complied with the recommendations in the Declaration of Helsinki, the Ethical Guideline for Medical and Health Research Involving Human Subjects, and the guidelines of the responsible Japanese governmental agency. All patients were required to provide written informed before enrollment. The trial protocol was registered with the University Hospital Medical Information Network Clinical Trials Registry (<http://www.umin.ac.jp/ctr/>: UMIN000005421).

Study design and endpoints

This phase II randomized controlled trial was designed to compare two surgical techniques: gastrectomy with omentectomy and omentum-preserving gastrectomy. Both procedures were performed via laparotomy, and the extent of nodal dissection was determined according to the Japanese Gastric Cancer Treatment Guidelines [14]. The primary endpoint was relapse-free survival (RFS), and the secondary endpoints were overall survival, blood loss, operation time, and surgical morbidity. Randomization and data handling for this study were performed by the Yokohama City University Center for Novel and Exploratory Clinical Trials (Y-NEXT).

Eligibility

The first preoperative eligibility criteria were histologically confirmed adenocarcinoma of stomach; clinical stage T2(MP)–T4a(SE), N0–N2, and M0 according to the Japanese Classification of Gastric Carcinoma [15]; an indication for R0 surgery; preoperative macroscopic type 0–3 or 5 disease; age of ≥ 20 years, Eastern Cooperative Oncology Group performance status of 0–2; and sufficient organ functions. The exclusion criteria were previous chemotherapy for GC, history of abdominal surgery except appendectomy and laparoscopic cholecystectomy, unstable angina or myocardial infarction within 6 months of registration, uncontrolled diabetes mellitus, respiratory disease requiring oxygen therapy, history of allergy or hypersensitivity to any drug, presence of acute inflammation, pregnancy, synchronous or metachronous (within 5 years) malignancy, and psychiatric disease that required treatment. After laparotomy and before initiating gastrectomy, the surgeons evaluated whether the patient fulfilled the second inclusion criteria: T2(MP)–T4a(SE) disease, possible macroscopic curative resection including R1 surgery based on positive peritoneal lavage cytology (CY1), possibility of achieving total omentectomy, and not requiring thoracotomy.

Randomization

After confirming the patient fulfilled the second eligibility criteria, the surgeons communicated this fact to the Y-NEXT via telephone, and the Y-NEXT immediately provided a randomized assignment (1:1) to the omentectomy group (group A) or the omentum preservation group (group B). The groups were balanced according to institution, T status (T2–3 vs. T4a), and type of gastrectomy (distal vs. total). Interventions were not masked for the patients or investigators.

Surgical methods

The operative approach was limited to open surgery and laparoscopic surgery was not allowed.

Group A (total omentectomy) was treated using gastrectomy, D2 lymphadenectomy, and total omentectomy without bursectomy. Depending on the primary tumor's location, the surgeon performed total or distal gastrectomy. The spleen was removed to dissect the splenic hilar lymph nodes as part of total gastrectomy according to the Japanese gastric cancer treatment guidelines (version 3, 2010) from when the study was designed [14]. However, after publication of the results from the phase III JCOG0110 trial, which evaluated splenectomy during total gastrectomy, the spleen was preserved for upper GC that did not invade the greater curvature [16].

Group B (omentum preservation) was treated using gastrectomy and D2 lymphadenectomy. The first part of the omentum was dissected at 3 cm below the right and left gastroepiploic arteries, with the preservation of the second part of the omentum.

The type of reconstruction was not specified in the study protocol, and the protocol treatment was considered completed when the surgery was finished. The protocol treatment was also terminated when apparent distant metastasis (M1) or direct invasion of the adjacent organs (T4b) was detected after enrollment. Any patients who were diagnosed with pathological stage II/III disease (except T1N2–3 or T3N0) were recommended to receive oral S-1 for 12 months as adjuvant therapy. To ensure surgical quality, only surgeons who had performed ≥ 50 gastrectomies were allowed to participate. Compliance with the assigned omentectomy procedure was validated based on case report forms.

