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ORIGINAL ARTICLE

Randomized controlled trial of the LigaSure vessel sealing system versus conventional open gastrectomy for gastric cancer

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Abstract
Purpose LigaSure, a bipolar electronic vessel sealing system, has become popular in abdominal surgery but few clinical studies have been conducted to evaluate its effectiveness in radical gastrectomy for gastric cancer.
Methods In this multicenter, prospective, randomized controlled trial, patients with curative gastric cancer were randomly assigned to undergo gastrectomy either with LigaSure or a conventional technique.
Results Of the 160 patients enrolled, 80 were randomized to the LigaSure group and 78 to the conventional group. Patient characteristics were well balanced in the two groups. There were no significant differences between the LigaSure and conventional groups in blood loss (288 vs. 260 ml, respectively; $P = 0.748$) or operative time (223 and 225 min, respectively; $P = 0.368$); nor in the incidence of surgical complications or duration of postoperative hospital stay. In a subgroup analysis of patients who underwent gastrectomy that preserved the distal part of the greater omentum, the use of LigaSure significantly reduced blood loss (179 vs. 245 ml; $P = 0.033$), and the duration of the operation (195 vs. 221 min; $P = 0.039$).
Conclusions LigaSure did not contribute to reducing intraoperative blood loss, operative time, or other adverse surgical outcomes. The usefulness of the device may be limited to a specific part of the surgical procedure in open gastrectomy.

Keywords LigaSure · Gastrectomy · Randomized controlled trial · Gastric cancer

Introduction

The LigaSure vessel sealing system (Valleylab, Boulder, CO, USA) comprises a recently developed surgical device that uses mechanical pressure and an enhanced form of

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bipolar electrocoagulation to achieve permanent vessel wall fusion by denaturing the collagen and elastin in vessel walls and re-forming them into a hemostatic seal. Laboratory experiments demonstrated that on average, the vessel seal formed by LigaSure can endure 400 mmHg of burst pressure, which is comparable to results obtained using surgical clips or sutures. Moreover, it enables dissection of vessels up to 7 mm in diameter [1].

LigaSure was initially used in urological surgery [2], splenectomy [3], gynecologic surgery [4], hemorrhoidectomy [5], and thyroidectomy [6], but it has also become widely prevalent in laparoscopic and open gastrointestinal surgery. In the past decade, numerous clinical studies have assessed the usefulness of LigaSure in several surgical series. Randomized controlled trials have demonstrated that LigaSure reduces operative time and blood loss in hysterectomy [7], esophagogastric devascularization plus splenectomy [8], and liver resection [9]. In their meta-analysis of nine prospective studies of thyroidectomy, Yao et al. [10] reported that using LigaSure reduced the operative time significantly.

Gastric cancer is the most common gastrointestinal neoplasm in East Asia [11]; thus, the intricate surgical technique of gastrectomy accompanied by radical lymphadenectomy has been developed and is now well established in Japan [12]. Japanese surgeons are familiar with conventional gastrectomy, which involves ligation of the blood and lymphatic vessels; however, the practical use of LigaSure in gastric resection has rapidly become popular since the Japanese health insurance organization approved its reimbursement for its use in open gastrointestinal surgery in 2009.

We conducted a multicenter, prospective, randomized controlled trial to evaluate the utility of LigaSure compared with conventional techniques during open radical gastrectomy for gastric cancer.

Methods

Patients

Eligibility criteria included histologically proven primary adenocarcinoma of the stomach; preoperative clinical tumor status of Stage IA–IIIB according to the 13th edition of the Japanese Classification of Gastric Carcinoma [13]; tumor deemed to be radically resectable by distal subtotal or total gastrectomy; age between 20 and 90 years, with a performance status of 0–1 according to the Eastern Cooperative Oncology Group (ECOG) scale; no prior chemotherapy or radiotherapy; no perioperative anticoagulant therapy with heparin; and no history of gastrectomy or other malignancies during the past 5 years. Patients scheduled to undergo laparoscopic or laparoscopic-assisted gastrectomy were excluded. All patients gave written informed consent before undergoing randomization.

After confirming that each patient met the eligibility criteria, surgeons informed the data center in Department of Gastroenterological Surgery at the Osaka University Graduate School of Medicine about their enrollment, up until the day before surgery. Patients were randomly assigned to undergo either gastrectomy using LigaSure (LigaSure group) or gastrectomy with conventional suture ligation techniques (conventional group). Assignments were balanced by the minimization method according to the institution and the type of gastrectomy (total vs. distal subtotal). The study protocol was approved by the institutional review board of each participating hospital.

Surgical methods

The surgeon performed radical total gastrectomy or distal subtotal gastrectomy and D1 lymphadenectomy for early gastric cancer (Stage IA) or D2 for advanced cancer, according to the Japanese guidelines for the treatment of gastric cancer [14]. Patients allocated to the conventional group underwent gastric resection and lymph node dissection with monopolar electrocautery, sutures, and ligatures. The use of bipolar electric scissors was permitted but other energy-dependent dissection devices were prohibited. In the LigaSure group, surgeons used LigaSure for hemostasis and tissue dissection as much as possible instead of the conventional methods, although the utilization of additional ligations with sutures was allowed to ensure hemostasis during the dissection of large vessels, such as the left gastric artery, splenic artery, or left-gastroepiploic artery. The protocol did not regulate the method of reconstruction, and Billroth I or Roux-en-Y anastomosis was selected by the surgeon in each institution.

Fifteen institutions belonging to the Osaka University Clinical Research Group for Gastrointestinal Surgery participated in this trial. Each hospital performs over 50 gastrectomies annually. All operations were conducted or supervised by expert surgeons, who are members of the Japanese Gastric Cancer Association, and the operator's experience in gastric cancer surgery was documented on the case report form.

Postoperative evaluation and endpoints

Operative methods and pathological results were recorded according to the 13th edition of the Japanese Classification of Gastric Carcinoma [13]. Data reflecting eight major morbidities, namely, postoperative bleeding, anastomotic leakage, pancreatic leakage, abdominal abscess, wound infection, bowel obstruction, pneumonia, and anastomotic

stenosis, were prospectively collected. Postoperative bleeding requiring transfusion was recorded as a morbidity. Drainage volume and duration of drain insertion were also recorded. Pancreatic leakage was defined as drainage output with an amylase level more than three times the upper normal serum value on or after postoperative day (POD) 5. Anastomotic leakage, abdominal abscess, bowel obstruction, pneumonia, and anastomotic stenosis were diagnosed based on clinical signs and symptoms or radiologic examination. Any other complications requiring pharmacologic or surgical treatment were recorded on a free format. Operative blood loss, operative time, duration of hospital stay, and re-operation details were recorded as well. Hospital mortality was defined as postoperative death of any cause within 30 days, or death during the same hospitalization. The total cost of surgery and hospitalization for each patient was calculated.

The primary endpoint of this study was intraoperative blood loss. Secondary endpoints were operative time, operative morbidity, duration of postoperative hospital stay, and total cost of hospitalization.

Statistical analysis

From the results of our recent studies, we estimated blood loss in the conventional group to be 300 ml [15, 16] and hypothesized that the use of LigaSure may reduce the blood loss by 25 % to 225 ml. The sample size was calculated to provide 80 % power to detect an effect size of 25 % using a one-sided alpha error of 5 % under normal distribution, with a standard deviation of 0.1 in both groups. The primary endpoint was evaluated using the *t* test. The calculated sample size was 61 patients for each group.

Differences in proportions between the two groups were evaluated using Fisher's exact test or the Chi square test. Differences in continuous variables including age, body mass index, tumor size, blood loss, and operative time between the two groups were tested with the Mann–Whitney U test. All *P* values were two-sided and reported as significant at $P < 0.05$, to provide conventional interpretation of the results. Statistical analysis was performed using SPSS, version 17.0 (SPSS, Chicago, IL, USA).

Results

Between January, 2009 and May, 2010, a total of 160 patients were enrolled from 15 hospitals and randomly assigned to either the LigaSure or the conventional group (Fig. 1). One patient allocated to the LigaSure group underwent gastrojejunostomy without gastric resection based on the intraoperative findings, and one patient allocated to the conventional group was diagnosed with esophageal cancer after randomization and underwent subtotal esophagectomy. These two patients were excluded from the analysis on surgical outcomes. The remaining 80 patients in the LigaSure group and 78 patients in the conventional group underwent the allocated surgery.

