laparoscopic proximal gastrectomy (LPG) is likely to be performed with increasing frequency in the near future, if the operative technique becomes well established.

The most difficult technical aspect of LPG may be the anastomosis and reconstruction method, which should prevent reflux esophagitis. Several authors have already reported novel techniques using various reconstruction methods, but an optimal method has not been established. Jejunal interposition acts as a substitute sphincter, which seems to be ideal for the prevention of postoperative reflux from the remnant stomach, but it is not widely used because of the difficulty of performing the complicated anastomotic procedures laparoscopically.

At our institution, open proximal gastrectomy with jejunal interposition (OPG-IP) has been performed since 1992, and LPG with jejunal interposition (LPG-IP) was introduced in 2010. In the present study, we describe our techniques and initial experiences with LPG-IP in the treatment of proximal gastric cancer and evaluate the safety of this approach through a retrospective data review comparing our results with the open procedure.

Methods

This retrospective study reviewed the records of gastric cancer surgery patients at the National Cancer Center Hospital East, Chiba, Japan. From August 1992 to September 2011, 298 proximal gastrectomies for gastric cancer were performed at our institution. OPG-IP was performed until August 2010, and from September 2010 LPG-IP was performed. We retrospectively compared surgical data of the patients who underwent LPG-IP until September 2011 ($n = 22$) with those who underwent OPG-IP with the same reconstruction procedures between January 2008 and August 2010 ($n = 68$; Fig. 1). The decision whether to perform OPG-IP or LPG-IP was based purely on the time period during which the operation was undertaken.

Patients were selected for proximal gastrectomy if they were diagnosed with T1N0M0 gastric cancer located in the proximal third of the stomach, and it was estimated that the distal half of the stomach could be preserved. Preoperative assessment was by gastroendoscopy, abdominal ultrasonography, barium swallow radiography, and computed tomography. After surgery, baseline analgesia was administered to all patients by continuous epidural infusion of ropivacaine plus fentanyl for 2 days, with additional analgesia administered if requested by the patient. Perioperative and postoperative management protocols (clinical pathways) were amended over time, and the length of hospital stay recommended by the protocol was progressively shortened. The latest clinical pathway was adopted in April 2009 and allows patients to start drinking on

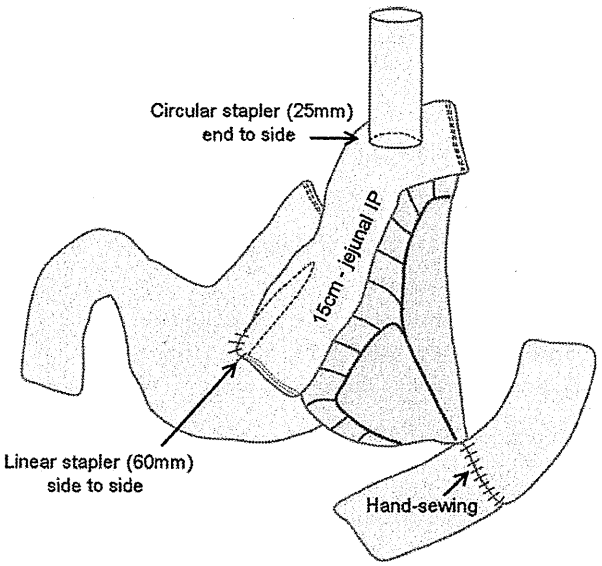

Fig. 1 Schematic of the completed reconstruction

postoperative day (POD) 1 and eating on POD 3 if there are no signs of major complications. Patients may be discharged from POD 8 if they are able to tolerate at least 50 % of a normal diet without fever, pain, or vomiting.

The following variables were recorded by retrospective review of the medical records: age, sex, body mass index (BMI), presence of comorbidity, tumor characteristics, operation time, estimated blood loss, number of times additional analgesia was administered, postoperative complications, number of harvested lymph nodes, and histological findings. To exclude differences due to changes in clinical pathways, parameters reflecting postoperative recovery, such as the time to first drinking or eating and time to hospital discharge, were compared only among patients who underwent surgery from April 2009 to September 2011: 22 patients in the LPG-IP group and 32 patients in the OPG-IP group. Postoperative complications were classified using the Dindo-Clavien classification [9], and complications were classified as grade II or higher were recorded. The extent of lymph node dissection followed the guidelines of the Japanese Gastric Cancer Association [10]. Staging was according to the 7th edition UICC TNM classification. Endoscopy was performed 6 months after surgery to evaluate reflux esophagitis and bile juice reflux into the interposed jejunum.

Surgical procedures for LPG-IP

The patient was placed in the supine position with legs apart. After placement of five trocars (Fig. 2), laparoscopic procedures were performed under a 10 mmHg CO_2 pneumoperitoneum. Mobilization of the stomach and *en bloc* systematic lymph node dissection were performed

laparoscopically. Esophagojejunostomy and jejunogastrostomy were performed laparoscopically, and creation of the jejunal interposition and jejunojejunostomy were performed via minilaparotomy. The distal half of the stomach, the greater omentum, and the spleen were preserved. The suprapancreatic lymph nodes (nos. 7, 8a, 9, and 11p) (Fig. 3A) and the lymph nodes around the cardia (nos. 1 and 2), the lesser curvature (no. 3), and the greater curvature (nos. 4sa and 4sb) were excised. The hepatic and pyloric branches of the vagal nerve were preserved on a case-by-case basis, and pyloroplasty was not performed. After mobilization of the proximal stomach, a detachable intestinal clip was placed on the abdominal esophagus as proximally as possible, and the esophagus was transected using an endoscopic linear stapler. A 5 cm transverse minilaparotomy incision was made in the upper left abdominal wall, and a wound retractor (Alexis Wound Retractor S; Applied Medical, Rancho Santa Margarita, CA) was inserted. The proximal-middle stomach was delivered via the minilaparotomy incision to determine the resection line by palpation of the marking clips placed during preoperative gastroendoscopy, and the stomach was then transected along the planned resection line using a linear stapler. The pneumoperitoneum was reestablished to find the ligament of Treitz, and the proximal jejunum was delivered via the minilaparotomy incision. A single-loop jejunal interposition (15 cm in length) was created approximately 20 cm from the proximal end of the jejunum (Fig. 3B). At the oral side of the jejunal interposition, the mesentery was divided vertically for approximately 7 cm, ligating the marginal artery. At the anal side of the jejunal interposition, the mesentery was divided along the intestine, sacrificing a 10 cm length of jejunum, similar to the procedure reported by Katai et al. [7]. Jejunojejunostomy was performed by hand via the minilaparotomy in an end-to-end fashion using the Gambee method. The mesenteric gap was sutured closed. The pneumoperitoneum was reestablished, and the anvil head of a 25 mm circular stapler (ECS; Ethicon Endosurgery, Cincinnati, OH) was fixed to the distal esophageal stump transabdominally after performing an intracorporeal handsewn pursestring suture via laparoscopy, as previously described by us for laparoscopic total gastrectomy [11]. The main body of the circular stapler was introduced into the jejunal interposition via its oral end and inserted into the abdomen through a surgical glove attached to the wound retractor to prevent the air leakage. The jejunal interposition was brought up in either antecolic or retrocolic fashion depending on the volume of adipose tissue in each case. Esophagojejunostomy was performed laparoscopically in an end-to-side fashion (Fig. 3C), and the oral stump of the interposed jejunum was closed by using an endoscopic linear stapler. A small opening was created on the anterior wall of the remnant stomach, and another small opening was created at the anal-side stump of the jejunal interposition. These openings were anastomosed in a side-to-side fashion using a 60 mm endoscopic linear stapler to form the jejunogastrostomy (Fig. 3D), and the entry hole for the stapler was closed by hand suturing. The esophagojejunostomy anastomosis was immersed in normal saline and tested for leaks by infusing air into the pouch lumen via a nasogastric tube and looking for escaping bubbles.

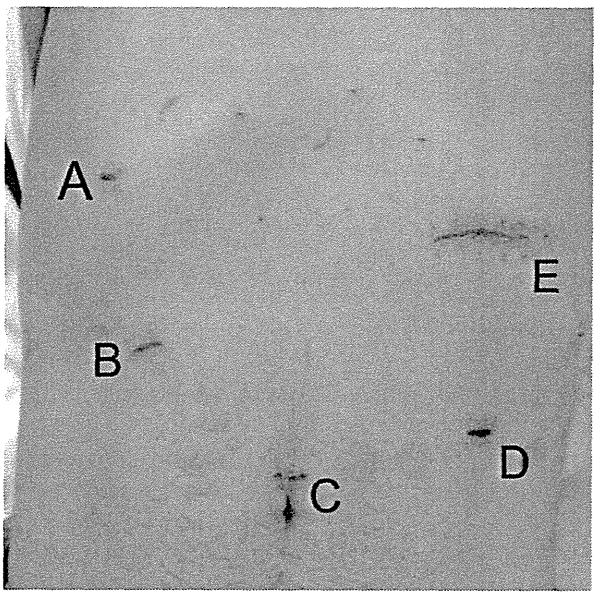

Fig. 2 Photo of the postoperative scars, indicating the placements of surgical ports. 5 mm ports were used at *A* and *D*, and 12 mm ports were used at *B*, *C*, and *E*. Port *E* was extended for the 50 mm minilaparotomy

Surgical procedures for OPG-IP

The same procedures as described above, including the same range of lymph node dissection and the same reconstruction method, were performed via an upper midline abdominal incision.

Statistical analysis

Statistical analyses were performed by using Student's *t* test, χ^2 test, or Fisher's exact probability test. A value of $p < 0.05$ was regarded as significant. All statistical analyses were performed by using Statistical Package for Social Science (SPSS) version 17.0 for Windows software (SPSS, Inc., Chicago, IL).