Surgical outcomes

Operative techniques and pathology results were recorded according to the Japanese Gastric Cancer Treatment Guidelines and the Japanese Classification of Gastric Carcinoma (14th edition) [14, 15]. Postoperative complications that occurred during the hospitalization or within 30 days after surgery were evaluated according to the Clavien–Dindo classification. Morbidities that were considered grade ≥ 3 were noted on the case report form [17]. The operation time, blood loss, and blood transfusion requirement values were also recorded.

Sample size

The sample size was calculated based on a hypothesis that the expected 3-year RFS rate was 70% for both groups. Using a non-inferiority margin of 7% for the 3-year RFS

rate (the rate for group B being 7% below that for group A), the total sample size to provide statistical power of 0.7 and type I error of 0.2 was calculated to be 245 patients. However, given that a few cases would inevitably be considered ineligible for registration, the number of patients was set to 250.

Statistical analysis

Morbidity and mortality rates were evaluated in the safety cohort, which was created by excluding ineligible cases from the intention-to-treatment cohort. Differences in those outcomes were evaluated using Fisher's exact test. Differences in length of hospital stay and blood loss were evaluated using the Wilcoxon test. All P-values were two-sided, and the statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

Results

Patients

Recruitment opened in April 2011 and closed in October 2018. The CONSORT diagram is shown in Fig. 1. At the first registration, 275 patients were enrolled although 8 patients were initially deemed ineligible and 16 patients were excluded because they did not fulfill the second eligibility criteria (generally because T4b tumors or peritoneal metastasis were found during surgery). Thus, 251 patients were enrolled at the second registration, although 4 patients were judged to be ineligible after the second registration. One patient had peritoneal metastasis that was found during gastrectomy and 3 patients had severe adhesions, which were possibly related to an unidentified history of laparotomy. The safety cohort included 247 patients (group A: 122 patients and group B: 125 patients). The patient and tumor characteristics were generally well

