**Table 1** Clinical characteristics and perioperative outcomes of the five patients

| Factors | |
|---|---|
| Sex (male:female) | 4:1 |
| Age (years)* | 60 (53–86) |
| Operating time (min)* | 199 (175–259) |
| Blood loss (g)* | 330 (300–730) |
| Number of retrieved lymph nodes* | 13 (11–22) |
| First solid food intake (postoperative days)* | 4 (4–5) |
| Postoperative hospital stay (days)* | 13 (11–14) |
| Postoperative death | 0 |
| Postoperative complications | 1 |
| Anastomotic leakage or stricture | 0 |
| Reflux esophagitis | 1 |

*Results are expressed as median (range) values

postoperative death or major postoperative complications such as anastomotic leakage or stricture. One patient complained of heartburn 1 month after discharge and endoscopic examination confirmed reflux esophagitis, which was treated effectively with camostat mesilate (Foipan®).

## Discussion

The epidemiology, pathogenesis, treatment, and prognosis of remnant gastric cancer after distal gastrectomy are well documented [11–14]; however, there is limited information on these subjects after proximal gastrectomy, which is a relatively new strategy not performed as often as distal gastrectomy[1, 2]. Our last two studies found a higher incidence of metachronous cancer in the gastric remnant after proximal gastrectomy than after distal gastrectomy [6, 9]. This implies that more cases of gastric remnant cancer will be encountered after proximal gastrectomy as it becomes widely accepted as a standard procedure and the surgical numbers increase [1, 2].

In gastric remnant cancer following distal gastrectomy with Billroth-II reconstruction, tumor infiltration to the jejunum is often accompanied by lymph node metastasis in the mesentery, with a reported incidence of 9–52 % [13–17]. This operation requires preservation of the vessels feeding the interposed jejunum, which is needed for easy re-reconstruction, making this operation inappropriate for gastric remnant cancer that infiltrates the jejunogastrostomy because potentially metastatic lymph nodes along the interposed jejunal artery cannot be completely dissected. If this is the case, total removal of the interposed jejunum along with its mesentery is recommended.

In the gastric remnant after proximal gastrectomy, the main lymphatic drainage pathways run along the right gastroepiploic and right gastric arteries. The left gastric, left gastroepiploic, posterior gastric and short gastric arteries were dissected and cut in the previous surgery, blocking these lymphatic pathways as well. Consequently, in the procedure we describe here, lymph node dissection is strongly recommended for stations #4d, 5 and 6 [10]. Furthermore, lymph node stations #8a, 12 and 14 can be cleared if lymph node metastasis is suspected at stations #4d, 5 and 6 during the operation. These recommendations will be supported by data we collect on the incidence of lymph node metastasis in the future.

The first patient on whom we performed this procedure underwent reconstruction by Billroth-II plus Braun's anastomosis between the interposed jejunum and the distal jejunum. This patient later complained of heartburn, found to be caused by an alkaline reflux esophagitis. In contrast, the other four patients who underwent reconstruction by Roux-en-Y anastomosis experienced no reflux symptoms. This suggests that 10 cm of preserved interposed jejunum is not long enough to stop bile reflux into the esophagus. Thus, we recommend reconstruction by Roux-en-Y anastomosis to maintain the patient's quality of life.

In conclusion, total resection of the gastric remnant after proximal gastrectomy and re-reconstruction with the preserved interposed jejunum is easy, safe and feasible. Since more cases of gastric remnant cancer after proximal gastrectomy are expected in the future, we recommend this surgical technique if it involves reconstruction with jejunal interposition.