Results

A total of 90 proximal gastrectomies, including 22 LPG-IP procedures and 68 OPG-IP procedures, were included in

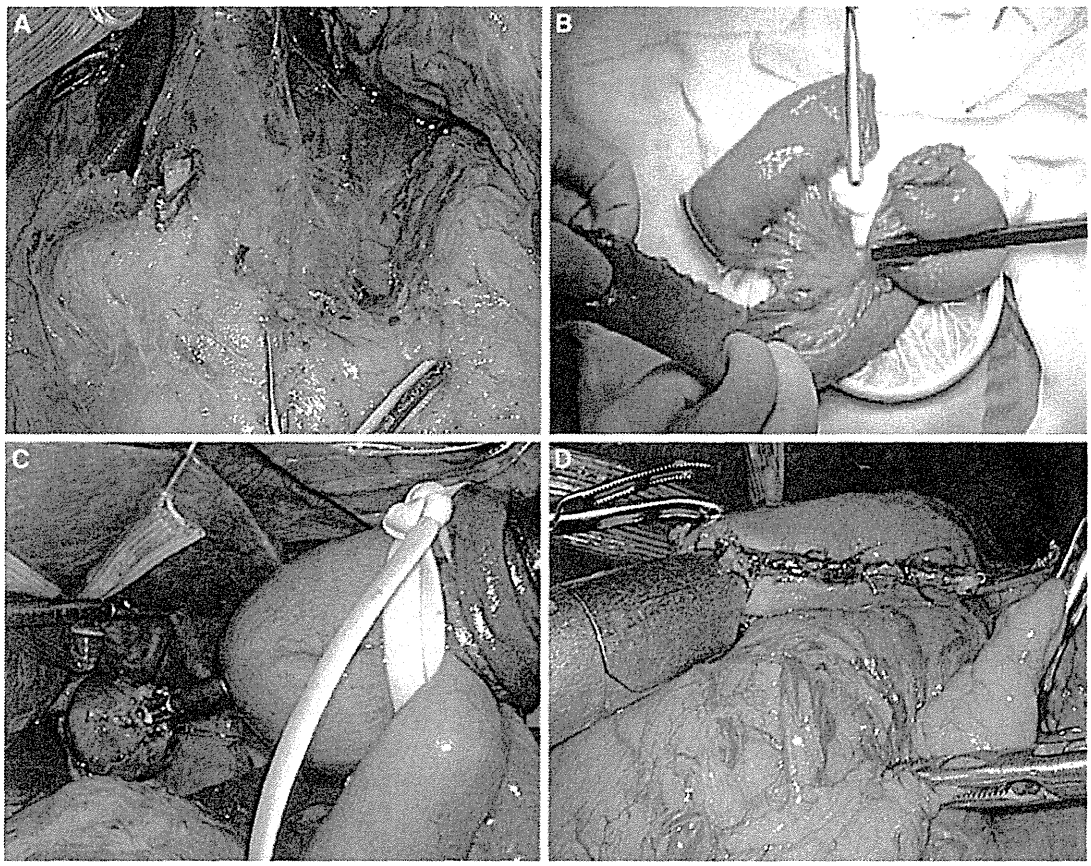

Fig. 3 **A** After lymph node dissection around the celiac artery. **B** Creation of the jejunal interposition via minilaparotomy. **C** Intracorporeal esophagojejunostomy using a *circular stapler*. **D** Intracorporeal jejunogastrostomy using a *linear stapler*

this study. No conversion to open surgery was recorded in the LPG-IP series. Patient characteristics are summarized in Table 1. There were no significant differences in age, sex, BMI, or presence of comorbidity between the two groups. Six patients (27 %) in the LPG-IP group and 15 patients (22 %) in the OPG-IP group underwent endoscopic submucosal resection before surgery and proceeded because pathological examination of specimens showed submucosal invasion or vessel infiltration, indicating the need for radical surgery with lymph node dissection. In the LPG-IP group, the jejunal interposition was brought up in antecolic fashion in 10 patients and in retrocolic fashion in 12 patients, and in the OPG-IP group the jejunal interposition was brought up in antecolic fashion in 21 patients and in retrocolic fashion in 47 patients, according to the surgeons' preferences and decisions. These proportions were not significantly different between groups.

Operation details are shown in Table 2. The operation time was significantly longer in the LPG-IP group (233 (range, 190–321) min) compared with the OPG-IP group (201 (range, 125–272) min; $p = 0.0002$), and the estimated blood loss was significantly less in the LPG-IP group (20 (range, 0–174) g) compared with the OPG-IP group (242 (range, 75–776) g; $p < 0.0001$). There was no difference in the number of harvested lymph nodes between the two groups. Pathological findings are shown in Table 2. There were no differences in the T factor, N factor, or TNM staging between the two groups. A negative surgical margin was achieved in all cases. The rate of accurate preoperative diagnosis in this study was 78.9 %.

Parameters for postoperative recovery are shown in Table 3. First drinking was on POD 1 and first eating was on POD 3 in both groups. Hospital discharge was on POD 11 in the LPG-IP group and on POD 10 in the OPG-IP group, which was not a significant difference. This indicates that most patients followed the planned clinical pathway. However, the number of times that additional analgesia was administered was significantly less in the LPG-IP group (2, range 0–5) compared with the OPG-IP group (4, range 0–9; $p < 0.0001$).

Postoperative complications in the two groups are listed in Table 4. The incidence rate of postoperative complications was not significantly different between the two groups (27 % in the LPG-IP group vs. 32 % in the OPG-IP group).

Table 1 Summary of patients with gastric cancer treated by laparoscopic and open proximal gastrectomy

	LPG-IP ($n = 22$)	OPG-IP ($n = 68$)	p value
Age (years)	64.3 ± 11.6	65.5 ± 9.0	NS
Sex (male/female)	18/4	52/16	NS
BMI	22.8 ± 3.3	22.4 ± 3.2	NS
ESD before surgery (yes/no)	6/16	15/53	NS
Comorbidity			
Absent/present	13/9	34/34	NS
Hypertension	5	20	
Diabetes mellitus	4	13	
COPD	1	1	
Arrhythmia	0	3	
Cardiac angina	2	1	
Other	0	2	

LPG-IP laparoscopic proximal gastrectomy with jejunal interposition, *OPG-IP* open proximal gastrectomy with jejunal interposition, *ESD* endoscopic submucosal dissection, *NS* not significant

Values are mean ± standard deviation

Table 2 Surgical and pathological findings in laparoscopic and open proximal gastrectomy

	LPG-IP ($n = 22$)	OPG-IP ($n = 68$)	p value
Operation time (min)	233 (190–321)	201 (125–272)	0.0002
Blood loss (g)	20 (0–174)	242 (75–776)	<0.0001
No. of dissected lymph nodes	17 (10–32)	20 (10–44)	NS
pT stage			NS
pT1a (M)	5	22	
pT1b (SM)	11	32	
pT2	4	5	
pT3	1	7	
pT4	1	2	
pN stage			NS
pN0	18	58	
pN1	2	8	
pN2	2	2	
TNM stage			NS
IA	16	50	
IB	1	9	
IIA	1	3	
IIB	2	2	
IIIA	2	4	

NS not significant

Values are median (range)

Table 3 Postoperative recovery after laparoscopic and open proximal gastrectomy using the current clinical pathway

	LPG-IP ($n = 22$)	OPG-IP ($n = 32$)	p value
Time to first drinking (POD)	1 (1–7)	1 (1–20)	NS
Time to first eating (POD)	3 (3–10)	3 (3–27)	NS
Time to hospital discharge (POD)	11 (7–32)	10 (7–34)	NS
Additional analgesia (number of times)	2 (0–5)	4 (0–9)	<0.0001

POD postoperative day, *NS* not significant

Values are median (range)

Anastomotic leakage occurred in two patients (9.1 %) in the LPG-IP group and five patients (7.4 %) in the OPG-IP group, all of which occurred at the esophagojejunostomy anastomosis. Among them, one patient in the LPG-IP group developed a grade II pancreatic fistula followed by secondary anastomotic leakage. One patient in the OPG-IP group with a major leakage required emergency reoperation via a thoracoabdominal approach for drainage (grade IIIb), but other patients were treated conservatively. Intra-abdominal hemorrhage requiring reoperation occurred in two patients in the OPG-IP group, and one patient required reoperation (grade IIIb). Anastomotic stricture at the esophagojejunostomy anastomosis occurred in two patients (9.1 %) in the LPG-IP group and four patients (5.9 %) in the OPG-IP group. All of these patients were successfully treated by outpatient endoscopic balloon dilatation. No

Table 4 Postoperative complications after laparoscopic and open proximal gastrectomy

	LPG-IP ($n = 22$)	OPG-IP ($n = 68$)	p value
Absent/present	16/6 (27 %)	46/22 (32 %)	NS
Wound infection, n	2 (9.1 %) grade II	6 (8.8 %) grade II	
Anastomotic leakage, n (%)	2 (9.1 %) grade II	5 (7.4 %) 4 grade II, 1 grade IIIb	
Intra-abdominal hemorrhage, n (%)	0	2 (2.9 %) 1 grade II, 1 grade IIIb	
Pancreatic fistula, n (%)	1 (4.5 %) grade II	1 (1.5 %) grade II	
Intra-abdominal abscess, n (%)	1 (4.5 %) grade II	2 (2.9 %) grade II	
Anastomotic stenosis, n (%)	2 (9.1 %) grade II	4 (5.9 %) grade II	
Cholecystitis, n (%)	0	2 (2.9 %) grade II	

NS not significant

Grade: according to Dindo-Clavien classification

patient complained of reflux symptoms after surgery, and there was no operation-related death. Follow-up endoscopy could be performed 20 of 22 patients (90.9 %) in the LPG-IP group and 61 of 68 patients (89.7 %) in the OPG-IP group. A small amount of bile juice reflux to the remnant stomach or interposed jejunum was observed in 25 % of patients, but esophagitis was recorded in only in one patient (1.1 %) in the OPG-IP group. Endoscopic survey of the remnant stomach was possible in all of the patients.

