

Safety and Feasibility of Linear Stapling Device with Bioabsorbable Polyglycolic Acid Sheet for Duodenal Closure in Gastric Cancer Surgery: A Multi-institutional Phase II Study

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Abstract

Background Duodenal stump fistula (DSF) after gastrectomy is of low frequency but a critical complication in gastric cancer surgery. Manual oversewing for reinforcement of the duodenal stump is not applicable when free longitudinal margin is short and has technical difficulties in laparoscopic surgery. This trial evaluated the safety and feasibility of using a linear stapler with bioabsorbable polyglycolic acid (PGA) sheet for duodenal stump closure and reinforcement in gastric cancer surgery.

Methods This multi-institutional, prospective phase II trial included gastric cancer patients who were scheduled to undergo distal or total gastrectomy with R-Y reconstruction. In all cases, duodenum was transected using a linear stapler with PGA sheet. The primary endpoint was the incidence of postoperative DSF. Sample size was set at 100 patients considering an expected value of 3% and threshold value of 8% with one-sided testing at a 10% significance level.

Results Between June 2014 and June 2015, a total of 100 patients were registered in this trial. Postoperative DSF was observed in two cases (2.0%, 90% CI 0.4–6.2%) which was developed on postoperative days 13 and 20. Intraoperative bleeding at the duodenal stump staple line was observed in one case but was easily controlled without additional suturing. Postoperative bleeding was not observed in any of the cases.

Conclusion This study suggested that the use of PGA sheet as a reinforcement material for closure of the duodenal stump during gastrectomy for gastric cancer is both safe and feasible.

Trial registration number UMIN 000014398

Introduction

Duodenal stump fistula (DSF) after gastrectomy with Roux-en-Y (R-Y) or Billroth-II reconstruction is a life-threatening complication in gastric cancer surgery. Its incidence is not so frequent, approximately 2–3%; however, its mortality rate is high, up to 9–46% [1–5]. DSF easily causes critical events such as intraperitoneal abscesses, bleeding, sepsis, and multiple organ failure, which could lead to mortality. Some of the various causes of DSF include inadequate stump closure, blood flow disturbances, local hematoma, and elevated intestinal pressure. Some surgeons believe that occurrence of DSF could

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be reduced by reinforcement of the suture line by manual oversewing after transection of the duodenum with a linear stapling device.

In recent years, laparoscopic gastrectomy for gastric cancer has become widespread not only in Japan but also in the world. In laparoscopic surgery, intracorporeal suturing and ligation procedures are technically difficult and time-consuming. Therefore, oversewing for reinforcement is often omitted after closure of the duodenum with a linear stapling device [3, 6]. In addition, even in open surgery, reinforcement is sometimes not performed if the tumor has widely extended to the duodenum exceeding the pylorus, since there is insufficient free longitudinal margin after the resection in such cases, making it difficult to take sutures on the staple line of the duodenal stump [2]. Although it is unclear whether reinforcement of suture line is necessary or not, if it is necessary, generally applicable method must be developed.

In the bariatric surgery for obesity, various materials including bioabsorbable membrane are frequently used for reinforcement of gastric staple lines during sleeve gastrectomy and gastric bypass procedures, in order to reduce staple line complications such as postoperative bleeding and leakage [7–9]. More recently, one convenient device was introduced for reinforcement of the staple line. That is a linear stapling device with bioabsorbable polyglycolic acid (PGA) sheets. Bioabsorbable PGA sheets are placed on the surface of both anvil and cartridge forks of the linear stapling device. When fired, tissue is stapled across the PGA sheets, by which staple line is reinforced.

We considered that this device has advantages of shortening time for reinforcement and of generalizability for application regardless of technical difficulties to close the duodenal stump. The purpose of this prospective study was to evaluate the safety and feasibility of using a linear stapler together with PGA sheet for duodenal stump closure in gastric cancer surgery.

Materials and methods

This study was designed as a multicenter, prospective phase II trial. The study protocol was approved by the institutional review boards (IRBs) of Aichi Cancer Center Hospital and Kanagawa Cancer Center before initiation of the study. The inclusion criteria were as follows: (1) gastric cancer patients who were scheduled to undergo open or laparoscopic (distal or total) gastrectomy with R-Y reconstruction using a surgical stapling device, (2) aged 20 years or older, (3) no history of upper abdominal surgery except laparoscopic cholecystectomy, (4) an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1, (5) adequate organ function, and (6) provided written

informed consent in person for participation in the study. The exclusion criteria were as follows: (1) women who were pregnant or possibly pregnant, or breastfeeding, (2) receiving continuous systemic (oral or intravenous) steroid therapy, (3) concurrent poorly controlled diabetes mellitus (HbA1c > 8.0%), (4) a history of allergy to nickel or chrome, (5) concurrent mental disorders or psychiatric symptoms judged to preclude participation in this study, and (6) judged by the investigator to be inappropriate as subjects of this study.