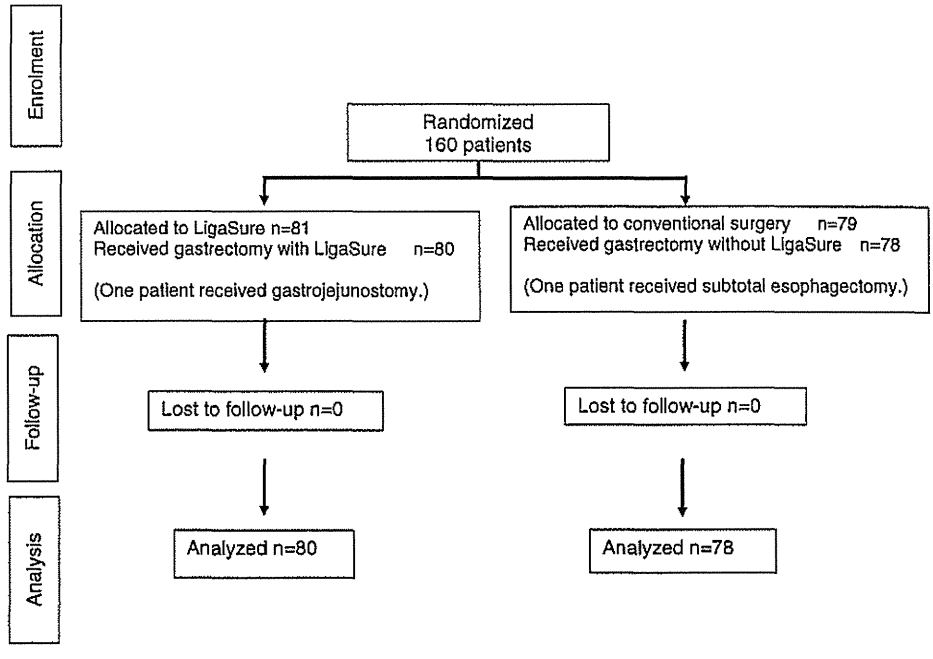

Fig. 1 Consort flow chart

Table 1 Patient characteristics

	LigaSure ($n = 81$)	Conventional ($n = 79$)	P
Age (years)			
Median (range)	72 (40–85)	69 (33–86)	0.178*
Sex			
Male	55	57	0.607**
Female	26	22	
Body mass index (kg/m^2)			
Median (range)	22.3 (15.3–29.9)	21.9 (12.8–30.5)	0.824*
Tumor size (cm)			
Median (range)	3.5 (0.5–17.5)	4.0 (0.5–13.0)	0.718*
Depth of tumor invasion			
T1	36	44	0.252**
T2 or higher	45	35	
TNM Stage			
I	48	48	0.838***
II	9	10	
III	17	17	
IV	7	4	
Anticoagulant use			
Yes	6	6	1.000**
No	75	73	

P values were calculated using the *Mann–Whitney U test for age, body mass index, and tumor size; **Fisher's exact test for sex, depth of tumor invasion, and history of anticoagulant use; and the ***Chi square test for TNM stage

Table 2 Details of the surgical procedures

	LigaSure ($n = 80$)	Conventional ($n = 78$)	P
Type of resection			
Total gastrectomy	25	19	0.377
Distal subtotal gastrectomy	55	59	
Reconstruction			
Billroth I	31	38	0.319
Roux-en-Y	49	40	
Lymph node dissection			
D0, D1	29	32	0.624
D2	51	46	
Cholecystectomy			
Yes	35	30	0.624
No	45	48	
Splenectomy			
Yes	11	7	0.454
No	69	71	
Omentectomy			
Yes	36	30	0.424
No	44	48	

All P values were calculated using Fisher's exact test

There were no significant differences between the groups in baseline characteristics that may affect surgical outcomes, such as body mass index, tumor size, tumor stage, and history of anticoagulant therapy (Table 1). Table 2 summarizes the details on the surgical procedures. There were 25 patients in the LigaSure group and 19 patients in the conventional group, who underwent total gastrectomy. The proportion of patients who underwent D2 lymphadenectomy, cholecystectomy, and splenectomy was comparable in the two groups. Omentum-preserving gastrectomy was performed in patients whose tumors did not reach the serosal surface of the stomach, based on macroscopic inspection. In these patients, the greater omentum was divided 3 cm away from the course of the gastroepiploic artery and the distal part of the greater omentum was preserved, whereas in patients with serosal infiltration, total omentectomy or bursectomy was performed. Omentectomy was performed in 36 patients in the LigaSure group and 30 in the conventional group ($P = 0.424$).

The primary end point of this study, median operative blood loss, was 288 ml in the LigaSure group and 260 ml in the conventional group ($P = 0.748$) (Table 3). The median operative time was similar in the two groups, at 223 min in the LigaSure group and 225 min in the conventional group ($P = 0.368$). The median daily volume of abdominal drainage fluid was 132 ml in the LigaSure group and 114 ml in the conventional group ($P = 0.418$), and the median duration of drainage was 7 and 6 days, respectively. When we examined these endpoints in a subgroup analysis of the patients who underwent omentum-preserving procedures, the blood loss was significantly lower in the LigaSure group than in the conventional group (179 vs. 245 ml, $P = 0.033$). The operative time was shorter in the LigaSure group, at 195 vs. 221 min ($P = 0.039$; Table 4).

Postoperative complications developed in 40 (25.3 %) patients: 24 from the LigaSure group and 16 from the conventional group ($P = 0.259$; Table 5). There were no significant differences between the groups in the eight major complications associated with gastrectomy. However, the incidences of pancreatic leakage and wound infection were slightly higher in the LigaSure group ($P = 0.094$). One patient in the LigaSure group underwent reoperation for residual tumor in the cut end of the stomach and five patients in the conventional group underwent reoperation, for postoperative bleeding, anastomotic leakage, anastomotic stenosis, bowel obstruction, and wound complications in the abdominal wall in one each. Two patients from the conventional group died during hospitalization, of tumor metastasis to the liver and peritoneum, and sepsis secondary to intestinal necrosis, respectively.

Table 3 Surgical outcomes

	LigaSure ($n = 80$)	Conventional ($n = 78$)	P
Blood loss (ml)			
Median (range)	288 (25–1430)	260 (40–1258)	0.748*
Operative time (min)			
Median (range)	223 (130–405)	225 (111–415)	0.368*
Blood transfusion			
Yes	6	8	0.586**
No	74	70	
Volume of drainage (ml/day)			
Median (range)	132 (8–1120)	114 (18–730)	0.418*
Duration of drainage (days)			
Median (range)	7 (1–36)	6 (1–108)	0.245*

P values were calculated using the *Mann–Whitney U test for operative time and blood loss, and **Fisher's exact test for blood transfusion

Table 4 Subset analysis of patients who underwent omentum-preserving gastrectomy and omentectomy

	LigaSure	Conventional	P
Omentum-preserving gastrectomy	($n = 44$)	($n = 48$)	
Blood loss (ml)			
Median (range)	179 (25–637)	245 (40–1105)	0.033
Operative time (min)			
Median (range)	195 (130–290)	221 (142–415)	0.039
Omentectomy	($n = 36$)	($n = 30$)	
Blood loss (ml)			
Median (range)	400 (75–1430)	305 (80–1258)	0.197
Operative time (min)			
Median (range)	244 (145–405)	236 (111–329)	0.122

P values were calculated using the Mann–Whitney U test

There were no postoperative deaths in the LigaSure group. The median hospital stay was 16 days (range 8–67) for the LigaSure group and 15 days (range 7–122) for the conventional group ($P = 0.333$; Table 5). There was no significant difference in the total cost associated with hospitalization between the LigaSure and conventional groups (median \$17,060 vs. \$16,520, $P = 0.702$).

Discussion

Several clinical studies have demonstrated that the LigaSure vessel sealing system decreases both the blood loss and operative time associated with hemorrhoidectomy [5, 17], hysterectomy [18, 19], splenectomy, [8] and hepatectomy [9]. In the present randomized controlled trial we hypothesized that the use of LigaSure might also improve the surgical outcomes of gastrectomy for gastric cancer, but surgery using the LigaSure technique was not shown to be significantly superior to conventional surgery.