Discussion

The choice of reconstruction method following LPG remains controversial. Because the optimal method has not been established, a number of techniques are currently used. Most past reports describe direct esophagogastric anastomosis, probably because it is very simple and requires only one anastomosis [12–16]. In these reports, direct esophagogastrostomy was performed by using a linear or circular stapler, with the addition of antireflux measures, similar to Toupet fundoplication. However, it may be impossible to completely prevent reflux in direct esophagogastrostomy. Jejunal interposition has been recognized as a favorable method for preventing severe postoperative reflux and is widely performed in open surgery, but LPG-IP has not gained wide acceptance because of its technical complexities. These complexities include the creation of a pedicled jejunal limb and the requirement for three anastomoses. Until recently, very few reports have described the outcomes of LPG-IP. The first report was by Uyama et al. [17] and described their entirely laparoscopic LPG-IP technique, which they had performed in four cases. Their technique was excellent, but the mean operative time (614 min) was long. In 2002, Ikeda et al. [18] reported three cases of hand-assisted LPG-IP, which shortened operation time. However, no study has evaluated the feasibility and safety of these techniques in a larger series. As far as we know, this is the largest study to report the outcomes of LPG-IP to date and the first to compare the results with open surgery.

At our institution, OPG-IP has long been a standard procedure for the treatment of early-stage gastric cancer in the proximal third of the stomach, and it was therefore natural for us to adopt jejunal interposition to laparoscopic surgery. Our results show that LPG-IP can be performed safely with an equivalent complication rate compared to open surgery. We did not experience any case with symptomatic postoperative reflux. Operation time was longer in laparoscopic surgery than in open surgery, but this difference was approximately 30 min and seems acceptable for a routine surgical procedure. In our procedure, transection of the stomach, creation of the jejunal interposition, and subsequent jejunojejunostomy were performed via minilaparotomy under direct vision, which might have contributed to time-saving. The proximal jejunum was easily delivered via the upper left abdominal incision, and the subsequent creation of the jejunal limb and jejunojejunostomy anastomosis also were easy. The other anastomoses (esophagojejunostomy and jejunogastrostomy) and systematic lymphadenectomy were performed laparoscopically, because laparoscopy provides better vision for these procedures than open surgery regardless of the size of the patient or the thickness of the abdominal wall. The shortened operation time also might be partly due to advancements in instrumentation and skills, because laparoscopic distal gastrectomy is frequently performed in our institution.

Postoperatively, leakage of the esophagojejunostomy anastomosis occurred in two patients (9.1 %) in the LPG-IP group and five patients (7.4 %) in the OPG-IP group. These incidences seem relatively high compared with other reports, which cannot be ignored. In one patient in the LPG-IP group, the pancreatic fistula caused the secondary anastomotic leakage. However, we were not able to determine the reasons for anastomotic leakage in the other patients. The high incidence may reflect the complexity of the jejunal interposition rather than the technical complexity of laparoscopic surgery, because the incidence was relatively high in both groups. This procedure has several different points from a Roux-en-Y anastomosis in total gastrectomy, which may be causes of tension to the interposed jejunum. We speculate that these tensions may influence the esophagojejunostomy. One possible cause of tension is a large feeding artery in a pedicle of the interposed jejunum, because we always make a large artery remain in the pedicle expecting sufficient blood supply. It seems that the retrocolic route may cause less tension when using a pedicled jejunum, but we experienced anastomotic leakage in four patients using the antecolic route and three using the retrocolic route, so the route did not appear to make a difference in this series. Another possible cause of tension to the interposed jejunum may be the remnant stomach, which is also a different point from Roux-en-Y. This tension is likely to be caused if the length of the interposed jejunum is short. We have believed that the 15 cm length interposed jejunum is ideal for the prevention of reflux esophagitis and for postoperative endoscopic survey, but there is not sufficient evidence to determine this definitively. Evaluation of a larger number of cases is required before the reasons for anastomotic leakage can be concluded. Our LPG-IP sample size was small, and it is possible that the incidence rate may be improved following an increase in patient numbers and surgical experience.

The incidence of stenosis at the esophagojejunostomy anastomosis was 9.1 % in the LPG-IP group and 5.9 % in

the OPG-IP group. The tendency for stenosis in open proximal gastrectomy has been reported; Katai et al. [19] reported an incidence of 6.3 %. The incidences recorded in this study seem higher than for total gastrectomy, in which esophagojejunal anastomosis is performed in the same manner [20]. The reason for this is unclear, but it is speculated that the small amount of reflux after partial gastrectomy causes stenosis [14]. We observed a small amount of bile reflux to the interposed jejunum in 25 % of patients on postoperative endoscopy. Stenosis also may be caused by tension to the interposed jejunum as mentioned above. The patients with stenosis were successfully treated by outpatient endoscopic balloon dilatation.

Pancreas-related complications are sometimes experienced in gastric cancer surgery, even when the pancreas is not obviously injured during lymph node dissection. This is probably due to thermal injury by surgical devices or retraction of the pancreas to obtain a better view around the celiac artery. One patient in the LPG-IP group developed a grade II pancreatic fistula, even though no pancreatic injury was recognized intraoperatively. As a result, this patient developed secondary anastomotic leakage. It is important to be conscious of handling the pancreas gently during lymph node dissection.

The relative invasiveness of the procedures is difficult to determine based only on our retrospective study with limited case numbers. Blood loss was significantly less in the LPG-IP group, with the difference being in excess of 200 g. This might be associated with more meticulous laparoscopic techniques due to the magnified view. Time to first drinking, time to first eating, and time to hospital discharge did not differ between the two groups, because the management protocol was same in both groups. However, the requirement for additional analgesia was significantly less in the LPG-IP group. Finally, the cosmetic result is unquestionably better in the LPG-IP group. These results suggest that LPG-IP may have a number of benefits, including a better postoperative quality of life.

Several oncological parameters were evaluated, although they were limited to short-term outcomes. The number of harvested lymph nodes was similar between the two groups, and the median number for both groups was more than 15, which is the number suggested for adequate resection in the American Joint Committee on Cancer guidelines. A negative surgical margin was achieved in all cases. These data suggest that LPG-IP is at least equivalent to OPG-IP in short-term oncological outcomes. The preoperative diagnosis of invasion depth is sometimes underestimated, and in our series some patients were finally diagnosed as T2 or T3, even though their preoperative diagnosis was T1. The rate of accurate preoperative diagnosis in this study was 78.9 %. This suggests that lymph node dissection in proximal gastrectomy should be performed to the level of the celiac trunk (nos. 7, 8a, 9, 11p), which we were able to achieve laparoscopically. Ideally, a more accurate preoperative diagnostic method for depth of invasion should be established.

In conclusion, our initial case series demonstrated that our technique for LPG-IP is technically feasible and safe, and provides similar curability and outcomes to open surgery in the short-term. Our study is limited by its retrospective nature, small number of patients, and short-term follow-up. In this kind of function-preserving surgery, long-term outcomes should be evaluated, including the patients' quality of life. Another large-scale study evaluating long-term outcomes is necessary to confirm these findings.

Disclosures Drs. Takahiro Kinoshita, Naoto Gotohda, Yuichiro Kato, Shinichiro Takahashi, Masaru Konishi, and Taira Kinoshita have no conflict of interest or financial ties to disclose.

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Surgical outcomes of laparoscopy-assisted gastrectomy versus open gastrectomy for gastric cancer: a case-control study

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Abstract
Background The aim of this study was to clarify the technical feasibility and oncological efficacy of laparoscopy-assisted gastrectomy (LAG) for gastric cancer compared with open gastrectomy (OG).
Methods Between April 2002 and March 2008, a series of 623 patients with gastric cancer underwent R0 gastrectomy (314 LAG patients and 309 OG patients). Age, gender, lymph node dissection, and pathological stage were matched by propensity scoring, and 212 patients (106 LAG and 106 OG) were selected for analysis after the exclusion of 40 patients who had proximal gastrectomy. Intraoperative factors, postoperative morbidity, long-term quality of life (QOL), and survival were evaluated. Moreover, these outcomes were also compared between the laparoscopy-assisted total gastrectomy (LATG) and the open total gastrectomy (OTG).
Results There was no significant difference in preoperative characteristics between the two patient groups. Regarding intraoperative characteristics, blood loss was significantly lower in the LAG group (143 ml) than in the OG group (288 ml), while operation time was significantly longer in the LAG group (273 min) than the OG group (231 min). The degree of lymph node dissection and number of retrieved lymph nodes did not differ between the two groups. There were no significant differences in postoperative courses or overall and disease-specific survival (89.8% vs. 83.6%, $P = 0.0886$; 100% vs. 95.2%, $P = 0.1073$) except time to first flatus and time to use of nonsteroidal anti-inflammatory derivatives between the two groups. Significantly fewer patients felt wound pain in the LAG group 1 year after surgery. Analyses between the LATG and OTG groups showed similar results.
Conclusions LAG for gastric cancer may be both feasible and safe. However, it will be necessary to conduct a well-designed randomized controlled trial comparing short-term and long-term outcomes between LAG and OG in a larger number of patients.

Keywords Gastric cancer · Laparoscopic gastrectomy · Open gastrectomy

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Gastric cancer is one of the most common causes of cancer-related death in the world, although its incidence has recently decreased [1]. Both early and advanced gastric cancer can be treated successfully with surgical resection, which includes laparoscopy-assisted gastrectomy (LAG) with lymph node dissection. The use of this technique for early gastric cancer was first reported in 1994 [2] and, since then, many studies have reported benefits of the technique such as reduced blood loss, decreased pain, early recovery of bowel movements, and short hospital stay [3–6]. Other studies have focused on its oncologic equivalency to open gastrectomy (OG) [7, 8]; however, the technique does involve a steep surgical learning curve [9].