**Conflict of interest** Isao Nozaki and his co-authors have no conflict of interest.

## References

1. Katai H, Sano T, Fukagawa T, Shinohara H, Sasako M. Prospective study of proximal gastrectomy for early gastric cancer in the upper third of the stomach. Br J Surg. 2003;90:850–3.
2. Katai H, Morita S, Saka M, Taniguchi H, Fukagawa T. Long-term outcome after proximal gastrectomy with jejunal interposition for suspected early cancer in the upper third of the stomach. Br J Surg. 2010;97:558–62.
3. Kitamura K, Yamaguchi T, Nishida S, Yamamoto K, Ichikawa D, Okamoto K, et al. The operative indications for proximal gastrectomy in patients with gastric cancer in the upper third of the stomach. Surg Today. 1997;27:993–8.
4. Kitano S, Adachi Y, Shiraishi N, Suematsu T, Bando T. Laparoscopic-assisted proximal gastrectomy for early gastric carcinomas. Surg Today. 1999;29:389–91.
5. Tokunaga M, Ohyama S, Hiki N, Hoshino E, Nunobe S, Fukunaga T, et al. Endoscopic evaluation of reflux esophagitis after proximal gastrectomy: comparison between esophagogastric anastomosis and jejunal interposition. World J Surg. 2008;32:1473–7.
6. Nozaki I, Kurita A, Nasu J, Kubo Y, Aogi K, Tanada M, et al. Higher incidence of gastric remnant cancer after proximal than distal gastrectomy. Hepatogastroenterology. 2007;54:1604–8.

7. Ohyama S, Tokunaga M, Hiki N, Fukunaga T, Fujisaki J, Seto Y, et al. A clinicopathological study of gastric stump carcinoma following proximal gastrectomy. Gastric Cancer. 2009;12:88–94.
8. Nunobe S, Ohyama S, Miyata S, Matsuura M, Hiki N, Fukunaga T, et al. Incidence of gastric cancer in the remnant stomach after proximal gastrectomy. Hepatogastroenterology. 2008;55:1855–8.
9. Nozaki I, Nasu J, Kubo Y, Tanada M, Nishimura R, Kurita A. Risk factors for metachronous gastric cancer in the remnant stomach after early cancer surgery. World J Surg. 2010;34: 1548–54.
10. Japanese Gastric Cancer A. Japanese Classification of Gastric Carcinoma - 2nd English Edition. Gastric Cancer 1998;1:10–24.
11. Sinning C, Schaefer N, Standop J, Hirner A, Wolff M. Gastric stump carcinoma - epidemiology and current concepts in pathogenesis and treatment. Eur J Surg Oncol. 2007;33:133–9.
12. Tanigawa N, Nomura E, Lee SW, Kaminishi M, Sugiyama M, Aikou T, et al. Current state of gastric stump carcinoma in Japan: based on the results of a nationwide survey. World J Surg. 2010;34:1540–7.
13. Sasako M, Maruyama K, Kinoshita T, Okabayashi K. Surgical treatment of carcinoma of the gastric stump. Br J Surg. 1991; 78:822–4.
14. Thorban S, Bottcher K, Etter M, Roder JD, Busch R, Siewert JR. Prognostic factors in gastric stump carcinoma. Ann Surg. 2000;231:188–94.
15. Han SL, Hua YW, Wang CH, Ji SQ, Zhuang J. Metastatic pattern of lymph node and surgery for gastric stump cancer. J Surg Oncol. 2003;82:241–6.
16. Kunisaki C, Shimada H, Nomura M, Hosaka N, Akiyama H, Ookubo K, et al. Lymph node dissection in surgical treatment for remnant stomach cancer. Hepatogastroenterology. 2002;49:580–4.
17. Yonemura Y, Ninomiya I, Tsugawa K, Masumoto H, Takamura H, Fushida S, et al. Lymph node metastases from carcinoma of the gastric stump. Hepatogastroenterology. 1994;41:248–52.