Table 5 Postoperative complications and hospital mortality

	LigaSure ($n = 80$)	Conventional ($n = 78$)	P
Total complications	24	16	0.259
Postoperative bleeding	0	1	0.494
Anastomotic leakage	0	1	0.494
Pancreatic leakage	7	1	0.094
Abdominal abscess	2	2	1.000
Wound infection	7	1	0.094
Bowel obstruction	4	3	1.000
Pneumonia	3	1	0.620
Anastomotic stenosis	2	1	1.000
Other	3	7	0.207
Re-operation	1	5	0.114
Hospital death	0	2	0.242
Postoperative hospital stay (days)	16 (8–67)	15 (7–122)	0.333

P values were calculated using Fisher's exact test

These findings can be explained by the varying utility of LigaSure from one type of surgery to another. Operations where LigaSure was shown to provide an advantage involve the excision of an organ where the vessel-sealing device can play a prominent role. In contrast, radical gastrectomy for gastric cancer consists of three different phases: resection of the stomach, lymphadenectomy, and reconstruction. Certainly, the vessel sealing system may be most useful during the resection phase, but it is not suitable for the meticulous manipulation involved in lymphadenectomy and bursectomy because the tip of the device is blunt. Moreover, LigaSure has almost no role in reconstruction and anastomosis, which are as time-consuming as resection of the stomach. It is likely that individual manual ligation and dissection take more time and incur more blood loss than mechanical sealing by LigaSure, but using LigaSure did not result in an overall reduction in the operative time or total blood loss from the beginning of laparotomy until skin closure. This explanation is supported by the results of the subgroup analysis of patients who underwent omentum-preserving gastrectomy. For these patients with relatively early stage cancers, the omentum was segmented in the middle and prophylactic lymphadenectomy and bursectomy were omitted, leading to a relatively dominant advantage of LigaSure in the course of the entire operation, with a 66 ml reduction in blood loss ($P = 0.033$) and a 26 min reduction in operative time ($P = 0.039$) compared with conventional surgery.

Contrary to our results, Lee et al. [20] reported that the use of LigaSure shortened the operative time and decreased blood loss in gastric cancer resection with D2 lymphadenectomy in a randomized controlled trial. This discrepancy may be due to differences in the surgical procedures defined by the protocols of the two trials. In the LigaSure group, they sealed all of the lymphatic ducts and blood vessels using LigaSure without any suture ligation, whereas in the present study we used hand ligation in addition to LigaSure to occlude the major arteries and vessels. We also used manual manipulation in the delicate parts of lymphadenectomy, even in the LigaSure group. A similar discrepancy was demonstrated between two randomized trials evaluating LigaSure in hepatic resection [9, 21], and those authors also attributed the discordant results to differences in surgical techniques between the two studies [21].

Although the overall incidence of operative complications did not differ significantly between the two groups in this study, it is noteworthy that the incidence of pancreatic leakage was slightly higher in the LigaSure group ($P = 0.094$). The reason for this is not clear, but we speculate that the mechanical compression of tissues adjacent to the pancreas with LigaSure may cause a minor leakage of pancreatic juice. Although our present study did not show a significant difference in the drainage volume between the two groups, a risk of pancreatic leakage and lymphorrhea with manipulation around the pancreas during lymphadenectomy with the use of LigaSure should be borne in mind. This is further supported by the previous report that the use of LigaSure increased the volume of the drainage fluid after radical gastrectomy compared with conventional surgery [20],

Multicenter randomized controlled trials of surgical procedures are affected by the experience of and variations among surgeons [22]. In the present study, the median blood loss and operative time (260 ml and 225 min), as well as the operative morbidity (20.5 %), in the conventional group was consistent with the results from our previous studies [15, 16]. Furthermore, we found no significant differences in the results of surgical outcomes between the participating hospitals (data not shown), indicating that the quality of surgery in our study is consistent.

In conclusion, the application of LigaSure to open gastrectomy for gastric cancer was not associated with a reduction in blood loss or operative time compared with conventional techniques. The effectiveness of the device is limited, and its use should be based on the individual operator's decision, depending on the type of surgery.

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Conflict of interest None declared.

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Prognostic Value of CEA and CK20 mRNA in the Peritoneal Lavage Fluid of Patients Undergoing Curative Surgery for Gastric Cancer

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Abstract

Background Peritoneal recurrence is the most common type of recurrence in gastric cancer. Although cytological examination of peritoneal lavage fluid has been used to predict peritoneal spread, peritoneal recurrences often occur even in patients with negative cytology. Our previous retrospective study suggested that reverse transcriptase-polymerase chain reaction (RT-PCR) using peritoneal lavage fluid may be useful for predicting peritoneal recurrence in patients with negative cytology. This prospective study was conducted to validate the clinical impact of this RT-PCR method.

Methods From July 2009 to June 2012, a total of 118 cT2-4 gastric cancer patients underwent surgery. Since 14 patients were ineligible because they had incurable factors, the remaining 104 eligible patients were evaluated for carcinoembryonic antigen (CEA) and cytokeratin 20 (CK20) messenger RNA (mRNA) using RT-PCR. If either CEA or CK20 mRNA was detected by RT-PCR, the patient was defined as PCR-positive as in our previous study. The association between recurrence-free survival (RFS) and background factors was analyzed using Cox proportional hazards models.

Results Of 104 patients, 16 (15.4 %) were positive for either CEA or CK20. PCR-positive patients had significantly worse RFS than PCR-negative patients (log-rank $p = 0.007$). Regarding the pattern of recurrence, 4 of 16 (25 %) PCR-positive patients and 2 of 88 (2 %) PCR-negative patients had peritoneal recurrence ($p < 0.001$), but there were no significant differences in recurrence at other sites. Cox multivariate analysis indicated only PCR-positivity as a significant predictor of poor RFS ($p = 0.029$).

Conclusion This prospective study demonstrated that CEA and CK20 PCR results could predict peritoneal recurrence after curative surgery.

Introduction

The prognosis of advanced gastric cancer remains poor, even after curative surgery. Peritoneal dissemination, mainly caused by the seeding of free cancer cells from the primary lesion, is the most common type of recurrence [1]. Cytological examination of peritoneal lavage fluid collected during surgery is used to predict peritoneal spread since positive peritoneal cytology (CY1) has been found to be an independent predictor of disease recurrence and poor overall survival [2–4]. However, peritoneal recurrences often occur even in patients with negative cytology, which indicates that cytological examination is not sensitive enough for the detection of residual cancer cells in the peritoneum.

Molecular diagnosis using reverse transcriptase-polymerase chain reaction (RT-PCR) has been used to detect cancer micrometastases [5–7]. Carcinoembryonic antigen (CEA) and cytokeratine-20 (CK20) are the most common targets for detecting isolated tumor cells using PCR [8–10],

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and we previously reported that, among 36 gastric cancer patients, PCR-positive patients had significantly worse survival than PCR-negative patients [11]. However, our previous study was retrospective in nature and included a small number of patients, so we conducted a prospective study to validate the prognostic value of molecular detection in over 100 patients undergoing curative surgery for gastric cancer.

Patients and methods

Patients

Peritoneal lavage fluid was prospectively collected during surgery from 118 consecutive patients with cT2-4 gastric cancer at Osaka University Hospital between July 2009 and June 2012. All patients were histologically diagnosed with adenocarcinoma of the stomach. Patients with incurable factors, such as peritoneal metastases (P1), CY1, or other distant metastases (M1) were excluded from this study.

Peritoneal lavage fluid was collected as described in our previous report [12]. In brief, peritoneal lavage fluid was immediately obtained from the pouch of Douglas and the left subdiaphragmatic space after laparotomy or the insertion of trocars. We injected 100 mL of normal saline and suctioned again. Approximately half of the sample was examined cytologically and the remainder was centrifuged at $300\times g$ for 5 min. Cells were then suspended in TRIzol reagent (Invitrogen, Carlsbad, CA, USA) and stored at −80 °C. Pathological staging of the tumor was based on the seventh edition of the International Union Against Cancer (UICC) tumor–node–metastasis classification guidelines [13]. The study protocol was approved by the institutional review board of Osaka University Hospital. All patients provided written informed consent for their samples to be used in research.