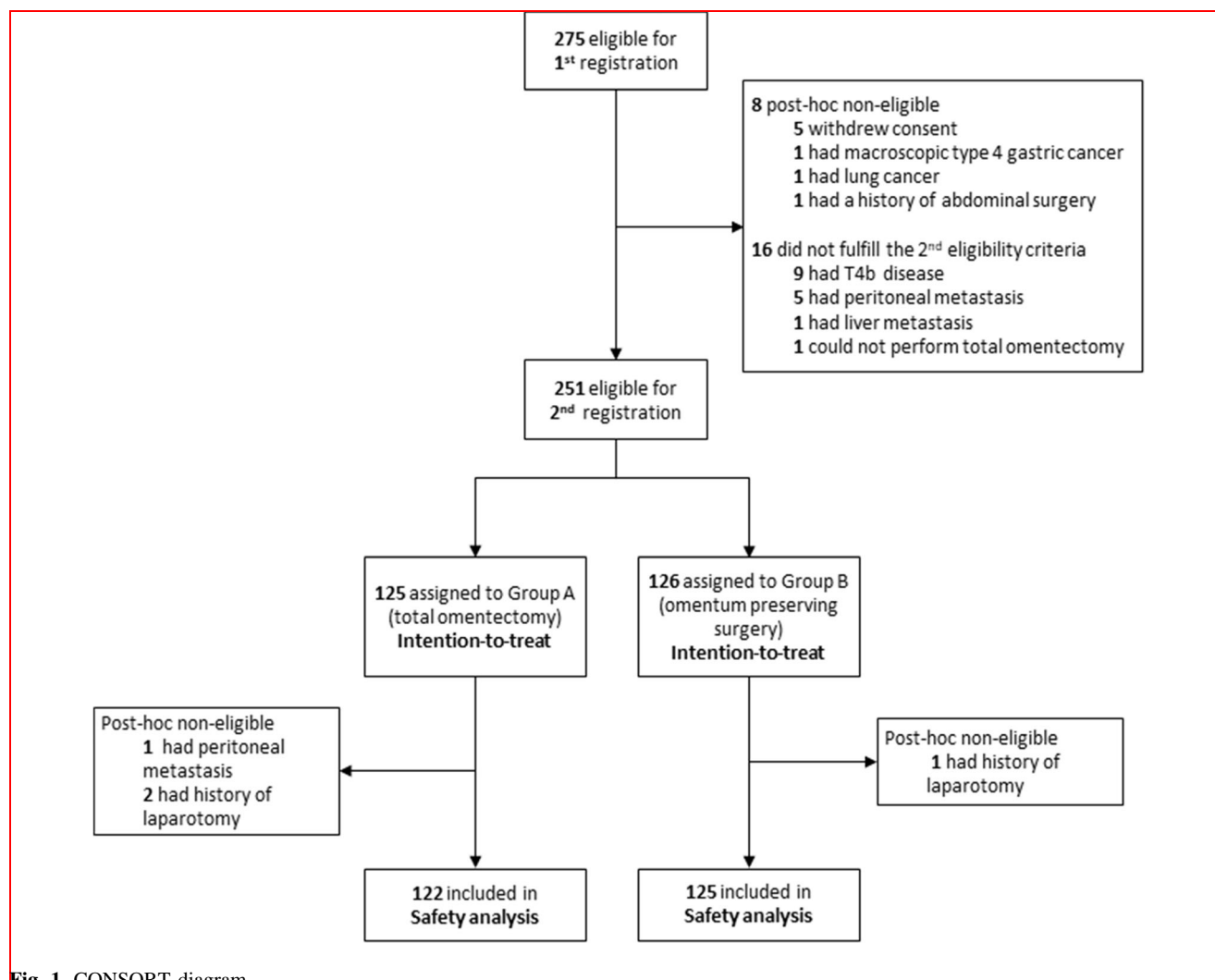


Fig. 1 CONSORT diagram

Table 1 Patient and tumor characteristics

		Omentectomy		<i>p</i> -value
		Yes Group A (N = 122)	No Group B (N = 125)	
Age, years	Median	71	74	0.003
	Range	30–90	45–89	
Sex	Male	89 (73%)	89 (71%)	0.778
	Female	33 (27%)	36 (29%)	
ECOG PS	0	105 (86%)	112 (89%)	0.736
	1	15 (12%)	11 (9%)	
	2	2 (2%)	2 (2%)	
Body mass index, kg/m ²	Median	22.4	22.2	0.721
	Range	14.8–31.8	14.5–32.1	
Tumor location	Upper	27 (22%)	26 (21%)	0.845
	Middle	49 (40%)	47 (38%)	
	Lower	46 (38%)	52 (42%)	
Macroscopic type (intraoperative)	Type 0	12 (10%)	13 (10%)	0.485
	Type 1	4 (3%)	11 (9%)	
	Type 2	45 (37%)	46 (37%)	
	Type 3	56 (46%)	51 (41%)	
	Type 4	1 (1%)	2 (2%)	
	Type 5	4 (3%)	2 (2%)	
Clinical tumor status	T1	0 (0)	0 (0)	0.507
	T2	30 (25%)	39 (31%)	
	T3	54 (44%)	49 (39%)	
	T4	38 (31%)	37 (30%)	
Clinical lymph node metastasis	N0	64 (53%)	68 (54%)	0.940
	N1	36 (30%)	35 (28%)	
	N2	22 (18%)	22 (18%)	
	N3	0 (0)	0 (0)	
Clinical stage	I	22 (18%)	26 (21%)	0.739
	II	64 (52%)	67 (54%)	
	III	36 (30%)	32 (26%)	
	IV	0 (0)	0 (0)	
Planned surgery	Total gastrectomy	44 (36%)	46 (37%)	1.000
	Distal gastrectomy	78 (64%)	79 (63%)	

ECOG PS Eastern Cooperative Oncology Group performance status

balanced between the two groups, with the exception of age (Table 1).