Original Paper

# Functional Outcomes According to the Size of the Gastric Remnant and Type of Reconstruction Following Open and Laparoscopic Proximal Gastrectomy for Gastric Cancer

*Eiji Nomura, Sang-Woong Lee, Takaya Tokuhara, Masaru Kawai and Kazuhisa Uchiyama*

Department of General and Gastroenterological Surgery, Osaka Medical College, Osaka, Japan

Corresponding author: Eiji Nomura, Department of General and Gastroenterological Surgery, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan; Tel.: +81-072-683-1221(ext 2361), Fax: +81-072-685-2057; E-mail: sur035@poh.osaka-med.ac.jp

## ABSTRACT

**Background/Aims:** We compared functional outcomes between different types of reconstruction following open or laparoscopic 1/2- or 2/3-proximal gastrectomy for gastric cancer. **Methodology:** Resection and reconstruction were performed by one of the following 6 methods, depending on the depth of cancer invasion and the date of the procedure relative to introduction of laparoscopic proximal gastrectomy: open proximal 2/3-gastrectomy with jejunal interposition (2/3PG-int, n=7), open proximal 1/2-gastrectomy with jejunal interposition (1/2PG-int, n=5), laparoscopic proximal 1/2-gastrectomy followed by double tract reconstructions with small (3cm) jejunogastrostomy (L1/2 PG-DT(S), n=19) and laparoscopic proximal 1/2-gastrectomy followed by double tract reconstructions with large (6cm) jejunogastrostomy (L1/2PG-DT(L), n=10). Open total gastrectomy with jejunal interposition (TG, n=12) and laparoscopic total gastrectomy with Roux-en-Y reconstruction (LTG, n=14) represented control procedures. **Results:** Comparison of postoperative/preoperative body weight ratios and food intake ratios revealed better preservation among patients with a larger remnant stomach and with easy flow of food into the remnant stomach (the 1/2PG-int and L1/2PG-DT(L) groups). **Conclusions:** Better functional outcomes were observed in patients with a large remnant stomach and with easy flow of food into the remnant stomach regardless of whether they underwent open or laparoscopic procedures.

**Key Words:** Gastric cancer; Laparoscopic and open proximal gastrectomy; Reconstruction; Surgical technique; Quality of life.

## INTRODUCTION

The incidence of early gastric cancer has increased in recent years (1). As patients are expected to survive for longer after surgery, there has been increasing demand for less invasive and safer operative procedures that are associated with improved postoperative quality of life (QOL) (2). For early primary gastric cancer located in the upper third of the stomach, we perform proximal gastrectomy. Various methods of open or laparoscopic resection with reconstruction have been devised over time (3-5). Standard proximal gastrectomy for early cancer, as defined by the Japanese gastric cancer treatment guidelines (6), requires resection of <1/2 of the stomach. However, when we began performing proximal gastrectomy, we performed resection of 2/3 of the proximal stomach for advanced gastric cancer with a depth of invasion confined to the muscularis propria. At that time, the criteria for proximal gastrectomy were: 1) a primary tumor located in the upper one-third of the stomach, 2) cancerous invasion not extending beyond the muscularis propria, and 3) no macroscopic evidence of lymph node metastasis at time of surgery (7). According to our analyses of postoperative QOL, the extent of the gastric resection and the manner of reconstruction and approach (open or laparoscopic) has been changing. As a result, in order to preserve >1/2 of the remnant stomach, we dropped the criterion for lack of extension beyond the muscularis propria. More recently, laparoscopic gastrectomy and reconstruction has been adopted as a feasible and potentially less invasive surgical approach (8,9).

At present we performed laparoscopic proximal gastrectomy for early gastric cancer, with reconstruction by the double tract method. In our study, we compared functional outcomes between different types of reconstruction following open or laparoscopic 1/2- or 2/3-proximal gastrectomy for gastric cancer.

## METHODOLOGY

### Patients and methods

The primary outcome measure was postoperative digestive function measured by postoperative/preoperative body weight ratio, postoperative/preoperative meal intake ratio and the degree of postprandial abdominal symptoms. Postoperative/preoperative meal intake ratio indicated approximately by the mean of the whole meal intake per day as compared to preoperative intake. These data were acquired at one time point, 6-12 months postoperatively, through an in-house questionnaire (**Table 1**). In addition, the findings of patients who underwent endoscopy postoperatively at our outpatient clinic were analyzed to investigate the incidence of esophagitis. Endoscopic findings of esophagitis were categorized by the Los

Hepato-Gastroenterology 2012; 59:1677-1681 doi 10.5754/hge12256
© H.G.E. Update Medical Publishing S.A., Athens

**TABLE 1.** Questionnaire survey about postoperative body weight, meal intake and abdominal symptoms.

1. Please state your body weight at present. _____kg

2. Please put a circle around the number below that fits your present postoperative whole amount of meal intake per day compared to your preoperative whole meal intake.