Initially, LAG was used to treat early gastric cancer, which required less extensive lymph node dissection. The incidence of laparoscopy-assisted distal gastrectomy (LADG) was initially high but, since 1999, when the first laparoscopy-assisted total gastrectomy (LATG) with lymph node dissection for gastric cancer was reported [10], the occurrence of LATG has gradually increased. Recently, the indication for LAG in some high-volume centers has been extended to include advanced gastric cancer [11, 12]. Small retrospective series [13, 14] and randomized prospective trials [15, 16] have compared surgical outcomes between LAG and OG for gastric cancer. However, many of these studies were based on a small number of patients and were restricted to LADG for T1 gastric cancers. The purpose of this study, therefore, was to compare early and long-term surgical outcomes via a statistically generated case-control study between LAG and OG for curatively resected gastric cancer at a single Japanese institute, therefore confirming the feasibility of LAG for gastric cancer.

Materials and methods

The institutional review board of the each institute involved in the study approved this case-control study. Surgery was performed after all possible alternative procedures or treatments had been explained to the patients and they had given their informed consent.

The first LAG for early gastric cancer was performed in April 2002 in the Department of Surgery Gastroenterological Center, Yokohama City University, Japan. Initially, LADG was performed, with laparoscopy-assisted proximal gastrectomy (LAPG) commencing in April 2004 and LATG in April 2006.

Between April 2002 and March 2008, a series of 623 patients with gastric cancer underwent curative gastrectomy classified as R0 (with no residual tumor) in the Department of Surgery Gastroenterological Center and the Department of Gastroenterological Surgery, Yokohama City University, Japan. Data were prospectively retrieved from operative and pathological reports, with follow-up data being obtained from the outpatient clinical database. Of these 623 patients, 40 who underwent laparoscopy-assisted proximal gastrectomy (LAPG) ($n = 28$) and open proximal gastrectomy (OPG) ($n = 12$) were excluded from this study because the number of patients was small. Of 583 remaining patients, 289 underwent LAG and 294 underwent OG.

Patients of both groups were matched for age, gender, lymph node dissection, and pathological stage by a propensity scoring system using SAS ver. 9.0 (SAS Institute, Cary, NC). According to statistical analysis, 212 patients (106 LAG patients and 106 OG patients) were selected for analysis.

All subjects were preoperatively confirmed by endoscopic biopsy analysis to have gastric cancer. Of the 212 patients (139 men and 73 women; age range 32–87 years; mean age ± standard deviation [SD] 65.1 ± 10.6 years), 155 underwent distal gastrectomy and 57 underwent total gastrectomy.

Preoperative evaluation

A preoperative evaluation of all patients was performed, consisting of a barium-swallow study, an endoscopic examination with a biopsy, and computed tomography (CT) scans. The tumor diameter and depth of invasion were measured by both endoscopic examination and a barium-swallow study. Lymph-node metastasis, depth of invasion, and staging were based principally on the Japanese Classification of Gastric Carcinoma, 2nd English edition [17]. Experienced pathologists at each institution participated in the study and ensured the quality of the pathological diagnoses.

Of the 212 registered patients, 71 had tumors located in the lower third of the stomach, 118 in the middle third of the stomach, 20 in the upper third of the stomach, and 3 occupied the entire stomach. Superficial-type tumors (flat or elevated, depressed, and mixed-type [elevated plus depressed]) were seen in 174 patients, well-defined tumors in 23, and ill-defined tumors in the remaining 15 patients.

The pathologic tumor diameter corresponded to the maximum microscopic length of the tumor, irrespective of depth. Patients were classified into two groups (<40 mm and ≥40 mm) based on the pathologic tumor diameter. Tumors <40 mm were observed in 114 patients and tumors ≥40 mm were observed in the remaining 98 patients. Histologically, T1 (mucosa, submucosa) was observed in 165 patients, T2a (muscularis propriae) in 24 patients, T2b (subserosa) in 13 patients, and T3 (serosa exposed) in 10 patients. Differentiated-type carcinoma was observed in 128 patients and undifferentiated-type carcinoma in 84. Lymph node metastasis was observed in 40 patients (18.9%). Of these, pN1 was observed in 31 patients and pN2 in 8. D1 + α lymph node dissection (lymph nodes along the left gastric artery, the common hepatic artery, or the celiac axis) was performed in 106 patients and D2 lymph node dissection in 106 patients. Among the registered patients, 140 were classified as stage IA, 48 as stage IB, 14 as stage II, and 10 as stage IIIA.

Surgical procedures

This LADG surgical procedure is described here. The surgical techniques for lymph node dissection are principally the same in LATG.

Patients were placed in a supine position under general anesthesia. The surgeon stood on the right side of the patient, the assistant surgeon stood on the left, and the surgeon handling the laparoscopy stood between the patient's legs. Initially, trocars were introduced into the right upper quadrant (5 mm), right middle quadrant (12 mm), subumbilical (12 mm; camera port), left middle quadrant (5 mm), and left upper quadrant (5 mm) of the abdomen. A flexible straightforward scope was used to maintain the optimal surgical field.

Laparoscopically, the greater omentum was divided into the inferior portion of the spleen using the LigaSure™ (Covidien, Mansfield, MA, USA) or harmonic scalpel during a pneumoperitoneum induced by pressure of 12 mmHg. After completion of the omentectomy, the root of the right gastroepiploic vein and artery were isolated and sealed using the LigaSure™ or harmonic scalpel with clips. The duodenum around the pylorus ring was isolated and fired using an EndoGIA™ Universal (60-3.5; Covidien), followed by sealing or clipping of the root of the right gastric artery.

After sealing or resection of the lesser omentum along the liver edge to the esophagogastric junction, lymph nodes along the common hepatic artery were dissected using the LigaSure™ or harmonic scalpel. The roots of the left gastric vein and artery were isolated and sealed using the LigaSure™ or harmonic scalpel with clips. The lymph nodes around the celiac trunk and the proximal part of the splenic artery were also dissected using the LigaSure™ Atlas or harmonic scalpel. Next, the lesser omentum was dissected from the lesser curvature of the stomach from the proximal side toward the anal side. The greater omentum was also dissected from the anal side toward the proximal side using the LigaSure™ or harmonic scalpel. Lymph node dissection was finished intracorporeally.

The upper abdominal region (at the same level as the duodenal stump) was opened by a 5-cm transrectal incision using a 120-mm LAPDISC device (Ethicon Endo-Surgery, Cincinnati, OH, USA). The stomach was pulled out extracorporeally, resected 4 cm from the greater curvature using scissors, and divided using EndoGIA™ Universal (60–3.5 or 60–4.8) at the proximal side of the tumor. No stringed seromuscular suture was added, but a purse-string suture was placed in the duodenal stump. A 25-mm aperture PPCEEA (Covidien) was then inserted into the duodenal lumen, and the purse-string suture was tied. The PPCEEA was inserted through the gastrotomy incision of the greater curvature side, and the center rod was passed through the posterior wall of the stomach. The PPCEEA was fired after the center rod and the anvil were connected, and a side-to-end gastroduodenostomy was completed. The field of operation was reexamined laparoscopically to confirm satisfactory hemostasis.

In the ODG group, lymph node dissection and division of the tissue were performed by ligation with absorbable strings and resected by scissors or electroscissors. Gastrectomy was performed with a GIA™ 80–3.8 stapler (Covidien) followed by seromuscular sutures using absorbable strings. Operative procedures for ODG were principally the same as those for LADG.

Neoadjuvant and adjuvant treatments

Neoadjuvant chemotherapy was not used in these patients. Adjuvant chemotherapy was used in patients with pathologically identified stage II or IIIA and who had given their informed consent. S-1 was administered orally twice daily for 1 week according to body surface area (BSA) as follows: BSA < 1.25 m^2, 80 mg/day; $1.25 \leq$ BSA < 1.50 m^2, 100 mg/day; 1.50 m$^2 \leq$ BSA, 120 mg/day for 1 year. A total of 12 patients underwent adjuvant chemotherapy.

Follow-up protocol

All patients underwent a blood examination every 3–4 months, a CT scan every 6 months, and an annual endoscopic examination. If gastrointestinal symptoms were reported, an additional examination was carried out. Follow-up continued up to the fifth year at an outpatient clinic. The mean follow-up time was 36.1 ± 22.9 months.

Statistical analysis

SPSS ver. 10.0 for Windows (SPSS Inc., Chicago, IL) was used for all statistical analyses. The χ^2 test or the Fisher exact test was applied to evaluate differences in proportions, and Student's t-test was used to evaluate continuous variables. Data are presented as mean $\pm$ standard deviation (SD). Survival probabilities were estimated using the Kaplan–Meier method and compared with the log-rank test. A probability value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Patient characteristics of the 212 case-matched patients are listed in Table 1. There were no significant differences in age, gender, body mass index (BMI), the American Society of Anesthesiologists (ASA) physical status classification, presence of comorbid disease or prior abdominal surgery.

Table 1 Patient characteristics

	LAG ($n = 106$)	OG ($n = 106$)	P
Age (mean) (years)	65.2 ± 11.2	65.0 ± 11.8	0.8905
Male/female	70/36	69/37	0.8851
Body mass index (mean) (kg/m^2)	23.0 ± 2.8	23.0 ± 3.6	0.9962
ASA score			0.8890
1	43	44	
2	57	53	
3	6	9	
Comorbid disease			
(+)	63	62	0.8990
Hypertension	32	37	
Diabetes mellitus	14	16	
Cardiovascular	11	17	
Hyperlipemia	12	11	
Pulmonary	10	5	
Cerebrovascular	3	7	
Renal	4	3	
Liver	4	3	
Thyroid	0	4	
Hematological	0	2	
Collagen disease	1	2	
Other cancers	12	11	
Prior abdominal surgery			
(+)	26	31	0.4386
Appendectomy	15	21	
Cholecystectomy	5	9	
Colectomy	3	6	
Gynecological	3	5	
Splenectomy	1	3	
Abdominal aorta aneurysm	0	2	

Intraoperative characteristics

There were significant differences in volume of blood loss and operation time between the two groups. In the LAG group, blood loss was significantly reduced ($P < 0.0001$) and operation time significantly longer ($P < 0.0001$) than in the OG group. However, the distribution of operative methods, the degree of lymph node dissection, and the number of retrieved lymph nodes did not differ between the two groups (Table 2).