Surgery

The operative details are shown in Table 2. Violation of the protocol treatment was not identified in either group. Although the proportion of total gastrectomy was almost balanced between the two groups, splenectomy was

slightly more common in group B. Relative to group B, group A had a significantly longer median operation time (+ 21 min) and tended to have greater median blood loss (+ 50 mL). The number of retrieved nodes was similar in both groups.

Table 2 Operative details

		Omentectomy		<i>p</i> -value
		Yes Group A (N = 122)	No Group B (N = 125)	
Performed surgery	Total gastrectomy	49 (40%)	44 (35%)	0.434
	Distal gastrectomy	73 (60%)	81 (65%)	
	Others	0 (0%)	0 (0%)	
Lymph node dissection	D1	1 (1%)	2 (2%)	1.000
	D1 +	9 (7%)	13 (10%)	
	D2	110 (90%)	107 (86%)	
	D2 +	2 (2%)	3 (2%)	
Combined organ resection		20 (16%)	21 (17%)	1.000
Splenectomy		7 (6%)	14 (11%)	0.171
Cholecystectomy		12 (10%)	8 (6%)	0.358
Transverse colon resection		1 (1%)	0 (0)	0.494
Left adrenal gland resection		0 (0%)	1 (1%)	1.000
Omentectomy		122 (100%)	0 (0%)	< 0.001
Thoracotomy		0 (0%)	0 (0%)	1.000
Reconstruction	Roux-en-Y	64 (53%)	59 (47%)	0.446
	Billroth I	58 (48%)	66 (53%)	
Residual disease	R0	112 (92%)	117 (94%)	0.863
	R1	7 (6%)	5 (4%)	
	R2	3 (3%)	3 (2%)	
Operation time, min	Median	225	204	0.022
	Range	77–453	65–580	
Blood loss, mL	Median	260	210	0.073
	Range	20–3100	0–378	
Blood transfusion		10 (8%)	10 (8%)	1.000
# of retrieved lymph nodes	Median	37	37	0.543
	Range	10–95	10–153	

Operative morbidity and mortality

One patient in group B experienced an intraoperative spleen injury that resulted in unplanned splenectomy. The postoperative morbidity rates were similar and < 10% in both groups (Table 3). Anastomotic leakage tended to be more common in group B than in group A (5% vs. 2%). Pancreatic fistula only occurred in group A (2%). Two patients in group B experienced postoperative bleeding, which involved the gastroduodenal artery in one case and an unidentified source of bleeding in the second case. Mortality was not identified in either group.

Pathology findings

There were no apparent differences in the pathology findings for the two groups (Table 4).

Discussion

To the best of our knowledge, this is the first randomized study to compare omentectomy and omentum preservation for locally advanced gastric cancer. Our hypothesis was that overall survival would be similar, but operative risk would be reduced by omentum preservation. However, we only identified small differences in operation time and blood loss, with similar overall morbidities in the two groups. These results suggested that operative risk was fairly similar between omentum-preserving surgery and omentectomy.

We observed that omentum preservation was associated with approximately 20 min shorter operation times and 50 mL less blood loss, although it was also associated with a slightly higher rate of splenectomy. The differences in operation time and blood loss might be emphasized if the

Table 3 Morbidity and mortality

	Omentectomy		<i>p</i> -value
	Yes Group A (N = 122)	No Group B (N = 125)	
Grade 3–4 morbidity	10 (8%)	11 (9%)	1.000
Anastomotic leakage	2 (2%)	6 (5%)	0.281
Pancreatic fistula	2 (2%)	0 (0)	0.243
Abdominal abscess	2 (2%)	3 (2%)	0.281
Postoperative bleeding	2 (2%)	0 (0)	0.243
Stenosis	1 (1%)	1 (1%)	1.000
Bowel obstruction	2 (2%)	2 (2%)	1.000
Pneumonia	2 (2%)	1 (1%)	0.619
Mortality	0 (0)	0 (0)	1.000