Surgical procedures

Surgical procedure was limited to distal or total gastrectomy (DG or TG) with lymphadenectomy under open or laparoscopic approach. The extent of lymph node dissection was decided according to the clinical T and N stage of the tumor, based on the third edition of the Japanese gastric cancer treatment guidelines. In all cases, duodenum was transected using a linear stapler with PGA sheet (Endo GIA Reinforced Reload with Tri-Staple™ Technology, 60-mm purple cartridge; Medtronic, North Haven, CT, USA) (Figs. 1, 2). Trimming of the excess of the stapled PGA sheet was not mandatory. Reconstruction was limited to the R-Y method.

Follow-up

All the enrolled patients were followed up at outpatient clinic in each hospital. Postoperative data were collected until 6 months after surgery.

Endpoints

The primary endpoint of this study was the incidence of postoperative DSF of grade II or more categorized by the Clavien–Dindo classification. DSF was defined as the presence of duodenal fluid in surgical drainage(s) or its leakage through the abdominal wall and was confirmed by CT scan and/or fistulography. DSF caused by other postoperative complications (e.g., pancreatic fistula) was also included as an event. The secondary endpoints were staple line bleeding, any staple malformations on duodenal stump, incidence of duodenal serosal injury, any additional suturing, blood loss, duration of surgery, incidences of intraoperative and postoperative adverse events, duration of drain placement, and duration of hospital stay. Staple malformation and serosal injury were evaluated intraoperatively, immediately after stapling. Staple line bleeding was evaluated twice, first, immediately after stapling and second, after reconstruction and before closure of the abdominal wall.



Fig. 1 Endo GIA Reinforced Reload with Tri-Staple™ Technology, 60-mm purple cartridge (Medtronic, North Haven, CT, USA). Bioabsorbable polyglycolic acid (PGA) sheets is preloaded in the cartridge

Study design and statistical analysis

In this phase II trial, the sample size was calculated to be 98 patients in order to provide an 80% power to detect the significance in the occurrence of the primary endpoint, with the hypothesis that the primary endpoint would have an expected value of 3% and threshold value of 8%, using one-sided testing at a 10% significance level. The total sample size was set at 100 patients considering some possible withdrawals. The expected and threshold values were decided according to the historical control to examine incidence of DSF in Aichi Cancer Center Hospital. Among 61 patients who had undergone R-Y reconstruction after gastrectomy for gastric cancer from January 2007 to March 2010, only two patients (3.3%) developed DSF. Thus, we considered that expected value of 3% and threshold value of 8% would guarantee safety in this phase II setting.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan [10]), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). The severity of surgical morbidity was evaluated by the Clavien–Dindo Classification [11, 12]. This trial was registered with UMIN-CTR, identification number UMIN 000014398 (<http://www.umin.ac.jp/ctr/index.htm>).