Pathological findings

There were significant differences in macroscopic tumor type between the two groups. In the LAG group, the macroscopically superficial type was more frequent, although the advanced well-defined and ill-defined types were less common than in the OG group (superficial/well-defined/ill-defined, 97/8/1 vs. 77/15/14, $P = 0.0004$). There were no significant differences in LAG vs. OG with respect to tumor location (lower/middle/upper/entire stomach, 36/56/13/1 vs. 35/62/7/2, $P = 0.4839$), tumor diameter (< 40 mm/≥ 40 mm, 61/45 vs. 53/53, $P = 0.2704$), histological type (differentiated/undifferentiated, 65/41 vs. 63/43, $P = 0.7788$), depth of invasion (T1/T2a/T2b/T3, 82/12/6/6 vs. 82/13/7/4, $P = 0.9182$), lymph node metastasis (N0/N1/N2, 84/16/6 vs. 89/15/2, $P = 0.3368$) or pathological stage (IA/IB/II/IIIA, 68/24/8/6 vs. 72/24/6/4, $P = 0.8495$).

Table 2 Intraoperative characteristics

	LAG ($n = 106$)	OG ($n = 106$)	P
Blood loss (ml)	142.7 ± 184.0	287.7 ± 72.2	<0.0001
Operating time (min)	272.6 ± 77.9	230.8 ± 75.9	<0.0001
Operative method			0.6421
Distal gastrectomy	79	76	
Total gastrectomy	27	30	
Lymph node dissection			0.7835
D1 + α[a]	52	54	
D2	54	52	
No. of retrieved lymph nodes	38.6 ± 32.1	32.5 ± 15.2	0.6438

[a] D1 + α is D1 plus lymph nodes along the left gastric artery or common hepatic artery or celiac axis

Postoperative clinical course

Passing flatus occurred significantly earlier and the time of use of nonsteroidal anti-inflammatory derivatives (NSAIDs) was significantly less frequent in the LAG group, although there was no significant difference in the peak value of C-reactive protein and white blood cells (WBC), time to soft diet, and length of hospital stay between the two groups. Moreover, the incidence of postoperative complications did not differ between the two groups (14 patients, 13.2% and 16 patients, 15.1%; $P = 0.6935$). Anastomotic leakage was the most frequent complication in both groups. Surgical site infection (SSI) was also relatively common, followed by pancreatic fistula (Table 3). Two patients in the OG group died during their hospital stay: one who suffered from idiopathic thrombocytopenia and was administered corticosteroids died of sepsis induced by anastomotic leakage, while the second died of venous thromboembolism (VTE) after surgery. The incidence of adjuvant chemotherapy did not differ between the two groups.

Table 3 Postoperative courses

	LAG (n = 106)	OG (n = 106)	P
Peak value of C-reactive protein (mg/dl)	12.0 ± 5.1	14.3 ± 7.3	0.6548
Peak value of WBC (/m^3)	13,000 ± 2,750	14,200 ± 4,130	0.5349
Time to first flatus (days)	1.7 ± 0.9	2.9 ± 1.3	0.0380
Time of use of NSAIDs	3.2 ± 1.2	5.8 ± 1.6	0.0345
Time to soft diet (days)	4.9 ± 0.9	4.8 ± 0.8	0.7560
Morbidities			
(+)	14	16	0.6935
Anastomotic leakage	6	6	
Surgical site infection	5	5	
Pancreatic fistula	1	2	
Cholecystitis	1	1	
Pneumonia	1	1	
Venous thromboembolism	0	1	
Postoperative hospital stay (days)	12.0 ± 2.5	12.5 ± 3.4	0.8785
Adjuvant chemotherapy	6	6	0.9999

NSAIDs nonsteroidal anti-inflammatory derivatives

Table 4 Long-term quality of life after gastrectomy

	LAG (n = 106)	OG (n = 106)	P
Body weight ratio[a]	0.88 ± 0.24	0.83 ± 0.24	0.5541
Volume of food[b]	0.79 ± 0.20	0.74 ± 0.18	0.5887
Heart burn or belch			
Present	18	28	0.0957
Abdominal discomfort			
Present	20	27	0.2471
Diarrhea			
Present	11	17	0.2236
Early-dumping syndrome			
Present	5	8	0.3905
Late-dumping syndrome			
Present	5	7	0.5522
Wound pain			
Present	3	11	0.0269
Performance status			0.7545
0	95	92	
1	10	12	
2	1	2	

[a] Body weight ratio is the present body weight/body weight before gastrectomy

[b] Volume of food is the present volume/volume before gastrectomy

Long-term quality of life (QOL)

QOL 1 year after surgery was compared in the both groups. There were significantly fewer patients in the LAG group who felt wound pain, although any other factors did not reach statistical significance between the two groups (Table 4). In the OG group, intestinal obstruction was observed in two patients and incisional hernia was detected in one patient.

Survival time

Five patients in the LAG group died (three from other cancers, one from cardiovascular reasons, one from pneumonia) although no patient died of gastric cancer. Eleven patients in the OG group died (four from cardiovascular reasons, two from gastric cancer, two from pneumonia, one from another cancer, one from VTE, and one from cerebrovascular disease). There were no significant differences in overall survival levels (89.8% vs. 83.6%; $P = 0.0886$) (Fig. 1) and disease-specific survival (100% vs. 95.2%; $P = 0.1073$) (Fig. 2) between the two groups.

Short- and long-term outcomes of LATG and OTG patients

Patient characteristics, intraoperative characteristics, postoperative course, long-term QOL, and survival time were compared between the LATG group (n = 27) and the OTG group (n = 30). There were significant differences in blood loss (ml) (155.0 ± 138.8 vs. 422.4 ± 350.4), time to first flatus (days) (1.9 ± 1.0 vs. 3.0 ± 1.4), time to use of NSAIDs (3.5 ± 1.3 vs. 6.2 ± 1.5), and wound pain (1 vs. 7) between the two groups. However, there were no significant differences in age (years) (67.4 ± 11.0 vs. 67.1 ± 6.6), gender (M/F) (21/6 vs. 20/10), BMI (kg/m^2) (23.5 ± 2.5 vs. 24.3 ± 4.3), ASA score (11/14/2 vs. 9/16/5), comorbid disease (16 vs. 21), prior abdominal surgery (5/22 vs. 9/21), operating time (min) (286.4 ± 68.0 vs. 262.1 ± 74.9), degree of lymph node dissection (6/21 vs. 12/18), number of retrieved lymph nodes (38.1 ± 13.9 vs. 36.8 ± 17.1), peak value of C-reactive protein (mg/dl) (14.8 ± 6.3 vs. 15.9 ± 6.7), peak value of WBC (/m^3) (13,200 ± 3,100 vs. 14,160 ± 5,230), time to soft diet (5.8 ± 1.2 vs. 6.0 ± 0.5), postoperative morbidities (7 vs. 5), postoperative hospital stay (days) (14.5 ± 3.5 vs. 15.6 ± 5.8), the incidence of adjuvant chemotherapy (2 vs. 2), body weight ratio after 1 year (0.79 ± 0.20 vs. 0.76 ± 0.29), volume of food (0.72 ± 0.25 vs. 0.70 ± 0.19), heart burn or belch (8 vs. 14), abdominal discomfort (9 vs. 14), diarrhea (5 vs. 7), early-dumping syndrome (2 vs. 3), late-dumping syndrome (2 vs. 3), and performance status (23/3/1 vs. 25/4/1) between the two groups. Moreover, there were

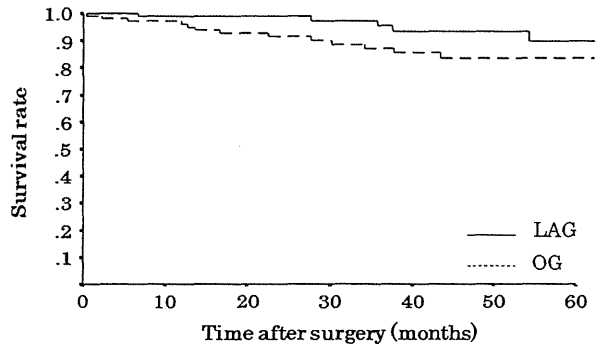

Fig. 1 There was no significant difference in overall survival between the LAG and OG groups (89.8% vs. 83.6%) ($P = 0.0886$)

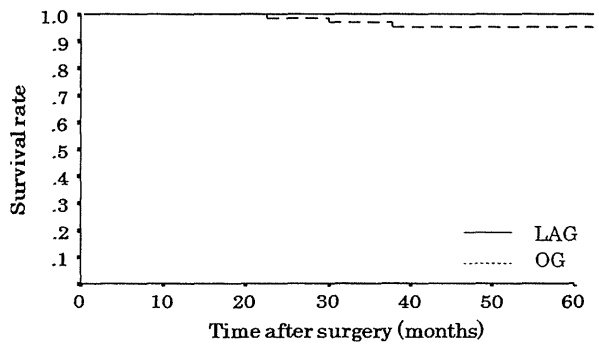

Fig. 2 There was no significant difference in disease-specific survival between the LAG and OG groups (100% vs. 95.2%) ($P = 0.1073$)

no significant differences in overall and disease-specific survival between the two groups (96.2% vs. 64.1 and 100% vs. 72.7%, respectively).

Discussion

This study showed that LAG for gastric cancer is feasible from the viewpoints of short-term safety and long-term oncologically comparable outcomes compared with conventional open surgery. In particular, this method provided earlier bowel recovery and reduced wound pain. Although the study was retrospective, it was case-controlled by matching age, gender, degree of lymph node dissection, and pathological stage to improve its impact.