splenectomy rates were similar in the two arms. Hasegawa et al. have reported that omentum preservation was associated with approximately 80 min shorter operation times and 170 mL less blood loss, based on a retrospective propensity score-matched analysis [10]. Ri et al. also reported that omentum preservation was associated with 38 mL less blood loss, albeit with similar operation times [12]. This may be because the omentum contains numerous blood and lymphatic vessels that are covered with fat tissue, which forces the surgeon to carefully dissect these

tissues if they wish to avoid bleeding while preserving the omentum. A manual dissection may be time-consuming, although surgeon workload and operation time might be improved by using new vessel sealing devices or ultrasonic cutting and coagulation devices. Previous studies have indicated that these devices are useful for dissecting the tissues while minimizing related bleeding [18, 19]. In contrast, omentectomy does not involve cutting large vessels but does require the surgeon to carefully dissect the membrane's attachment to the transverse colon. Thus, the new devices may not be preferable to traditional scissors or an electric scalpel. Nevertheless, care is still needed, as sharp dissection may induce bleeding from small regional blood vessels.

The present study revealed that omentectomy and omentum-preserving surgery had similar morbidity rates, although splenectomy was more common in the omentum preservation group. Although splenectomy is a well-known risk factor for morbidity, especially for pancreatic fistula, we observed that pancreatic fistula and abdominal abscess were more common in the omentectomy group. Thus, preserving the omentum may prevent pancreatic fistula or abdominal abscess, as the omentum theoretically prevents the spread of local inflammation to the whole abdomen. A multicenter cohort study has also indicated that the rates of pancreatic fistula and abdominal abscess were 5.7% among patients who underwent omentectomy but only 3.0% among patients who underwent omentum-preserving

Table 4 Pathological findings

		Omentectomy		<i>p</i> -value
		Yes Group A (N = 122)	No Group B (N = 125)	
Pathological tumor status	T1	20 (16%)	31 (25%)	0.249
	T2	21 (17%)	21 (17%)	
	T3	42 (34%)	31 (25%)	
	T4	39 (32%)	42 (34%)	
Pathological lymph node metastasis	N0	44 (36%)	54 (43%)	0.356
	N1	29 (23%)	25 (20%)	
	N2	25 (21%)	17 (14%)	
	N3	24 (20%)	29 (23%)	
Pathological stage	I	26 (21%)	38 (30%)	0.396
	II	48 (40%)	40 (32%)	
	III	41 (34%)	40 (32%)	
	IV	7 (6%)	7 (6%)	
Histological type	Differentiated	56 (46%)	67 (54%)	0.201
	Undifferentiated	58 (48)	55 (44%)	
	Others	8 (7%)	3 (3%)	

surgery [12]. Anastomotic leakage was slightly more common in the omentum preservation group, although the rates were < 5% in both groups and not significantly different. The preserved omentum might interfere with movement of the ante-colic jejunum to meet the esophagus, and surgeons must also avoid placing excessive tension on the jejunum in order to minimize the risk of anastomotic leakage. Nevertheless, it is unclear whether the increased rate of anastomotic leakage was related to chance or the omentum preservation.

The morbidity rate was 8% in our omentectomy group, which is slightly lower than the rate from the phase III JCOG1001 trial (bursectomy vs. non-bursectomy). In that trial, the non-bursectomy arm underwent the same procedure as our omentectomy group and the incidence of grade 3–4 morbidities was 11% [8]. However, the non-bursectomy arm of the JCOG1001 trial had a higher rate of splenectomy (27%) than in our trial (6% in group A) [8]. Our morbidity rate for omentectomy is also slightly lower than the rate from the phase III JCOG0110 trial (splenectomy vs. spleen-preserving surgery). The morbidity rate was 16.7% in the spleen-preservation arm of that trial [16], although all of the patients in the JCOG0110 trial underwent total gastrectomy. Thus, our overall morbidity rate of 8% after omentectomy seems reasonable.