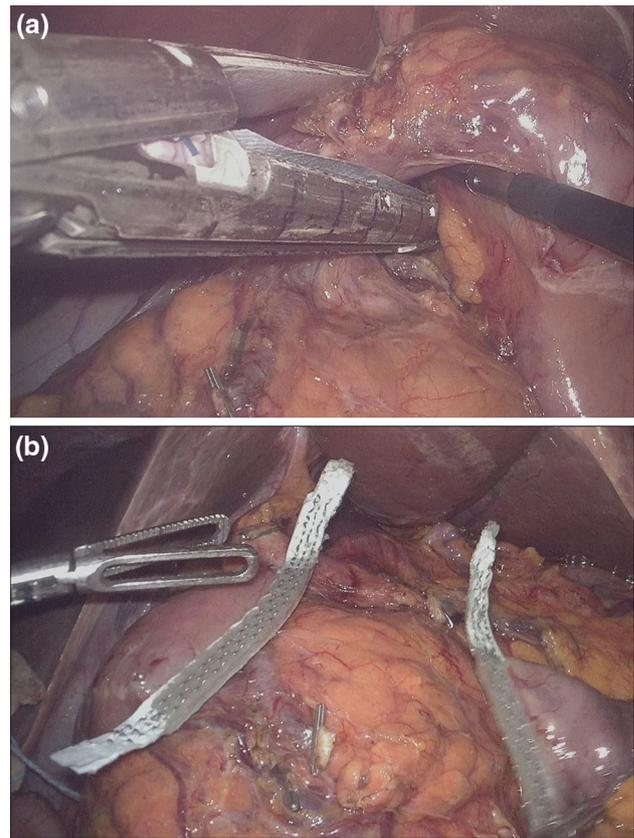


Fig. 2 Intraoperative images of duodenal stump closure during laparoscopic gastrectomy. **a** A linear stapling device with PGA sheet is applied to duodenal bulb with same manner as regular liner stapling device. **b** After duodenal transection, the staple line is overlaid with PGA sheet

Results

Between June 2014 and June 2015, a total of 100 patients were registered in this trial. Table 1 shows the patients' characteristics. Seven patients (7%) received neoadjuvant chemotherapy before surgery. Incidence of early gastric cancer (T1) was only 39%. Table 2 shows details of the surgical procedures. DG and TG were performed in 39 and 61 patients, respectively. All patients underwent R-Y reconstruction. Open gastrectomy (OG) was performed in 55 patients, while laparoscopic gastrectomy (LG) was performed in 44 patients, and one case of LG was converted to OG. The median duration of surgery was 306.5 min. Median blood loss was 155 g.

Closure of the duodenal stump was performed using a linear stapler with PGA sheet as reinforcement material in all 100 cases. There was no usage of the linear stapler with reinforcement material on any other part of the gastrointestinal tract. To transect the duodenum using this device, no special technique was required except for cutting the tip of the connected stapled PGA sheet after stapling.

Table 1 Patient characteristics

Number of patients	100
Gender (male/female)	70/30
Age (median, range)	68 (34–83)
Body mass index (kg/m ²) (median, range)	22.7 (16.1–28.6)
Neoadjuvant chemotherapy (yes/no)	7/93
Primary tumor location abdominal esophagus/upper third of stomach/middle third of stomach/lower third of stomach	1/45/45/9
Tumor invasion to duodenum (yes/no)	2/98
Clinical T stage (T1/T2/T3/T4)	39/19/13/29
Clinical node status (N0/N1/N2/N3)	77/16/6/1
Clinical M stage (M0/M1)	100/0
Clinical stage (I/II/III/IV)	57/26/17/0
Tumor size (cm) (median, range)	4.3 (0.7–18.0)
Pathological T stage (T1/T2/T3/T4)	43/13/11/33
Pathological node status (N0/N1/N2/N3)	50/15/14/21
Pathological M stage (M0/M1)	94/6
Pathological stage (I/II/III/IV)	46/17/31/6

Trimming of the excess portion of the stapled PGA sheet was performed in 40 cases (40%). No staple malformation or duodenal serosal injuries were observed. Intraoperative bleeding at the duodenal stump staple line was observed in one case of LG immediately after closing the duodenum. The amount of bleeding, however, was very small, and it was easily controlled with electrocautery. There were no cases in which bleeding was confirmed just before abdominal wall closure. None of the cases required additional suturing along the staple line of the duodenal stump.

Postoperative grade II complications occurred in 11 cases, and grade III complications occurred in 10 cases until 6 months after surgery (Table 3). No grade IV or higher complications were observed. The incidences of complications were not significantly different between OG and LG. Postoperative DSF was observed in two cases. Thus, point estimate was 2.0% and upper limit of 90% confidence interval was 6.2%. One of these patients (grade IIIb), who underwent laparoscopic distal gastrectomy, developed DSF on postoperative day 13 after the initial discharge. He was readmitted and underwent drainage surgery for the DSF and was discharged on day 45 after the initial surgery. The other patient (grade II), who underwent open total gastrectomy with splenectomy, developed DSF, which was diagnosed by contrast radiography through postoperative drainage tube during conservative treatment for a pancreatic fistula on postoperative day 20 and recovered with conservative treatment and was discharged