The indication for LADG has been expanding worldwide. Many studies have reported short-term safety and long-term oncological feasibility of LADG for gastric cancer, and most studies described its advantages, including small skin incision, less blood loss, early recovery from surgical stress, reduced pain, less impaired pulmonary function, and equal postoperative complications compared with ODG [7, 8]. Although most of these comparative studies were retrospective and were based on a small number of patients, a Korean prospective randomized trial showed that morbidity and mortality did not differ between LADG and ODG groups [16].

In the present study, blood loss was significantly reduced and operating time was significantly longer in the LAG group, which is comparable to the results of earlier studies. In our previous study that focused on the surgical learning curve of LADG by a single surgeon, blood loss was reduced to 175 ml after performing 20 cases and to 80 ml after 60 cases. Operating time was shortened to 230 min after 60 cases [9]. This suggests that LADG surgical stress could be reduced through following the surgical learning curve, despite the fact that the learning curve in our study demands more case experience compared to ODG. Nevertheless, once the LAG learning curve plateaus, this technique may offer advantages over OG. Another study [18] reported a shorter LADG learning curve than the one stated in our previous study. Quality of surgical procedure, degree of lymph node dissection, and previous experience of gastrectomies may all contribute to differences in the length of the surgical learning curve.

In the present study, about 25% of patients underwent LATG in each group. The laparoscopic techniques of LATG are more difficult to perform than LADG, and it takes more experience to perform them safely and satisfactorily. Thus, operating time and blood loss in this study are comprehensive. This study showed that LATG also offered reduced blood loss, earlier recovery, and less pain compared to OTG although each group was small. The advantage of LATG may be steady according to the surgical learning curve. Although no previous reports have discussed the surgical learning curve of LATG, it would be useful to conduct such a study to clarify the validity of this operation.

The incidence of postoperative morbidity in the LAG groups in the present study was similar to that of other reports [15, 16, 19, 20], and there was no difference in the incidence of morbidity between the LAG and OG groups in this study. Therefore, LAG for gastric cancer may be acceptable from this viewpoint. Anastomotic leakage was the most frequent postoperative morbidity and was observed mainly after total gastrectomy in both groups. A stable and safe technique for esophagojejunostomy should therefore be developed, irrespective of the surgical approach.

In this study, there was no significant difference in time to soft diet or postoperative hospital stay between the two groups, although many studies reported earlier bowel movement, soft diet intake, and shorter postoperative hospital stay with LAG compared with OG [3–6]. We applied the same clinical path for each gastrectomy in our institute and as a result postoperative courses were similar between the two groups in this study. Moreover, because hospitalization costs are met by the Japanese government

insurance system, patients hesitate to be discharged earlier. It is therefore difficult to compare the length of hospital stay between Japan and Western countries. However, minimally invasive surgery yielded earlier bowel recovery and reduced pain in this study; earlier soft diet intake and shorter hospital stay will be expected by changing the clinical path of the LAG group in the future.

Assessment of long-term QOL showed reduced wound pain in the LAG group, although gastroenterological symptoms did not differ between the two groups. The similar surgical manipulation in the abdominal cavity may provide equivalent long-term QOL in the both groups.

Recently, comparative studies of surgical outcomes between LADG and ODG for advanced gastric cancer have been reported [11, 12] that argued the feasibility of LADG for advanced gastric cancer. In this study, about 25% of patients in each group had advanced gastric cancer and underwent D2 gastrectomy, resulting in a relatively low incidence of postoperative morbidity. In addition, both overall and disease-specific survival did not differ between the LAG and OG groups in this study. Most other retrospective reports reported the oncological equivalency of the laparoscopic versus the open approach, although sample sizes were relatively small [13, 15]. In this case-controlled study, patient backgrounds were made appropriately uniform by the propensity scoring system to reduce statistical bias and to improve significance. Although this was not a randomized prospective study, survival outcomes may nevertheless be reliable such that LAG can achieve an oncologically equivalent resection.

In conclusion, LAG for gastric cancer may be both feasible and safe. This novel method would offer advantages over OG according to the surgical learning curve. However, it will be necessary to conduct a well-designed randomized controlled trial comparing short-term and long-term outcomes between LAG and OG in a larger number of patients.

Disclosure Drs. Chikara Kunisaki, Hirochika Makino, Takashi Kosaka, Takashi Oshima, Ryo Takagawa, Jun Kimura, Hirotoshi Akiyama, Masataka Taguri, Satoshi Morita, and Itaru Endo have no conflicts of interest or financial ties to disclose.

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Laparoscopy versus open distal gastrectomy by expert surgeons for early gastric cancer in Japanese patients: short-term clinical outcomes of a randomized clinical trial

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Abstract
Background Short-term outcomes of laparoscopy-assisted distal gastrectomy (LADG) and open DG (ODG) have been investigated in previous clinical trials, but operative techniques and concomitant treatments have evolved, and up-to-date evidence produced by expert surgeons is required to provide an accurate image of the relative efficacies of the treatments. The purpose of this study was to compare laparoscopic versus ODG with respect to specific primary and secondary short-term outcomes.
Methods From October 2005 to February 2008, a total of 64 patients with early gastric cancer were randomly assigned to the LADG or the ODG group. One patient was excluded due to concurrent illness unrelated to the intervention, so the data from 63 patients were analyzed. The primary short-term outcome was the 4-day postoperative use of analgesics. Secondary short-term outcomes were postoperative residual pain, complications, days hospitalized, blood data, days with fever, and days to first flatus.
Results There was a significant difference in favor of LADG for postoperative use of analgesics ($P = 0.022$). Unexpectedly, there was no significant difference in degree of pain in the immediate postoperative period, putatively due to the optimal use of analgesics. Of the secondary outcomes, residual pain at postoperative day 7 ($P = 0.003$) and days to first flatus ($P = 0.001$) were significantly better with LADG. Postoperative complications, number of days hospitalized, and number of days with fever were also better with LADG, but the differences were not significant. Blood data representing inflammation (WBC and CRP) showed marked differences, especially on postoperative day 7 ($P = 0.0016$ and $P = 0.0061$, respectively).
Conclusions LADG performed by expert surgeons results in less postoperative pain accompanied by decreased surgical invasiveness and is associated with fewer postoperative inconveniences. No preliminary suggestions of changes in long-term curability were observed. LADG for early gastric cancer is a feasible and safe procedure with short-term clinical results superior to those of ODG.

Keywords Laparoscopic gastrectomy · Randomized controlled trial · Short-term outcome · Expert surgeon

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The most common type of cancer in Japan is gastric cancer. Open gastrectomy combined with lymph node dissection has been a standard approach for gastric tumor resection. In recent years, the number of operations for gastric cancer, particular early tumors, has increased due to advances in diagnostic techniques. Alongside these advances, endoscopic treatments [1, 2] and other minimally invasive

treatments [3, 4], in which the extent of gastric resection is reduced, have been developed. The use of laparoscopy-assisted distal gastrectomy (LADG) [5], which was performed for the first time in Japan in 1991 for early gastric cancer and which is an intermediate procedure between endoscopic treatment and open gastrectomy, is spreading gradually because it offers excellent curability [6–8]. However, LADG has not yet become a standard technique. It has been pointed out that besides being complicated [9], troublesome, and time-consuming to perform, LADG requires specific technical skill [10–12].

Retrospective studies have been conducted to compare LADG with conventional open distal gastrectomy (ODG), and LADG has been shown to be superior to ODG with respect to postoperative pain and operative invasiveness [13–15]. There have also been initial reports of randomized controlled trials (RCT) [16–21] that compared LADG with ODG. However, because surgical techniques and the care of patients in general have improved, we felt that it was timely to compare LADG and ODG performed by expert surgeons in current hospital care settings [22].

The purpose of this study was to compare laparoscopic versus open DG performed by expert surgeons with respect to the primary outcome (postoperative use of analgesics) and the secondary outcomes (postoperative residual pain, complications, days hospitalized, blood data, days with fever, and days to first flatus). Long-term outcomes will be formally reported in a later publication.

Methods

Between October 2005 and February 2008, a single-center, open, randomized clinical trial, comparing laparoscopy-assisted and conventional ODG performed by expert surgeons was conducted. Both LADG and ODG were performed by a single gastrointestinal surgical team with extensive experience with open and laparoscopic procedures. Two surgeons (SS and SK), who had performed more than 100 LADG procedures combined, performed LADG, and three surgeons (SS, SK, and NF), who each had performed more than 500 ODG operations, performed ODG. Our team had performed over 400 LADGs, and our learning curve was that of a pioneer surgeon with LADG and still decreasing (Supplementary Fig. 1), but blood loss had become constant after 100 cases (Supplementary Fig. 2). Both LADG and ODG were performed by the expert surgeons mentioned above as the main operators.

The study was approved by the Institutional Review Board and written informed consent was obtained from all patients. The computer-generated, nonstratified, blocked randomization scheme was managed centrally and concealed at the moment of inclusion. Surgery was scheduled to be performed within 7 days of patient registration. Due to the pragmatic nature of the trial, surgeons, care providers, and patients could not be blinded to the type of treatment that was performed. The study was registered via the University Medical Information Network (UMIN) Clinical Trial Registry (UMIN-CTR) system (registry number UMIN000001513).

Primary and secondary outcomes

The primary short-term outcome of this study was postoperative use of analgesics, which was represented by the total number of postoperative uses of any of the following analgesics: extra boluses of pain blocker pump, indometacin suppository, and pentazocine hydrochloride for pain relief over 4 postoperative days. The secondary outcomes included the reduced postoperative residual level of pain (visual analog scale (VAS)) [24] score on individual post-operative days (1, 2, 3, and 7 days) to support data to confirm any clinical benefits on pain; intraoperative and postoperative complication rates; number of days of postoperative hospitalization; postoperative inflammatory response and nutrition status; and postoperative inconveniences such as number of days with fever (>37 °C), number of days to resumption of oral intake, and number of days to first flatus.