Quantitative RT-PCR

RNA isolation and RT-PCR were performed using a method similar to those in our previous studies [11, 12]. Frozen samples in TRIzol reagent were thawed and total RNA was extracted using the acid guanidinium thiocyanate-phenol–chloroform method [14]. Its concentration was determined spectrophotometrically by measuring the absorbance of RNA at 260 nm. First strand complementary DNA (cDNA) was synthesized from total RNA (1 μg), mixed with RT reaction reagents, including oligo-(dT)15 primer, using the protocol recommended by the manufacturer (Promega, Madison, WI, USA). CEA-specific oligonucleotide primers for RT-PCR were 5′-TCTGGAACTTCTCCTGGTCTCTC AGCTGG-3′ (forward) and 5′-TGTAGCTGTTGCAAATG CTTTAAGGAAGAAGC-3′ (reverse) to amplify a 160 bp PCR product. CK20-specific oligonucleotide primers for RT-PCR were 5′-GGTCGCGACTACAGTGCATATTACA -3′ (forward) and 5′-CCTCAGCAGCCAGTTTAGCAT TATC-3′ (reverse) to amplify a 121 bp PCR product. The integrity of extracted RNA was confirmed by RT-PCR analysis of a housekeeping gene, porphobilinogen deaminase (*PBGD*). Primer sequences for *PBGD* were 5′-TGTCT GGTAACGGCAATGCGGCTGCAAC-3′ (forward) and 5′-TCAATGTTGCCACCACACTGTCCGTCT-3′ (reverse). The integrity of all RNA samples was verified by quantitative RT-PCR for *PBGD* in each sample. The emission intensity of SYBR Green was detected in real time with the LightCycler 3.5 instrument (Roche Diagnostics, Mannheim, Germany). The external standards were prepared by serial dilution (1:1–1:10,000) of cDNA from the MKN45 cell line. CEA messenger RNA (mRNA) was detected to 10,000 times attenuation (1:10,000), and CK20 mRNA was detected to 500 times attenuation (1:500). If either CEA or CK20 mRNA was detected by RT-PCR analysis, the patient was defined as PCR-positive, similar to our previous study [11].

Statistical analysis

Patient clinicopathological data were prospectively recorded. The relationship between RT-PCR results and various background factors was assessed using the χ^2 test. Recurrence-free survival (RFS) was defined as the time from surgery to first recurrence. RFS was censored at the time of the last follow-up or death without recurrence. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. The impact of background factors (age, sex, histology, neoadjuvant chemotherapy, and pathological T and N stages) on survival was analyzed with univariate and multivariate Cox proportional hazards models. p values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS Statistics software, version 20 (IBM Corp., Armonk, NY, USA).

Results

PCR results

From July 2009 to June 2012, a total of 118 patients with cT2-4 gastric cancer underwent surgery; 14 were ineligible due to incurable factors such as P1, CY1, or M1. The remaining 104 eligible patients were evaluated for CEA and CK20 mRNA using RT-PCR. Among the 104 patients, 11 patients (10.6 %) were positive for CEA and ten patients (9.6 %) were positive for CK20 (Table 1). In total,

Table 1 RT-PCR positive rate for each marker

CK20	CEA, *n* (%)	
	Positive	Negative
Positive	5 (4.8 %)	5 (4.8 %)
Negative	6 (5.8 %)	88 (84.6 %)

CEA carcinoembryonic antigen, *CK* cytokeratin, *RT-PCR* reverse transcriptase-polymerase chain reaction

16 patients (15.4 %) were positive for either CEA or CK20, and we defined these patients as PCR-positive.

We examined the relationship between the PCR results and background factors (Table 2). The PCR-positive group included more female patients and higher pathological N-stage patients than the PCR-negative group ($p = 0.032$, $p = 0.029$). No significant relationship was observed with other background factors, including age, histology, surgical approach, neoadjuvant chemotherapy, clinical T or N stage, and pathological T stage. Regarding the neoadjuvant chemotherapy, we used three types of regimens; S-1 plus cisplatin ($n = 6$), S-1 plus docetaxel ($n = 2$), and S-1 plus cisplatin plus docetaxel ($n = 12$). There was no significant difference in neoadjuvant regimens between PCR-positive and negative patients ($p = 0.25$).

Prognostic value of CEA and CK20 mRNA

The median follow-up in this prospective study was 18.2 months, during which 7 of 16 (44 %) PCR-positive patients and 13 of 88 (15 %) PCR-negative patients had recurrences ($p = 0.007$). PCR-positive patients had significantly worse RFS than PCR-negative patients (log-rank $p = 0.007$) (Fig. 1), and the hazard ratio for recurrence in PCR-positive patients was 3.28 (95 % confidence interval [CI] 1.31–8.24). The 2-year RFS rate in PCR-positive patients was 50.3 %, while that of PCR-negative patients was 83.0 %. Regarding the pattern of recurrence, 4 of 16 (25 %) PCR-positive patients and 2 of 88 (2 %) PCR-negative patients had peritoneal recurrence ($p < 0.001$), while PCR-positive and -negative patients were similar with respect to other sites of recurrence (Table 3).

We conducted Cox univariate and multivariate analyses to find independent prognostic factors of RFS. The multivariate analysis indicated that PCR-positivity was a significant predictor of poor RFS ($p = 0.029$) (Table 4).

Table 2 Relationship between PCR results and background factors

Factors	PCR-positive ($n = 16$)	PCR-negative ($n = 88$)	*p* value*
Age, years			0.30
≤65	4 (25 %)	34 (39 %)	
>65	12 (75 %)	54 (61 %)	
Sex			0.032
Male	8 (50 %)	67 (76 %)	
Female	8 (50 %)	21 (24 %)	
Histology			0.74
Differentiated	8 (50 %)	48 (55 %)	
Undifferentiated	8 (50 %)	40 (45 %)	
Surgical approach			0.71
Open	15 (94 %)	80 (91 %)	
Laparoscopic	1 (6 %)	8 (9 %)	
Neoadjuvant chemotherapy			0.52
Yes	4 (25 %)	16 (18 %)	
No	12 (75 %)	72 (82 %)	
cT			0.86
T2	3 (19 %)	18 (20 %)	
T3	6 (38 %)	27 (31 %)	
T4	7 (44 %)	43 (49 %)	
cN			0.50
N0	6 (38 %)	47 (53 %)	
N1	4 (25 %)	17 (19 %)	
N2–3	6 (38 %)	24 (27 %)	
pT			0.14
T1–2	2 (13 %)	33 (38 %)	
T3	10(63 %)	42 (48 %)	
T4	4 (25 %)	13 (15 %)	
pN			0.029
N0	5 (31 %)	52 (59 %)	
N1	4 (25 %)	22 (25 %)	
N2–3	7 (44 %)	14 (16 %)	

Data are presented as *n* (%)

PCR polymerase chain reaction

* χ^2 test

Discussion

Peritoneal recurrence of gastric cancer occurs often, even in patients who have undergone curative resection. Although peritoneal lavage cytology has been widely used for the detection of isolated tumor cells and prediction of peritoneal recurrence, the sensitivity is relatively low. Our previous retrospective study involving 36 gastric cancer patients suggested that RT-PCR of peritoneal lavage fluid may be useful in predicting peritoneal recurrence in patients with negative cytology (CY0) [11]. This prospective study involving over 100 patients undergoing curative surgery for cT2-4 gastric cancer revealed that PCR results were a significant and independent prognostic factor of RFS. Indeed, 25 % of PCR-positive patients experienced peritoneal recurrence, compared with only 2 % of PCR-

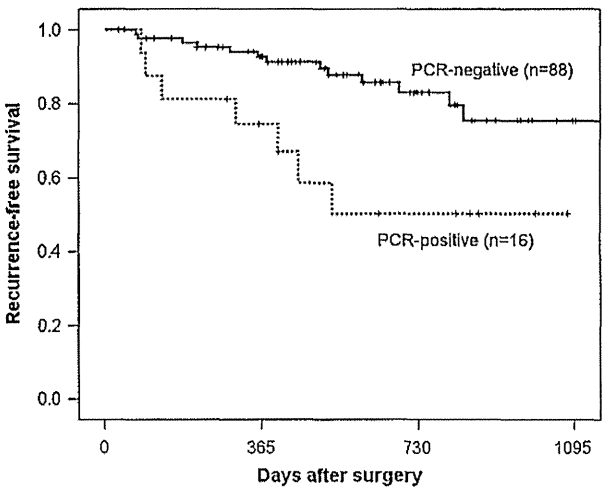

Fig. 1 Recurrence-free survival of PCR-positive patients ($n = 16$) versus PCR-negative patients ($n = 88$). *PCR* polymerase chain reaction

Table 3 Sites of tumor recurrence

Site	PCR-positive ($n = 16$)	PCR-negative ($n = 88$)	p value*
Peritoneum	4 (25 %)	2 (2 %)	<0.001
Liver	2 (13 %)	8 (9 %)	0.67
Lymph nodes	1 (6 %)	2 (2 %)	0.38
Others	1 (6 %)	2 (2 %)	0.38

Data are presented as n (%). Both groups had one duplicate site of recurrence

PCR polymerase chain reaction

* χ^2 test

negative patients. Therefore, this study demonstrated the clinical usefulness of PCR of peritoneal lavage fluid.