1) 20%
2) 40%
3) 60%
4) 80%
5) 100%
6) Other_____%

3. Please put a circle around the number below that fits your description of abdominal symptoms that occur often, especially after meals at present.

1) Borborygmus (stomach rumbling)
2) Abdominal pain
3) Diarrhea
4) Nausea, or vomiting
5) Abdominal sensation of feeling full
6) Abdominal discomfort
7) Heart burn, or reflux
8) No symptom

Angeles classification (10).

This study evaluated a total of 24 patients who underwent open gastrectomy for cancer between April 1992 and June 2001 and a total of 43 patients who underwent laparoscopic gastrectomy for cancer between April 2006 and June 2010 at our institution. Patients between 2002 and 2005 underwent open proximal gastrectomy with jejunal pouch interposition, but this procedure was abandoned because of occurrence of stasis in the jejunal pouch and reflux esophagitis. Up to 2001, we performed resection of two-thirds of the proximal stomach for advanced gastric cancer with a depth of invasion confined to the muscularis propria and performed resection of one-half of the proximal stomach for early gastric cancer with a depth of invasion confined to the submucosal layer. This was accompanied by dissection of perigastric lymph nodes up to D1+ (dissection of lymph node stations 7, 8a, 9 and 11p in addition to the perigastric nodes) (11). The hepatic and pyloric branches of the vagus nerve were routinely preserved, but preservation of the celiac branch was not considered. Clinicopathological findings of the gastric resections were recorded according to the Japanese classification of gastric carcinoma 2nd English edition (12).

### Surgical procedures

For 2/3-gastrectomy, the resection line was, in principle, 5cm of the lesser curvature and 10cm of the greater curvature measured from the pyloric ring. For 1/2-gastrectomy, the resection line was, in principle, 10cm of the lesser curvature and 15cm of the greater curvature measured from the pyloric ring. The tumor was confirmed to be located in the upper third of the stomach preoperatively and intraoperatively. This was often ascertained through preoperative upper gastrointestinal series or endoscopic submucosal tattooing with 0.1mL India ink. Resection and reconstruction were performed by one of the following 6 methods, depending on the depth of cancer invasion and the date of the procedure relative to introduction of laparoscopic proximal gastrectomy: open proximal 2/3-gastrectomy with jejunal interposition (2/3PG-int), open proximal 1/2-gastrectomy with jejunal interposition (1/2PG-int), laparoscopic proximal 1/2-gastrectomy followed by double tract reconstruction with small (3cm) jejunogastrostomy (L1/2 PG-DT(S)), and laparoscopic proximal 1/2-gastrectomy followed by double tract reconstruction with large (6 cm) jejunogastrostomy (L1/2PG-DT(L)). Open total gastrectomy with jejunal interposition (TG) and laparoscopic total gastrectomy with Roux-en-Y reconstruction (LTG) for cancer which was located in the upper third or middle third of the stomach represented control procedures.

In open proximal and total gastrectomy, following resection, simple jejunal interposition in the PG-int and TG groups was performed by interposing either a 20-30cm segment of jejunum between the esophagus and residual stomach or 30-40cm of jejunum between the esophagus and duodenum, respectively. Pyloroplasty was omitted. After 2001, to comply with the Japanese guidelines for the treatment of gastric cancer (6), only patients with a preoperative diagnosis of up to T1 stage with no markedly enlarged regional lymph nodes, as detected by computerized tomography (CT), were considered to be eligible for proximal gastrectomy. For advanced gastric cancer with a depth of invasion confined to the muscularis propria, we performed laparoscopic total gastrectomy.