Patients

Patients were eligible for inclusion if they were over 20 and under 75 years of age and if they were diagnosed with gastric cancer in the middle or lower part of the stomach for which distal gastrectomy was indicated. Since elderly patients have more concurrent illnesses, which may affect both short-term and long-term outcomes, patients >75 years of age were excluded from this study. All patients enrolled in this study had a diagnosis of early gastric cancer with wall invasion confined to the mucosa or submucosa. Exclusion criteria were past history of gastric cancer, previous open surgery of the upper abdomen, past history of other types of cancers and cancer treatment, serious heart, lung, kidney, blood and/or metabolic disease, New York Heart Association Class III or IV classification of cardiac patients, and Class III, IV, or V of the Hugh-Jones dyspnea criteria.

Sample size calculations were done for the primary short-term outcome using the PASS program (NCSS Statistical Software, Kaysville, UT) and were based on detecting the difference between the LADG and ODG groups in terms of frequency of use of analgesics 4 days postoperative. Assuming that the baseline number of analgesics use during the 4 postoperative day is 14 times and 2 time reduced use in the LADG group, which correspond to an analgesics use incidence ratio of 0.75 of two groups, by means of a comparison for count data that followed Poisson distribution, with a type I error probability

of 0.05 and power of 0.8, the recommended sample size was 50. To guard against type I error, 60–70 patients were included. The sample size analysis for secondary outcomes was simply an estimate of the number.

Prespecified protocols were defined for intraoperative anesthesia, surgical procedures, preoperative and postoperative clinical assessments, and postoperative care as follows:

Intraoperative anesthesia

The participants received 5–10 mg of diazepam as premedication 1 h before they were taken to the operating room. To anesthetize the patient, an epidural catheter was inserted between the 7th and 8th or 8th and 9th thoracic vertebrae (T7/8 or T8/9) and placed in the epidural space. For a test dose, 3 mL of 1 % xylocaine was used. Five minutes later, 10 mL of 1 % carbocaine was injected as the main dose. After that, 5 mL of 1 % carbocaine was additionally administered every 45 min.

Surgical procedures

The extent of systemic lymph node dissection was determined according to the Japanese Classification of Gastric Carcinoma (2nd English edition) [23]. The anastomotic and reconstructive methods and the extent of lymph node dissection were standardized in both procedures. To facilitate the accurate comparison of surgical outcomes of LADG and ODG, similar anastomosing, suture instruments, and hemostatic devices were used and the same clinical path was adopted in both arms of the trial.

The incision made for the open cases was from the subxiphoid process to the subnavel region (around 20 cm in length). In LADG, a 4–5-cm minilaparotomy was initially made below the xiphoid process. To elevate the liver, a suture was placed around the falciform ligament, which was then pulled out of the abdomen. A Lap Disk Mini (Hako Shoji, Tokyo, Japan) was placed into the minilaparotomy. A flexible fiberscope with a 5-mm tip (Olympus Optical Co., Ltd., Tokyo, Japan) was inserted through the Lap Disk. The abdominal cavity was inflated with carbon dioxide to maintain an intra-abdominal pressure of 8 mmHg. A 5-mm camera port was inserted below the umbilicus. Two 5- and 12-mm trocars were placed in the left and right sides of the abdomen, respectively.

For both LADG and ODG, the greater omentum was laparoscopically dissected using ultrasonically activated coagulating shears (Harmonic Scalpel; Ethicon Endo-Surgery, Cincinnati, OH, USA), and the lymph nodes along the right gastroepiploic vessels (No. 4d) were removed. The left gastroepiploic vessels were exposed and divided near the spleen using the Harmonic Scalpel, and the lymph nodes along the left gastroepiploic vessels (No. 4sb) were taken out. Then, the right gastroepiploic vessels were exposed and divided and the infrapyloric lymph nodes (No. 6) were dissected, completing the procedure at the greater curvature of the stomach.

In LADG, another trocar was inserted through the Lap Disk Mini before starting the procedure at the lesser curvature of the stomach. A snake retractor was inserted through the port to displace the left lobe of the liver upward, thereby providing a good view of the lesser curvature. The retractor was fixed to a surgical arm to secure a stable field of view. In both LADG and ODG, the lesser omentum was dissected, the right gastric artery was exposed and divided, and the suprapyloric lymph nodes (No. 5) were dissected. The lymph nodes along the common hepatic artery (No. 8a) were dissected, and the left gastric vein was exposed and divided. Next, the left gastric artery was exposed and divided at its root, and the lymph nodes along the left gastric artery (No. 7) were removed. At the same time, the lymph nodes around the celiac artery (No. 9) were taken away. The right paracardial lymph nodes (No. 1) and the lymph nodes along the lesser curvature (No. 3) were finally dissected.

In LADG, reconstruction was performed extracorporeally by Billroth type I anastomosis under direct vision through the minilaparotomy, as in ODG. The stomach was then pulled out of the abdominal cavity. A purse-string suture instrument was placed on the duodenum and the duodenum was transected. Next, the anvil head of a Premium Plus CEEA stapler, 28 mm in diameter (Tyco Healthcare, Norwalk, CT, USA), was inserted into the cut end of the duodenum. The distal two thirds of the stomach was resected using a GIA (Tyco Healthcare), and then mechanical anastomosis of the posterior wall of the remnant stomach and duodenal stump was performed. If the gastric remnant was small or tension was noted at the anastomosis in obese patients, Roux-en-Y reconstruction was performed.

The reconstruction method just described for the laparoscopic procedure is very similar to that for open surgery, and the device used is exactly same as used in open surgery. After hemostasis and washing, the abdomen was closed to complete the operation.

Preoperative and postoperative clinical assessments

Age, sex, body mass index (BMI), previous abdominal surgery, concurrent illness, and the American Society of Anesthesiologists (ASA) classification of physical status were obtained from the patients' medical records. Operative findings such as the extent of lymph node dissection, operative time, estimated blood loss, and number of dissected lymph nodes were recorded. Operative blood loss

was the sum of the volume of aspiration blood from the operative fields and the increased volume from the net gauze weight. Hematological and blood chemical data (IL-6 levels, white blood cell (WBC) counts, C-reactive protein (CRP) levels, total protein levels, and albumin levels) were obtained on postoperative days 1, 3, and 7. The first three factors reflect acute inflammation status and the last two factors represent nutritional status.

In addition, surgical parameters such as operative time, number of dissected lymph nodes, and blood loss were recorded for reference purposes, because previous retrospective studies [13–15] and RCTs [16–21] routinely included such comparisons. Resected specimens were examined to determine tumor size, histological type, depth of tumor invasion, presence of lymph node metastasis, and pathological tumor stage according to UICC staging.

Postoperative pain management

After surgery, the analgesic pump (Create Medic, Tokyo, Japan) was connected to the epidural catheter and 0.2 % ropivacaine was continuously administered at a flow rate of 5 mL/h for 2 days postoperatively. When a patient requested additional pain relief medication due to pain, an attending doctor or a nurse administered additional 2-mL bolus doses of the anesthetic by pushing the button attached to the pump, similar to patient-controlled anesthesia (PCA). This was described in the nurse's record. If the pain was not alleviated after the administration of additional anesthetic, a 25-mg indometacin suppository was concurrently used. If this still did not reduce the pain, pentazocine (15 mg) was injected intramuscularly. No number was defined as a limit for the analgesic pump; use of indometacin suppositories or pentazocine hydrochloride injections was limited to at most 3 times each. Other morphine equivalents to control pain were not included in this study. Postoperative pain was objectively evaluated using a 10-cm VAS score [24] and the evaluation time was set at 2–4 h after the completion of surgery and 1, 3, and 7 days postoperatively. The decisions on the timing of oral medication, removal of the epidural catheter, and discharge from the hospital were standardized according to prespecified protocols in the clinical path.

The same clinical path was used for both LADG and ODG

The same clinical path was implemented for all study patients. The clinical path included five important factors: (1) preoperative education and counseling, (2) pain control, (3) physiotherapy, (4) nutritional support, and (5) surgical care. As to factor (1), all patients as well as their family members and care givers, were given detailed counseling by a trained nurse to help them understand and prepare themselves for the operation and the perioperative period. An estimated discharge plan was also explained to them. The standard used to allow discharge was that the patient had no complications to be treated, and they could eat more than half a serving of rice porridge. For factor (2), all patients were preoperatively counseled by the trained pain nurse regarding postoperative pain management, including in the use of epidural analgesia and PCA. Perioperatively, individual anesthetists decided on the type of analgesia to be used. Briefly, the rules to control pain were as follows: The first choice for postoperative pain was the analgesic pump in a PCA manner. The second and third choices were 25 mg of indometacin suppository and/or subsequent intramuscular administration of 15 mg of pentazocine hydrochloride, if the pain continued. Epidural catheters were routinely removed on postoperative day 2. For factor (3), prior to surgery, all patients were educated by a trained nurse on breathing exercises. Cigarette smoking was strongly discouraged. On the first postoperative day, patients were started on a structured mobilization plan to encourage early ambulation. For factor (4), prior to surgery, all patients were assessed and approved for this study by a dietician based on good nutritional status, and no special supplements were given. Liquid diets were restarted on postoperative day 3. Finally, for factor (5), all operations were performed and managed by the upper gastrointestinal (UGI) surgical team. Nasogastric tubes were removed on postoperative day 1. Drains were mandatory in all cases and were removed once the output was clear following the introduction of oral fluids. For the prophylaxis of deep vein thrombosis, all patients wore pressure stockings. Skin staples were removed on postoperative day 7.

Once the decision for surgery was made, attending surgeons would initiate the entry into the pathway, usually at the outpatient clinics and occasionally in the wards. A preprinted checklist that included pre- and postoperative orders was used. This checklist covered the routine aspects of patient care such as preoperative tests and postoperative care. All patients in the prepathway group were managed in the conventional manner by individual surgeons.