Table 2 Detail of surgical procedures

Operation time (min) (median, range)	306.5 (146–520)
Blood loss (g) (median, range)	155 (0–3020)
Operative procedure	
Open total gastrectomy (OTG)	35
Open distal gastrectomy (ODG)	21
Laparoscopic total gastrectomy (LTG)	26
Laparoscopic distal gastrectomy (LDG)	18
Conversion to open procedure, <i>n</i> = 44 ^a (yes/no)	1/43
Reconstruction method (Roux-en-Y/others)	100/0
Extent of lymph node dissection (D1/D1+/D2)	1/39/60
Combined resection	
None	75
Spleen	15
Gallbladder	8
Others	4
Intraoperative adverse events (overall)	5
Spleen injury	2
Pancreas injury	1
Esophagus injury	1
Bleeding from inferior epigastric vessels	1
Trimming of the excess portion of the stapled PGA sheet (yes/no)	40/60
Staple line hemostasis on duodenal stump (yes/no)	1/99
Staple malformations on duodenal stump (yes/no)	0/100
Duodenal serosal injury (yes/no)	0/100
Additional suture on duodenal stump staple line (yes/no)	0/100
Perioperative blood transfusion (yes/no)	4/96
Drain placement (yes/no)	92/8
Duration of drain placement, <i>n</i> = 92 (days) (median, range)	6 (1–133)
Reoperation (yes/no)	4/96

^aConversion to open procedure was counted for all patients who underwent laparoscopic gastrectomy

on day 39 after the initial surgery. Postoperative bleeding was not observed in any of the cases. The median duration between initial surgery and discharge was 10 days (range 6–135). Seven cases including one DSF case were readmitted due to complications after the initial discharge. In-hospital deaths and deaths within 6 months after surgery were not observed.

Discussion

This is the first prospective study to evaluate safety of using a linear stapler together with a bioabsorbable PGA sheet for duodenal stump closure during gastrectomy for

Table 3 Postoperative grade II or higher complications until 6 months after surgery

	CDC grade II		CDC grade III	
	Overall	OG/LG	Overall	OG/LG
Overall ^a	11 (11%)	9/2	10 (10%)	4/6
Duodenal stump fistula (DSF)	1	1/0	1	0/1
Pancreatic fistula	6	4/2	2	0/2
Intraabdominal abscess	3	2/1	1	0/1
Anastomotic leak ^b	1	1/0	0	0/0
Anastomotic stenosis	0	0/0	3	0/3
Ileus	1	1/0	3	2/1
Pneumonia	1	0/1	1	0/1
Pleural effusion	0	0/0	3	2/1
Enteritis	2	2/0	0	0/0
Others	4	3/1	0	0/0

CDC Clavien–Dindo classification, OG open gastrectomy, LG laparoscopic gastrectomy

^aSome patients had multiple complications

^bAnastomotic leak except for DSF

gastric cancer. As compared to manually oversewing for reinforcement, this device has advantages of shortening time for reinforcement and of generalizability for application regardless of technical difficulties. We set primary endpoint as incidence of DSF in this study because DSF is rare but critical complication in gastric cancer surgery. In the present study, incidence of DSF was 2.0% and upper limit of 90% confidence interval was 6.2%, which was lower than prespecified values of 3% and 8%, respectively. These results suggested that linear stapling device with bioabsorbable PGA sheet was safe for duodenal stump closure in gastric cancer surgery.

Previously, several reports examined the incidence of DSF after gastrectomy. Cozzaglio et al. [3] reported that the incidence of DSF was 2.5% (205/8268) in a retrospective study of 16 hospitals. They also reported that surgery to treat DSF was performed in 75 of the 205 patients (36.6%), although approximately 60% of 75 patients underwent manual oversewing on the duodenal stump. Orsenigo et al. [2] reported in a single-center study that the incidence of DSF was 2.5% (32/1287). Among 32 patients who developed DSF, 17 patients had undergone reinforcement of manually oversewing. In our historical control at Aichi Cancer Center, DSF was observed in two (3.3%) among 61 patients despite that manually sewing was added for reinforcement of staple line of the duodenal stump. Thus, DSF would be unavoidable event even though adding manually sewing. In the present study, the incidence of DSF was 2.0% which was similar to these previous reports, indicating that safety of linear stapling device with bioabsorbable PGA sheet was similar to conventional method of adding manually sewing.