The RT-PCR technique has become popular as a highly sensitive method for detecting cancer cells. CEA is the most common tumor marker, and has been reported to be a reliable target for the detection of isolated tumor cells [10, 15, 16]. Ito et al. [17] reported that survival in patients with positive CEA mRNA was significantly worse than in patients with negative CEA mRNA in their retrospective study. However, another study reported that CEA frequently resulted in false positives [18], because the expression level of CEA mRNA was heterogeneous in gastric tumors [16] and there is weak expression in non-cancerous cells, such as mesothelial cells [10]. Thus, in order to more precisely predict recurrence, it may be necessary to use multiple markers [16, 19, 20]. Since CK20 is usually expressed in adenocarcinomas, it is one of the candidates for improving the sensitivity of gastric cancer cell detection [21]. Tamura et al. [22] reported that detection of CEA and CK20 mRNA by RT-PCR with peritoneal lavage fluid was useful for identifying patients at high risk of peritoneal recurrence. However, their study included many patients with incurable factors such as P1, CY1, or M1. Such incurable patients should be treated with intensive chemotherapy, regardless of PCR results. Therefore, we only included patients without incurable factors in this study in order to identify patients who need intensive adjuvant chemotherapy.

Although we successfully demonstrated associations between peritoneal recurrence and CEA and CK20 PCR results in our preliminary reports, one limitation of this study was the relatively small number of patients and the short follow-up period. Although our study could not evaluate overall survival due to the low number of events, RFS could be evaluated. We think a multicenter study with a larger cohort and a longer follow-up period is required to evaluate the generalizability of this method.

In conclusion, our prospective study confirmed our preliminary findings that CEA and CK20 RT-PCR results could predict peritoneal recurrence after curative surgery. This sensitive system can be used to identify high-risk patients who require intensive adjuvant chemotherapy and close follow-up. When this system is used as a preoperative screening tool, with peritoneal lavage fluid collected by staging laparoscopy, we can also do neoadjuvant chemotherapy for PCR-positive patients before surgery.

Table 4 Univariate and multivariate Cox analysis of recurrence-free survivals

	Univariate		Multivariate	
	HR(95 % CI)	p value	HR (95 % CI)	p value
Age (≤65 years)	1.06 (0.43–2.59)	0.90	1.07 (0.37–3.11)	0.90
Sex (male)	1.72 (0.57–5.13)	0.33	3.02 (0.89–10.3)	0.077
Histology (undifferentiated)	1.95 (0.75–5.08)	0.17	1.95 (0.71–5.38)	0.20
Neoadjuvant chemotherapy (yes)	2.27 (0.87–5.94)	0.094	2.02 (0.72–5.63)	0.18
pT (T3–4)	3.51 (1.02–12.0)	0.046	2.17 (0.59–8.01)	0.24
pN (N1–3)	1.88 (0.78–4.55)	0.16	1.44 (0.55–3.73)	0.46
PCR (positive)	3.28 (1.31–8.24)	0.011	3.49 (1.14–10.7)	0.029

CI confidence interval, *HR* hazard ratio, *PCR* polymerase chain reaction

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Conflicts of interest The authors have no conflicts of interest to declare.

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Randomized clinical trial

Ten-year follow-up results of a randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy for adenocarcinoma of the oesophagogastric junction or gastric cardia

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Background: The optimal surgical approach for treatment of oesophagogastric junction (OGJ) cancer is controversial. A randomized clinical trial (JCOG9502) comparing transhiatal (TH) and left thoracoabdominal (LTA) approaches was stopped after the first interim analysis owing to limited efficacy for LTA resections. Complete 10-year follow-up data are now available.

Methods: Patients with histologically proven adenocarcinoma of the OGJ or gastric cardia with oesophageal invasion of 3 cm or less were randomized to a TH or LTA approach. Both groups underwent total gastrectomy and splenectomy with D2 nodal dissection plus para-aortic lymphadenectomy above the left renal vein. For LTA, a thorough mediastinal lymphadenectomy below the left inferior pulmonary vein was also mandatory. The primary endpoint was overall survival.

Results: A total of 167 patients (82 TH, 85 LTA) were enrolled. The 10-year overall survival rate was 37 (95 per cent c.i. 26 to 47) per cent for the TH approach and 24 (15 to 34) per cent for the LTA technique ($P = 0{\cdot}060$). The hazard ratio for death was 1·42 (0·98 to 2·05) for the LTA technique. Subgroup analysis based on the Siewert classification indicated non-significant survival advantages in favour of the TH approach.

Conclusion: LTA resections should be avoided in the treatment of adenocarcinoma of the OGJ or gastric cardia. Registration number: NCT00149266 (https://www.clinicaltrials.gov).

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Introduction

The incidence of adenocarcinoma of the oesophagogastric junction (OGJ) has increased in developed countries over the past 20 years[1,2]. Although surgery is considered essential as part of a curative treatment strategy for most patients, survival remains poor even in those who undergo R0 resection, with or without additional therapy[3]. To improve the R0 resection rate and long-term outcomes, extended surgery with *en bloc* lymphadenectomy has been attempted for many years. When considering tumours arising from the cardia (Siewert type III[4]), or those at the OGJ (Siewert type II) with minimal oesophageal extension where total gastrectomy seems appropriate, left thoracoabdominal (LTA) and transhiatal (TH) approaches have been advocated for curative resection. There is no clear information to indicate whether the operative approach influences long-term outcome.

In East Asian countries, including Japan, the majority of OGJ tumours are Siewert types II and III[5]. The incidence of lower mediastinal lymph node metastasis from type II and III tumours is reported to range from 10 to 40 per cent[6–12]. Some institutions prefer the LTA to the TH approach in order to perform lymph node dissection in the lower mediastinal field and obtain a safe surgical margin[6,7], whereas others prefer the TH technique owing

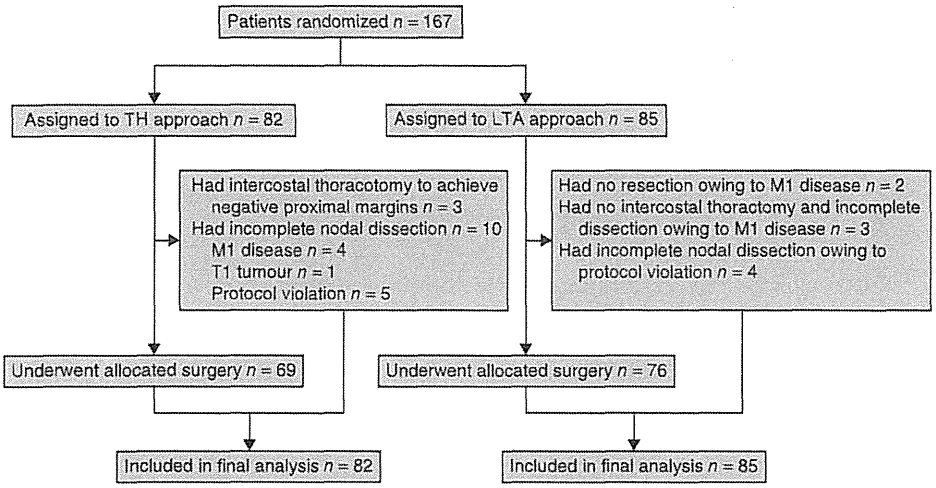


Fig. 1 CONSORT diagram for the JCOG9502 trial. TH, transhiatal; LTA, left thoracoabdominal

to lower postoperative morbidity and the poor prognosis of patients with metastasis in the lower mediastinum[8,9]. To evaluate the survival benefit of these two approaches, the Japan Clinical Oncology Group (JCOG) initiated a phase 3 open-label randomized clinical trial in 1995.

In this trial, JCOG9502, 167 patients with adenocarcinoma of the OGJ or gastric cardia were enrolled. The first interim analysis conducted in December 2003 showed that the predictive probability of the LTA approach being significantly better than the TH technique was as low as 3·7 per cent, although the LTA operation resulted in increased postoperative morbidity[13]. The recommendation from the JCOG Data and Safety Monitoring Committee to close study accrual and publish the results was accepted. It seems important, therefore, to report the long-term data, to ensure that the conclusion reached in the earlier publication remains valid, because many surgeons in Japan and some in the West still recommend the LTA approach[14,15]. The present report is the result of the final analysis, based on 10 years of follow-up data.