After 2006, a laparoscopic approach was adopted for proximal gastrectomy. One-half of the proximal stomach was resected and double tract reconstruction in the LPG-DT groups was performed by interposing a 15cm segment of jejunum between the esophagus and residual stomach.

In brief, the jejunum is divided 20cm distal to the ligament of Treitz. The anvil head of the circular stapler (PCEEA™ (Covidien)) is inserted into the esophageal stump. A side-to-side jejunojejunostomy is created by anastomosis between the divided oral jejunum and 30cm of anal jejunum. An entry hole for the circular stapler is made halfway (15cm) along the anal jejunal stump and the circular stapler is used to achieve esophagojejunostomy intracorporeally. After connecting the anvil head of the stapler and the circular stapler, we fashion an end-to-side esophagojejunostomy. After removing the circular stapler, the anastomosis between the entry hole and the oral edge of the remnant stomach is made by hand sewing through an umbilical wound. Patients were divided into two groups based on the length of jejunogastrostomy, either 3cm or 6cm. These procedures are illustrated in **Figure 1**.

Statistical analysis was performed using Students *t*-test and the $c^2$ test. A *p*-value of less than 0.05 was considered to be significant.

## RESULTS

Of the 67 patients who underwent proximal gastrectomies, 24 patients underwent an open procedure and 43 patients underwent a laparoscopic procedure. All patients completed the questionnaires on digestive functions. Patient demographics, stratified according to the surgical procedure, are presented in **Table 2**. No significant differences among the four experimental groups undergoing different procedures were observed in gender, age, or clinical stage. Patients in the TG group were significantly younger than those in the LTG or L1/2PG-DT(S) groups. Follow-up revealed that there was no evidence of recurrence at 1 year after surgery in any of the patients.

### Functional outcomes at 6-12 months

Comparison of postoperative/preoperative body weight ratios (**Figure 2**) revealed better preservation of postoperative body weight among those with a larger remnant stomach and with easy flow of food into the remnant stomach (1/2PG-int and L1/2PG-DT(L) groups). The postoperative/preoperative food intake ratio was also higher in the 1/2PG-int and L1/2PG-DT(L) groups than in the other groups (**Figure 3**). Complaints of postprandial symptoms were more common after the TG, LTG and L1/2PG-DT(S) procedures than after the other procedures (**Figure 4**). Borborygmus (41.6%, 5/12) was frequent in the TG group, nausea (42.9%, 3/7) was frequent in the 2/3PG-int group, abdominal heavy feeling (35.7%, 5/14) was frequent in the LTG group, and heartburn (21.1%, 4/19) was frequent in the L1/2PG-DT(S) group, while these symptoms were rarely observed in 1/2PG-int and L1/2PG-DT(L) groups. However, there were no significant differences among the six groups. In summary, 1/2PG-int was significantly superior to the 2/3PG-int and TG procedures in terms of postoperative body weight ($p$=0.0094 and $p$=0.0319, respectively). L1/2PG-DT(L) was significantly superior to the LTG procedure with respect to postoperative body weight ($p$=0.0029) and was significantly superior to the LTG and TG procedures in terms of preservation of meal intake ($p$=0.0059 and $p$=0.0024, respectively). Thus, better functional outcomes were observed in patients with large gastric remnants and with easy flow of food into the remnant stomach, while no major differences were observed among TG, 1/3PG-int and LTG when the remnant stomach was small, and with small quantity of inflow to the remnant stomach.

The incidence of reflux esophagitis on endoscopic examination in the TG, 2/3PG-int, 1/2PG-int and L1/2PG-DT(L) groups was 0%, that in the LTG group was 7.1% (1/14), and that in the L1/2PG-DT(S) group was 10.5% (2/19). Reflux esophagitis in the L1/2PG-DT(L) group was not observed based on endoscopy. The endoscope could reach the remnant distal stomach in only two of seven patients in the 2/3PG-int group and four of five patients in the 1/2PG-int group, while the remnant stomach could be observed in all patients in the L1/2PG-DT group. Namely, a 15cm interposed jejunal segment in L1/2PG-DT(L) group prevented the occurrence of reflux esophagitis and helped the observation of the remnant distal stomach by endoscopy.