Gastrointestinal anastomotic failure, one of the major complications of gastric cancer surgery, is reportedly around 0.2–4.3% in the previous reports [13–17], and it typically appears approximately during 1 week after surgery. Most of these failures are considered to be directly related to the suture or staple site, such as incomplete sutures, local hematomas, blood flow disturbances, and intestinal pressure elevation. The mean onset time of DSF was reportedly 6 days in the Cozzaglio's study and 6.6 days in the Orsenigo's study [2, 3]. However, in our historical control at Aichi Cancer Center Hospital, DSF was observed in two patients on postoperative days 3 and 15, and the latter was diagnosed to be secondary DSF during the conservative treatment for pancreatic fistula. Also in the present study, DSF observed in two patients was occurred on postoperative days 13 and 20, which were delayed as compared to the previous reports. Both patients with DSF in this study presented high levels of amylase in the drainage fluid in the early postoperative period and were diagnosed postoperatively with pancreatic fistula. In one patient, the pancreatic fistula subsided after conservative treatment and the patient could be discharged, but perforative peritonitis, which was diagnosed as being due to DSF, occurred on postoperative day 13. In another patient, DSF was diagnosed on postoperative day 20 by drainage imaging that was performed during conservative treatment for a pancreatic fistula. In both of these patients, it was thought that DSF has occurred secondarily to a pancreatic fistula, and this resulted in the later occurrence of DSF as compared to previous two reports. As pancreatic fistula is a serious complication, observed in around 0.4–12.6% of gastric cancer surgery [16–20], it might be

difficult to avoid the secondary DSF after pancreatic fistula despite the reinforcement with manual oversewing or PGA sheet on the duodenal stump.

Surgeons often experience bleeding at the staple line just after resecting the duodenum. Once bleeding occurred, bleeding must be controlled by electrocautery or manually sewing. Bleeding at the staple line may be caused by mismatching of the staple height and thickness of the tissue, but too tight stapling might cause ischemia at the stump which leads to DSF. In the present study, only one patient presented bleeding from the duodenal stump staple line intraoperatively, and in this patient, hemostasis was achieved easily in a short amount of time using electrocautery. Surgeons sometimes experience postoperative bleeding after simple stapling; however, postoperative bleeding was not observed in this or any other patient. Moreover, no patient developed early DSF after surgery. These results suggested that bioabsorbable PGA sheet helps to avoid bleeding without causing ischemia at the stump, which would contribute to shorten operation time and decrease morbidity such as postoperative bleeding or early DSF. Thus, this device is considered to be safe and feasible. Bioabsorbable PGA sheet placed between the staple might decrease mismatching of the staple height and thickness of the tissue without increasing risk of DSF.

In contrast, the linear stapling device with reinforcement material has a disadvantage, which is the additional financial cost. It takes around 220 USD when using conventional stapler but takes 380 USD when using this device in retail price. However, Japanese National Health Insurance System reimburses the cost of the reinforcement material in addition to that of linear stapling device.

There are several limitations to this study. First, this study is limited by its single-arm, phase II design, and selection bias may have influenced the results. In fact, as safety and feasibility of linear stapling device with reinforcement material had not been confirmed, we excluded the patients with severe comorbidities such as the patients receiving continuous systemic steroid therapy or poorly controlled diabetes mellitus. Therefore, safety and feasibility of this device in such patients with severe comorbidities are unclear. Second, the sample size in this study was relatively small, at 100 patients, and the 90% confidence interval was wide, up to 5.8% (0.4–6.2%). For these reasons, reliability of point estimate of 2% is limited. The incidence of DSF is low in general, and only two patients developed this complication in this study. We therefore could not analyze and identify risk factors for the development of DSF. In future, if a linear stapling device with reinforcement material becomes more commonly used at the duodenal stump closure site during gastrectomy for gastric cancer, it would be possible to confirm the safety and feasibility of this device in such patients with severe

comorbidities and, moreover, identify the accurate incidence and risk factors for DSF from a greater number of patients.

In conclusion, this study suggests that the use of a reinforcement material for closure of the duodenal stump during gastrectomy for gastric cancer is both safe and feasible. Although duodenal stump closure using a linear stapling device with reinforcement material involves additional cost, it has advantages of not requiring a substantial amount of time and of generalizability for application regardless of technical difficulties. It can be used easily in laparoscopic gastrectomies, in which intracorporeal suturing and ligation procedures are technically difficult, or even when the tumor is near the pylorus and the free margin is limited in open gastrectomies. Further verifications in a large-scale comparative study are necessary to determine the optimal method for duodenal stump closure.

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Compliance with Ethical Standards

Conflicts of interest Takaki Yoshikawa received lecture fee from Covidien, Olympus, and Johnson and Johnson. The other authors declare no potential conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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