Methods

JCOG9502 was designed as a multicentre prospective randomized phase 3 trial. The study protocol was approved by the JCOG Clinical Trial Review Committee and the institutional review boards of all 27 participating Japanese hospitals before study initiation. All patients provided written informed consent. The eligibility criteria for the study consisted of histologically confirmed adenocarcinoma of the gastric body or cardia with oesophageal invasion of 3 cm or less, cT2–4 category, age 75 years or less, no distant metastasis, no lymph nodes larger than 1 cm in the hepatoduodenal ligament or para-aortic field, a forced expiratory volume in 1 s of at least 50 per cent, and an arterial oxygen tension of at least 9·3 kPa while breathing ambient air.

Procedures

After confirming eligibility, surgeons contacted the JCOG Data Centre by telephone to receive a randomly generated assignment (1 : 1) into one of the treatment groups. A minimization method was used to stratify treatment groups according to institution, cT category (cT2 *versus* cT3/4) and Borrmann type (0–2 *versus* 3 or 5) for random number generation.

The TH approach consisted of total gastrectomy with D2 lymphadenectomy including splenectomy. Additional dissection of the lymph nodes along the left inferior phrenic vessels and the para-aortic nodes lateral to the aorta and above the left renal vein was performed in patients with curable disease. This included patients with positive findings on peritoneal lavage cytology, but without overt peritoneal metastasis. All procedures were undertaken via laparotomy, and the lower mediastinum was accessed transhiatally. Mediastinal resection included the lower oesophagus and perioesophageal lymph nodes only.

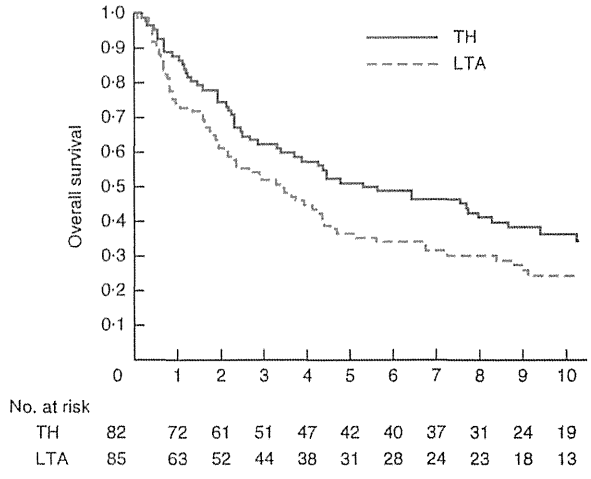
An oblique incision over the left thorax and abdomen was made for the LTA approach, followed by the same procedure in the abdominal cavity as for the TH operation. In the thoracic cavity, a thorough mediastinal node dissection below the left inferior pulmonary vein was undertaken with appropriate oesophagectomy.

Each surgeon selected the type of reconstruction. If the operation was considered curative (no macroscopic residual

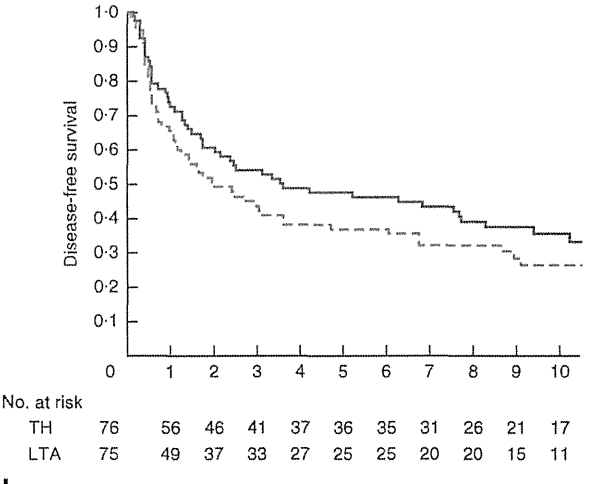
Table 1 Patient characteristics

	TH group ($n=82$)	LTA group ($n=85$)
Age (years)*	60 (36–75)	63 (38–75)
Sex ratio (*M* : *F*)	71 : 11	63 : 22
Borrmann type		
0–2	36	37
3 or 5	46	48
Siewert classification†		
Type II	52	43
Type III	27	36
Non-OGJ tumour	3	4
Tumour size (cm)*†	6·2 (2·5–19)	7·0 (2·0–18)
Histological type†		
Differentiated	42	43
Undifferentiated	40	40
Clinical tumour category‡§		
cT2	20	20
cT3/4	62	65
Pathological tumour category†‡§		
pT1b	2	1
pT2a	10	6
pT2b	24	35
pT3	39	37
pT4	7	4
Pathological node category†‡		
pN0	14	15
pN1	24	27
pN2	30	25
pN3/4	14	16
Pathological node category†§		
pN0	14	15
pN1	35	28
pN2	16	26
pN3	17	14
No. of positive nodes*†	5 (0–53)	5 (0–52)
Histological oesophageal invasion (cm)*†	1·6 (0–4·5)	1·2 (0–7·0)
Residual tumour		
R0	76	75
R1/2	6	10

*Values are median (range). †Data not available for two patients in the left thoracoabdominal (LTA) group who did not undergo surgical resection owing to M1 disease. ‡Japanese Classification of Gastric Carcinoma, 12th edition[16]; §International Union Against Cancer (UICC) TNM classification, 6th edition[17]. TH, transhiatal; OGJ, oesophagogastric junction.



a Overall survival



b Disease-free survival

Fig. 2 Kaplan–Meier curves of **a** overall and **b** disease-free survival in all randomized patients by treatment group. TH, transhiatal approach; LTA, left thoracoabdominal approach. **a** Hazard ratio (HR) 1·42 (95 per cent c.i. 0·98 to 2·05; $P=0·970$ and $P=0·060$, 1- and 2-sided log rank test respectively); **b** HR 1·28 (0·87 to 1·89; $P=0·892$ and $P=0·215$, 1- and 2-sided log rank test respectively)

disease), no further treatment was allowed unless recurrence was diagnosed.

Statistical analysis

The primary endpoint was overall survival (OS). Secondary endpoints were disease-free survival (DFS), morbidity and mortality, postoperative symptoms and postoperative respiratory function. All in-hospital deaths and deaths within 1 month of surgery were defined as hospital mortality. Operative procedures and pathology results were recorded according to the 12th edition of the Japanese Classification of Gastric Carcinoma (JCGC)[16]. Tumour stage is reported here using the sixth edition of the TNM classification[17]. All tumours were classified as Siewert type II, type III, or non-OGJ if the tumour epicentre was located more than 5 cm distal to the OGJ based on pathological examination of the resected specimen.

Table 2 Sites of first recurrence

	TH group ($n=82$)	LTA group ($n=85$)	P^*
Lymph nodes	12 (15)	19 (22)	0·235
Peritoneum	9 (11)	10 (12)	1·000
Liver	8 (10)	9 (11)	1·000
Lung	5 (6)	5 (6)	1·000
Pleura	3 (4)	1 (1)	0·362
Other	5 (6)	2 (2)	0·271

Values in parentheses are percentages. TH, transhiatal; LTA, left thoracoabdominal. *Fisher's exact test, two-sided.

The original intention was to recruit 302 patients to achieve a one-sided α of 0·05 and statistical power of 80 per cent to detect a difference between the two groups, assuming a 5-year survival rate of 15·5 per cent for the TH approach *versus* 26·0 per cent for the LTA procedure. The projected accrual period was 4 years. After 8 years of slow accrual, the JCOG Data and Safety Monitoring Committee approved an amendment to the sample size and analysis plan. The amended sample size was 250, with a one-sided α of 0·1 and power of 80 per cent, with an accrual period of 12 years in total and 8 years of follow-up. Three interim analyses were planned.