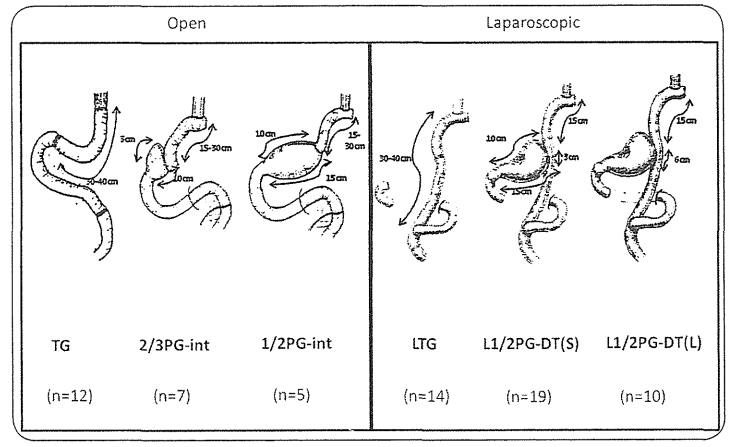


**FIGURE 1.** Schematic illustrations of surgical procedures. TG: open total gastrectomy with jejunal interposition. 2/3PG-int: open proximal 2/3-gastrectomy with jejunal interposition. 1/2PG-int: open proximal 1/2-gastrectomy with jejunal interposition. LTG: laparoscopic total gastrectomy with Roux-en-Y reconstruction. L1/2 PG-DT(S): laparoscopic proximal 1/2-gastrectomy followed by double tract reconstruction with small (3cm) jejunogastrostomy. L1/2PG-DT(L): laparoscopic proximal 1/2-gastrectomy followed by double tract reconstruction with large (6cm) jejunogastrostomy.

**TABLE 2.** Preoperative and postoperative characteristics of patients according to type of reconstruction.

| | TG | 2/3PG-int | 1/2PG-int | LTG | L1/2PG-DT(S) | L1/2PG-DT(L) |
|---|---|---|---|---|---|---|
| **Gender (M:F)** | 5:7 | 6:1 | 5:0 | 8:6 | 15:4 | 9:1 |
| **Age (years)** | 54.3 ±12.7* | 65.3 ±11.1 | 59.8 ±10.4 | 66.1 ±8.9* | 65.1 ±9.4* | 69.2 ±11.2** |
| **Stage** | | | | | | |
| 1A | 11 | 4 | 5 | 6 | 15 | 8 |
| 1B | 0 | 3 | 0 | 4 | 3 | 1 |
| II | 1 | 0 | 0 | 4 | 1 | 1 |

*VS*: $p<0.05$; *VS**: $p<0.01$. *Ages in the TG group were significantly lower than those in the LTG or L1/2PG-DT(S) groups ($p<0.05$). **Ages in the TG group were significantly lower than those in the L1/2PG-DT(L) group ($p<0.01$).

## DISCUSSION

Most patients with advanced gastric cancer in the upper one-third of the stomach have poor prognoses and undergo total gastrectomies or combined resections with the spleen (13). Because the rate of lymph node metastasis for early gastric cancer in the upper third of the stomach is low, a more conservative surgical approach in accordance with the early stage of the cancer should be selected, similar to treatment for gastric cancer in the lower or middle third of the stomach (7). Proximal gastrectomy is one such approach. Gastric cancer treatment guidelines call for use of proximal gastrectomy only when more than one-half of the distal stomach can be preserved for T1, N0 gastric tumors in the upper one-third of the stomach (6). Some researchers reported that there were few significant differences between total and proximal gastrectomy in postoperative QOL (14). In addition, the preserved distal stomach may be a site for cancer as well.