Statistical analyses

Statistical analyses were planned on an intention-to-treat basis. No stopping rules were defined. The statisticians (LB and GW) performed the analyses on a data set in which the coding of the surgical groups was concealed. Count variables were modeled directly with negative binomial regression, yielding rate ratios and their confidence intervals. Differences in the presence of complications were tested by Fisher's exact test and modeled by logistic regression, yielding odds ratios and their confidence

intervals. Continuous outcomes were analyzed with *t*-tests or Wilcoxon's rank-sum tests. All analyses were conducted using STATA 10 (StataCorp LP, College Station, TX, USA). A *P* value of 0.05 (2-sided) was considered significant.

Results

Patients

A total of 68 patients were screened for eligibility, of which 64 were deemed eligible and randomly allocated to the treatment arms (Fig. 1). There was no allocation factor in this study. In the ODG arm, one patient was excluded due to concurrent illness that was discovered during the hospital stay; the illness was not related to the intervention. The analyzable population therefore consisted of 63 patients, with 31 patients in the LADG arm and 32 patients in the ODG arm. Assessments of these arms with regard to prognostic indicators at baseline revealed no significant differences (Table 1).

Primary outcomes

The top part of Table 2 gives the result of the primary outcome analysis. There was 7 times less use of analgesics during the postoperative day in the LADG group compared to the ODG group. Since the number of analgesics use is a count variable and Poison-distributed (Fig. 2A), we performed a negative binomial regression with bootstrap-based standard errors for the coefficient. The analgesics use incidence ratio of LADG to ODG (exponential form of the difference in the number of analgesics use per day between two groups) was 0.68 (95 % CI = 0.49–0.95) and indicates

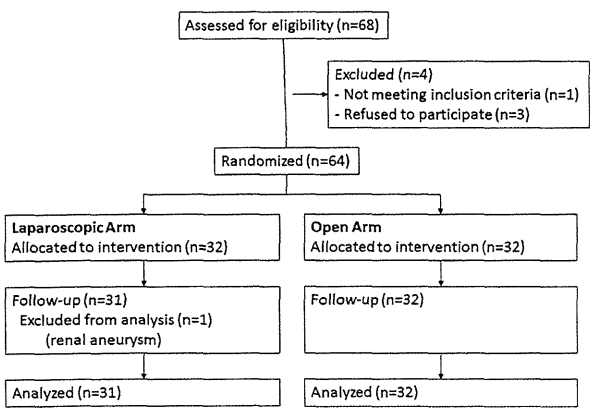

Fig. 1 Flowchart of the randomized clinical trial of laparoscopy-assisted distal gastrectomy (*LADG*) versus open distal gastrectomy (*ODG*)

Table 1 Baseline characteristics of the patients

	LADG ($n = 31$)	ODG ($n = 32$)
Age (years)	58 (SD = 9.6)	61 (SD = 7.6)
Sex (female/male)	14/17	7/25
Body-mass index (kg/m^2)	22.6 (SD = 3.0)	22.6 (SD = 3.8)
Concurrent illness		
Present/absent	13/18	11/21
Hypertension	7	5
Diabetes mellitus	4	4
Cardiac infarction	1	1
Depression	0	1
Arrhythmia	1	0
ASA classification		
I	15	18
II	16	14

LADG laparoscopy-assisted distal gastrectomy, *ODG* open distal gastrectomy, *ASA* American Society of Anesthesiology

a lower rate of analgesics use in the LADG group than in the ODG group ($P = 0.022$), and the difference in the required number of analgesics was shown in Fig. 2B. Reflected in this finding, the number of the use of epidurals was lower in the laparoscopy group than in the open group (Fig. 2C, there was no statistical difference), and pentazocine hydrochloride was used much less frequently in the laparoscopic group ($n = 1$) than in the open group ($n = 9$).

Secondary outcomes

The lower part of Table 2 gives the results of the secondary outcome analysis. As expected, after self-controlled use of analgesics, residual pain as measured by VAS scores did not differ significantly in the immediate postoperative period (1, 2, and 3 postoperative days, Fig. 2D). However, as the standardized analgesic regimen was stopped on postoperative day 3, the Wilcoxon's rank-sum test indicates there was less pain in the LADG group on postoperative day 7 ($P = 0.003$)(Fig. 2C, D).

There were no intraoperative complications in either treatment arm. In the LADG group, one patient had a postoperative complication (anastomotic stenosis). In the ODG group, five patients had postoperative complications (bleeding in 2, abdominal abscess in 1, pneumonia in 1, and wound infection in 1). The odds ratio for this comparison, based on the logistic regression coefficient, was 0.14 (95 % CI = 0.02–1.28), indicating a lower risk of complications in the LADG group but it was not significant ($P = 0.1$). All complications were treated conservatively to full recovery, except for the patient with postoperative bleeding; that patient underwent blood transfusion and

Table 2 Short-term primary and secondary clinical outcomes

	LADG[a] ($n = 31$)	ODG[a] ($n = 32$)	Comparison[b]	P value
Primary outcomes				
Number of administered analgesics	14.6 (10.1)	21.5 (14.6)	0.68 (0.49–0.95)	0.022
Secondary outcomes			–	
Residual pain at POD 7	5.3 (9.07)	12.8 (15.4)		0.003
Postoperative complications	1	5	0.14 (0.02–1.28)	0.1
Intraoperative complications	0	0		–
Days to first flatus	1.6 (SD = 0.7)	2.3 (SD = 1.0)	0.70 (0.55–0.87)	<0.001
Days of fever	2.5 (SD = 1.7)	3.5 (SD = 2.2)	0.72 (0.53–1.02)	0.06
Days of postoperative hospitalization	9.1 (SD = 1.1)	10.0 (SD = 3.1)	0.90 (0.77–1.06)	0.2

[a] Descriptive data from count and continuous variables are expressed as means with standard deviation

[b] Comparisons of the count variables are made via incidence rate ratios from negative binomial regression coefficients. Comparison of "residual pain before discharge" was made via Wilcoxon's signed rank test. Comparison of event variable "postoperative complications" was made via odds ratios from logistic regression with P value from Fisher's exact test

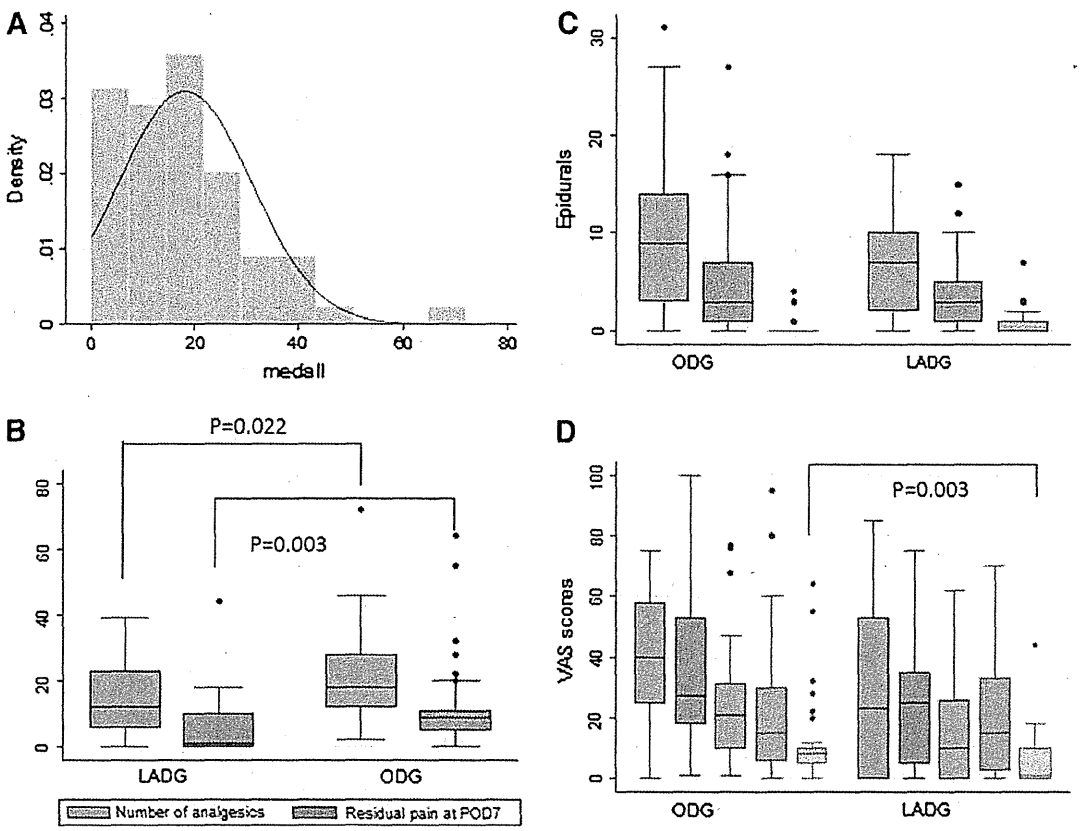

Fig. 2 **A** With pain medications as the outcome, the variable is not normally distributed but is a count variable with a Poisson distribution. **B** The primary short-term outcome is significantly different, as shown in the *blue box*. A robust difference ($P = 0.003$) is present in residual pain at POD 7 (see *red box*). **C** The number of epidural analgesics used is shown for the LADG and ODG groups, with no significant difference between the groups. *Blue*, *red*, and *green boxes* indicate the required number of epidurals at postoperative days 0, 1, and 2, respectively. **D** VAS scores at POD 1 (*red*), 2 (*green*), 3 (*orange*), and 7 (*gray*) are shown. The *blue box* is sum data. A significant difference is present only for POD 7 (Color figure online)

emergency surgery. The patient's postoperative course was nevertheless favorable and the patient was discharged 12 days after surgery.

The postoperative hospital stay and days with fever exceeding 37 °C after surgery both were almost 1 day shorter in the LADG group. These parameters are also