OS was measured from the date of randomization to the date of death from any cause. Among patients who underwent R0 resection, DFS was measured from the date of randomization to the date of the first observation of disease recurrence or death from any cause. OS and DFS curves were estimated using the Kaplan–Meier method and compared with the log rank test. Subgroup analysis was performed by means of Cox regression to assess statistical interactions between treatment approach and 12 patient characteristics. Postoperative factors were also included in the Cox regression analysis to estimate their influence on survival. Two-sided P values were calculated for all tests. As the study was planned for one-sided testing, one-sided P values are presented for the primary endpoint. $P < 0·050$ was judged to be statistically significant. All analyses were based on an intention-to-treat basis. Statistical analyses were performed with SAS® version 9·2 (SAS Institute, Cary, North Carolina, USA).

Results

Between July 1995 and December 2003, 167 patients were enrolled, of whom 82 were randomly assigned to the TH and 85 to the LTA approach (*Fig. 1*). Baseline characteristics of the two groups were similar, except for Siewert classification (*Table 1*). There were 95 Siewert type II and 63 type III tumours. Seven patients had large gastric tumours invading the oesophagus that could not be classified by Siewert type. At operation, 141 patients (62 TH, 79 LTA) underwent mediastinal node dissection and 145 (72 TH, 73 LTA) had para-aortic node dissection. The rate of metastasis in mediastinal nodes was 5 per cent (3 of 62) in the TH group and 11 per cent (9 of 79) in the LTA group. The metastasis rate in para-aortic nodes was 18 per cent (13 of 72) and 12 per cent (9 of 73) respectively.

Operative details, including morbidity and mortality, postoperative symptoms and postoperative respiratory function, have been reported previously[13,18]. Median duration of surgery was 33 min longer for the LTA procedure than for the TH approach ($P=0·127$). Median blood loss was similar in the two groups (655 *versus* 673 ml for LTA and TH group respectively; $P=0·949$), but allogeneic blood transfusion was used more frequently in the LTA group (39 of 85, 46 per cent) than in the TH group (25 of 82, 30 per cent) ($P=0·056$). Patients in the LTA group had a higher morbidity rate: 42 (49 per cent) *versus* 28 (34 per cent) ($P=0·060$). For six selected major complications (pancreatic fistula, abdominal abscess, pneumonia, anastomotic leak, empyema thoracis and mediastinitis), the incidence was significantly higher following the LTA than the TH procedure: 35 (41 per cent) *versus* 18 (22 per cent) ($P=0·008$). There were two treatment-related deaths, both in the LTA group.

Median follow-up for all censored patients was 10·6 (range 5·1–17·1) years at the last follow-up in December 2012. There had been 52 and 63 deaths in the TH and LTA group respectively, with 42 and 50 patients respectively dying from cancer. The 5- and 10-year OS rates for all randomized patients were 51 (95 per cent c.i. 40 to 61) and 37 (26 to 47) per cent respectively for the TH approach, and 37 (26 to 47) and 24 (15 to 34) per cent for the LTA approach (*Fig. 2a*). The log rank test showed marginal differences between the groups (2-sided $P=0·060$, 1-sided $P=0·970$), and the hazard ratio (HR) for the LTA *versus* the TH approach was 1·42 (95 per cent c.i. 0·98 to 2·05). After adjustment for cT category and Borrmann type, stratified P values were 0·102 in two-sided and 0·949 in one-sided log rank tests, and the HR was 1·36 (0·94 to 1·98). In multivariable Cox regression analysis with seven baseline variables (age, sex, Borrmann type, Siewert classification, tumour size, histological type, cT category (JCGC 12th edition)), the HR was essentially unchanged: HR 1·33 (0·91 to 1·95). Per-protocol analysis (145 patients) also showed a HR of 1·44 (0·96 to 2·15) (2-sided $P=0·076$, 1-sided $P=0·962$) (*Fig. S1*, supporting information).

Among patients who underwent R0 or R1 resection, initial sites of recurrence were lymph nodes (31 patients), peritoneum (19), liver (17), lung (10), pleura (4) and other sites (7). The pattern of recurrence was similar in the two

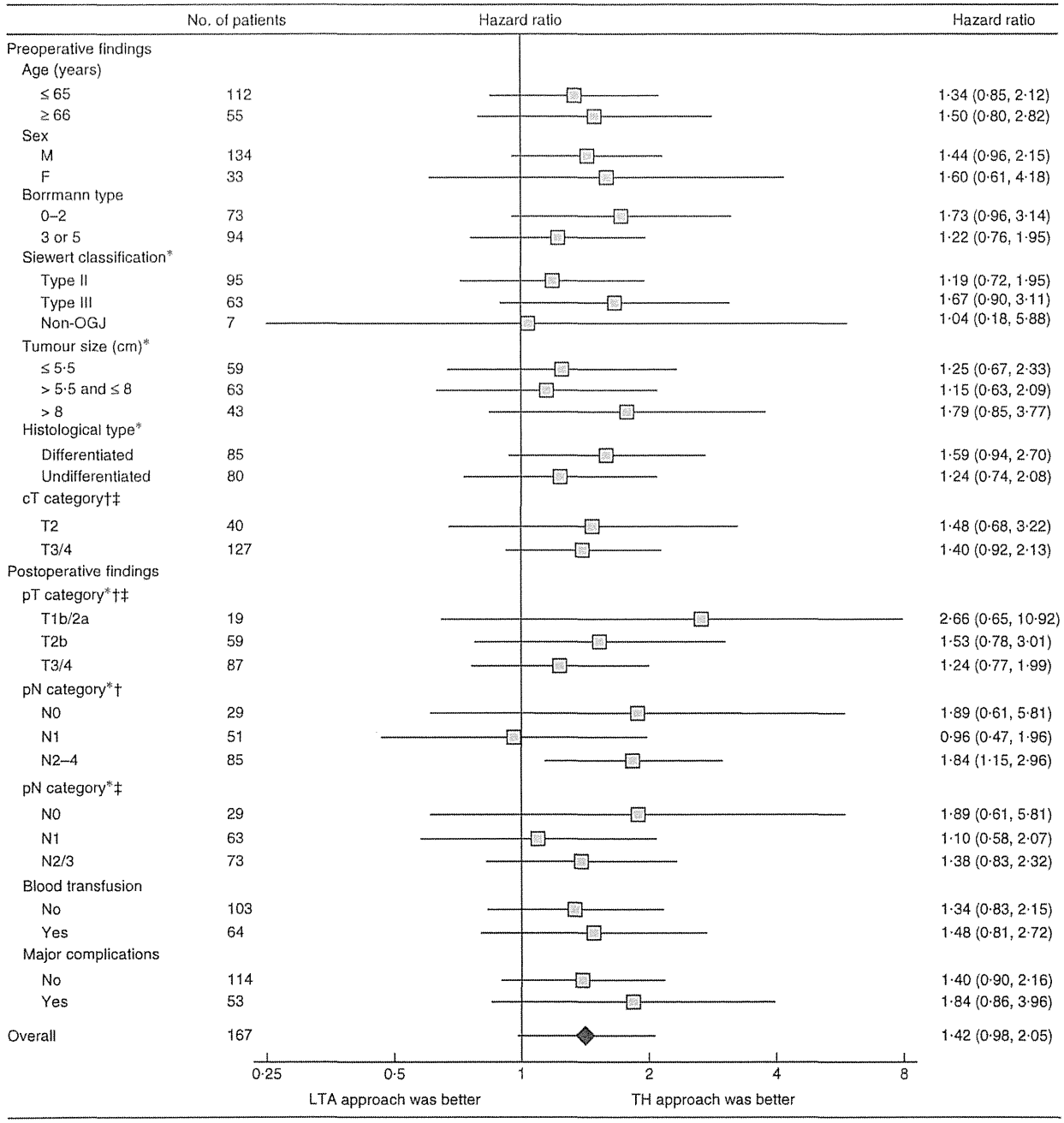


Fig. 3 Forest plot for overall survival in the subgroup analysis. *Data not available for two patients in the left thoracoabdominal (LTA) group who did not undergo surgical resection owing to M1 disease. Hazard ratios are shown with 95 per cent c.i. OGJ, oesophagogastric junction; TH, transhiatal. †Japanese Classification of Gastric Carcinoma, 12th edition[16]; ‡International Union Against Cancer (UICC) TNM classification, 6th edition[17]