Open surgery remains the standard approach for advanced GC. However, omentum preservation would be useful during laparoscopic surgery, where omentectomy can be complicated, time-consuming, and hazardous. A previous report comparing omentectomy and omentum preservation during laparoscopic surgery revealed that omentum preservation shortened the mean operation time by 15 min, and only omentectomy was associated with organ injury [11].

Our study has two important limitations. First, a small phase II trial cannot definitively confirm the safety and efficacy of omentum preservation. Our findings suggest that the risks of omentectomy and omentum preservation were generally similar, although the slight imbalance in the splenectomy rates might lead to underestimation of the risk associated with omentum preservation. Second, we did not consider long-term morbidities, such as bowel obstruction, although omentum preservation would theoretically reduce intestinal adhesions that could lead to bowel obstruction.

Conclusions

The present study revealed that the operative risks were generally similar between omentum-preserving surgery and omentectomy for locally advanced GC.

Acknowledgements We thank all of the patients, their families, the investigators, and medical staff members who participated in this study.

Author contributions SH, TY, and TY conceived of and designed the trial. HM and TY were the principal investigators. MT, HM, TY, and TY were responsible for the data analysis. All authors contributed to the data acquisition and interpretation. HM, TY, and TY draft the article. All authors contributed to the writing of the final manuscript and approved the final version. All authors agree to be accountable for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with ethical standards

Conflict of interest Dr. Yamada reports personal fees from ONO Pharmaceutical and personal fees from Bristol-Myers Squibb, outside the submitted work. Dr. Yamanaka reports grants and personal fees from Takeda, grants and personal fees from Chugai, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Taiho, grants and personal fees from Daiichi-Sankyo, grants from Ono, grants and personal fees from Bayer, grants from Merck Serono, grants from Astellas, grants from Eli Lilly, personal fees from Pfizer, personal fees from Sysmex, personal fees from Huya Biosciences, and personal fees from Gilead Sciences, outside the submitted work. Dr. Rino reports personal fees from Taiho pharmaceutical, personal fees from Abbott, personal fees from Asahi Kasei, personal fees from Daiichi-Sankyo, personal fees from Tsumura & Co, personal fees from Covidien, personal fees from Zeria pharmaceutical, personal fees from EA Pharma, personal fees from Johnson and Johnson, personal fees from Otsuka, other from Lilly, other from Bristol-Myers Squibb, other from Daiichi-Sankyo, other from Johnson and Johnson, other from Otsuka, and other from Taiho pharmaceutical, outside the submitted work. Dr. Oshima reports grants from Taiho pharmaceutical Co., Ltd, grants from Chugai pharmaceutical Co., Ltd, grants from Ono pharmaceutical Co., Ltd, grants from Daiichi-Sankyo pharmaceutical, grants from Nippon Kayaku Co., Ltd, grants from Eli Lilly Japan K. K., personal fees from Nippon Kayaku Co., Ltd, personal fees from Ono pharmaceutical Co., Ltd, personal fees from Bristol-Myers Squibb K. K., personal fees from Taiho pharmaceutical Co., Ltd, personal fees from Chugai pharmaceutical Co., Ltd, and personal fees from Eli Lilly Japan K. K., outside the submitted work. Dr. Yoshikawa reports personal fees from MSD, personal fees from BMS, personal fees from ONO, personal fees from Taiho, personal fees from Chugai, personal fees from Nihon Kayaku, grants and personal fees from Lilly, personal fees from Pfizer, personal fees from TERUMO, personal fees from Johnson and Johnson, and personal fees from Covidien, outside the submitted work; All the remaining authors have no conflicts of interest to declare.

Ethical approval This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry (<http://www.umin.ac.jp/ctr/>: UMIN000005421) and was approved by the ethical review boards of the participating institutions. All patients provided informed consent before enrollment.

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