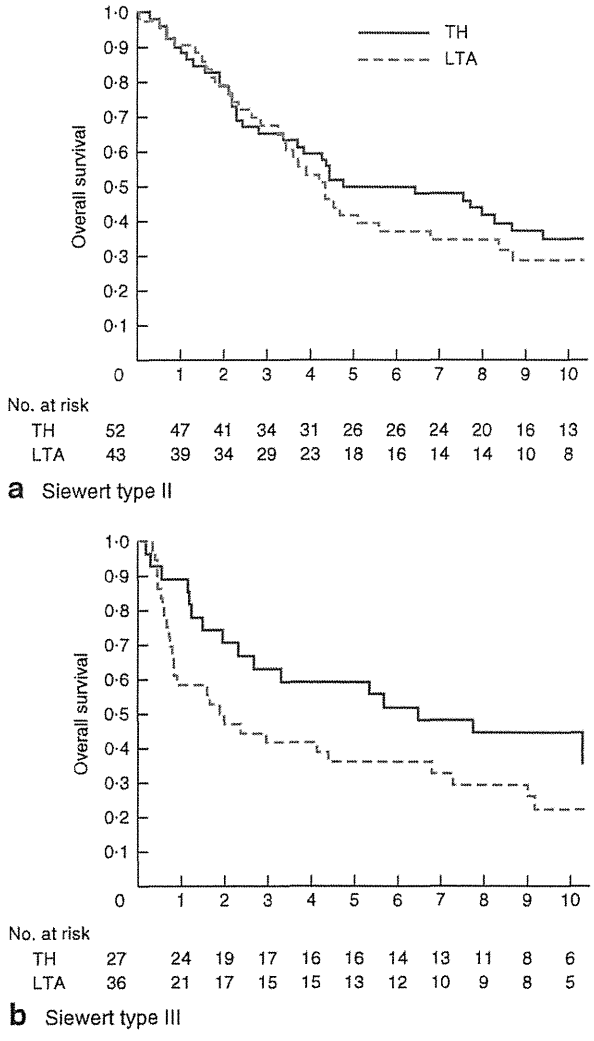


Fig. 4 Kaplan–Meier curves of overall survival in patients with **a** Siewert type II and **b** Siewert type III tumours by treatment group. TH, transhiatal approach; LTA, left thoracoabdominal approach. **a** Hazard ratio (HR) 1·19 (95 per cent c.i. 0·72 to 1·95; $P = 0·496$, 2-sided log rank test); **b** HR 1·67 (0·90 to 3·11; $P = 0·102$, 2-sided log rank test)

groups (*Table 2*). The 5- and 10-year DFS rates were 47 (95 per cent c.i. 36 to 58) and 36 (25 to 47) per cent for the TH approach, and 37 (26 to 48) and 26 (16 to 37) per cent for the LTA approach ($P = 0·215$) (*Fig. 2b*). The HR for the LTA group compared with the TH group was 1·28 (0·87 to 1·89).

There were no significant interactions between treatment effects and the patient characteristics examined (*Fig. 3*). For the 95 patients with Siewert type II tumours, 5- and 10-year OS rates were 50 (95 per cent c.i. 36 to 63) and 35 (22 to 48) per cent respectively for the TH approach, and 42 (27 to 56) and 29 (16 to 43) per cent for the LTA approach (HR 1·19, 95 per cent c.i. 0·72 to 1·95; $P = 0·496$) (*Fig. 4a*). Among 63 patients with Siewert type III tumours, 5- and 10-year OS rates were 59 (39 to 75) and 44 (26 to 62) per cent respectively for the TH approach, and 36 (21 to 51) and 22 (10 to 38) per cent for the LTA approach (HR 1·67, 0·90 to 3·11; $P = 0·102$) (*Fig. 4b*). For the subgroup of patients with type III tumours, excluding those with major complications from the survival analysis, the difference in OS between the groups was significant (HR 2·00, 0·99 to 4·05; $P = 0·050$).

The rate of metastasis in mediastinal lymph nodes was 10 per cent (8 of 81) for type II tumours compared with 5 per cent (3 of 55) for type III. The metastasis rate in para-aortic lymph nodes was 9 per cent (8 of 86) for type II compared with 22 per cent (12 of 54) for type III tumours. The 5-year OS rate for 22 patients with pathologically confirmed metastasis in the para-aortic nodes was 18 (95 per cent c.i. 6 to 36) per cent.

Discussion

This final analysis, based on 10-year follow-up data, has confirmed the conclusion reached in the earlier publication of the interim analysis[13]. Compared with the TH approach, the LTA approach offered no improvement in OS or DFS. The LTA technique did not reduce rates of cancer recurrence in lymph nodes, but was associated with greater morbidity and mortality. Although the LTA approach involved no increase in blood loss, more patients assigned to this approach received allogeneic blood transfusion, mainly to correct haemodynamic instability in the early postoperative period[13]. LTA cannot, therefore, be justified for the treatment of adenocarcinoma of the OGJ or gastric cardia if the length of oesophageal invasion is 3 cm or less.

Omloo and colleagues[19] reported the final results of a Dutch trial comparing a right thoracic with the TH approach for Siewert type I and II tumours. In their trial, subgroup analysis revealed a 14 per cent 5-year OS advantage with the right thoracic approach for patients with type I tumours, but no difference for patients with type II tumours (27 per cent *versus* 31 per cent in the TH group). The present study confirms the results of the Dutch study for patients with type II tumours based on surgical approach. For patients with type III tumours, the LTA approach was associated with a 22 per cent lower 10-year OS rate than the TH technique, and this difference in OS between the two groups occurred within 1 year after surgery. Although the reason for worse survival of patients who underwent LTA in this subgroup is unclear, the greater

need for allogeneic blood transfusion and increased postoperative morbidity compared with that in the TH group may be relevant. The earlier results of the trial[18] also noted more weight loss, postoperative symptoms and respiratory dysfunction following the LTA operation. In the analysis of patients with type III tumours, excluding those with postoperative complications, OS was significantly better in the TH group despite the biases inherent in this *post hoc* method. This finding strengthens the recommendation that LTA should be avoided, at least for patients with Siewert type III tumours.

This study is also informative regarding para-aortic lymph node metastasis from tumours of the OGJ, as prophylactic dissection of the para-aortic nodes lateral to the aorta and above the left renal vein was required in both treatment groups. The rate of metastasis in the para-aortic nodes among patients who had dissection was 15·2 per cent (22 of 145), and the 5-year OS rate of patients with pathologically confirmed metastases in the para-aortic nodes was 18 (95 per cent c.i. 6 to 36) per cent. Previous studies[20,21] reported metastasis to the para-aortic field in approximately 15 per cent of OGJ cancers, representing the most frequent site of nodal recurrence. Para-aortic lymph node dissection has been identified as an independent prognostic factor in patients with pT3/4 Siewert type II tumours[22]. Although the randomized clinical trial (JCOG9501)[23] failed to show a survival advantage for prophylactic para-aortic lymph node dissection in patients with gastric cancer, the possibility of improving survival with prophylactic para-aortic lymph node dissection in patients with Siewert type II or III tumours remains unclear, as these patients were excluded from JCOG9501.

Many institutions include neoadjuvant or adjuvant therapy in their standard treatment protocols for patients with oesophageal or gastric cancer. A Dutch randomized clinical trial[24] evaluating preoperative chemoradiotherapy using carboplatin and paclitaxel for oesophageal or OGJ tumours demonstrated significantly better OS in a preoperative chemoradiotherapy group *versus* surgery alone. In East Asia, two large-scale randomized clinical trials[25,26], each with over 1000 patients, have evaluated postoperative chemotherapy for resectable gastric or OGJ cancer; both demonstrated a significant survival benefit with postoperative chemotherapy. As the present study did not allow neoadjuvant or adjuvant treatment until recurrence, the isolated effect of the TH *versus* the LTA approach on survival without any treatment interactions associated with perioperative treatment could be evaluated. Selection of the appropriate surgical procedure is still an important issue for OGJ adenocarcinoma irrespective of the addition of other treatments.

There are some limitations to this study. As it was terminated before the planned sample size had been reached, the power to detect a difference between the groups was reduced. Despite this, the interim results were sufficient to reach the conclusion that LTA did not improve survival compared with the TH approach, and this has been validated in this final analysis. Another limitation is that the distribution of Siewert tumour types was not well balanced between the groups. Because the Siewert classification of OGJ tumours had not been proposed at the time of trial initiation[4], it was not used for stratification at randomization, and assignment of the Siewert classification was made after surgery. As the results of a *post hoc* subgroup analysis may include some distortion, caution should be used when interpreting the results regarding Siewert classification.

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Supporting information

Additional supporting information may be found in the online version of this article:

Fig. S1 Kaplan–Meier curves of overall survival in per-protocol population by treatment group (TIFF file)