In our opinion, the utility of proximal gastrectomy was unclear. A laparoscopic approach was recently reported as a feasible and potentially less invasive option, and application of this technique for total or proximal gastrectomy has been increasing (8,9,15). In our study, the functional outcomes of patients treated by open or laparoscopically assisted proximal gastrectomy were compared with respect to approach, size of the remnant stomach and type of reconstruction. As a result, comparison of the postoperative/preoperative meal intake ratios revealed better preservation of postoperative meal intake among those with a larger remnant stomach and higher capacity (the 1/2PG-int and 1/2PG-DT(L) groups). The postoperative/preoperative body weight ratio was also higher in the 1/2PG-int and 1/2PG-DT(L) groups. There were no significant differences in postoperative QOL among the 2/3PG-int, 1/2PG-DT(S) and TG groups. These results suggest that preservation of the remnant stomach was necessary in proximal gastrectomy and that a larger remnant stomach was associated with better outcome. Postoperative body weight, an important index of QOL, was higher in 1/2PG groups, so reduction of the extent of gastrectomy is fundamental to this more conservative surgical approach. Regardless of preservation of the pyloric ring in the 2/3PG-int group, there were no significant differences between postoperative QOL in the 2/3PG-int group and that in the TG group. These results suggest that preservation of the pyloric ring is not effective in patients with a small remnant stomach.

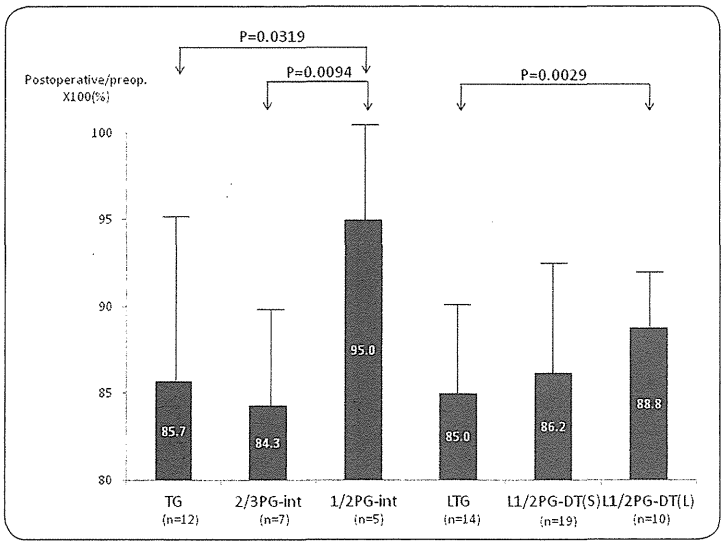


**FIGURE 2.** Postoperative/preoperative body weight ratios (%).

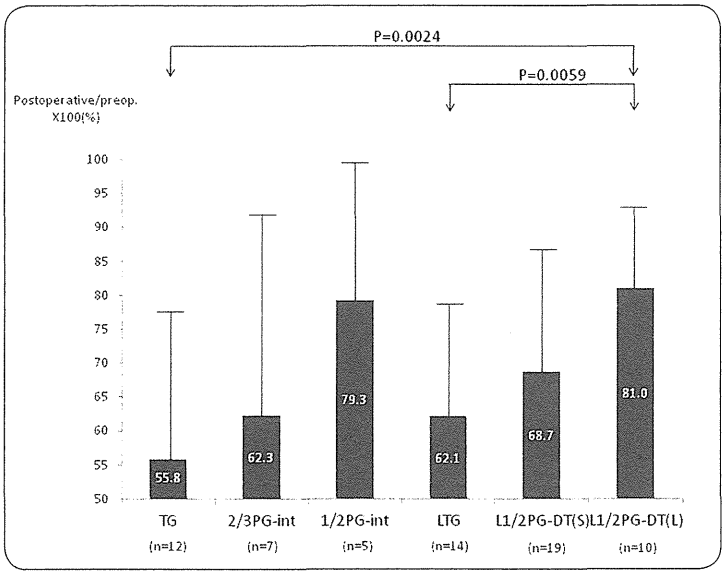


**FIGURE 3.** Postoperative/preoperative meal intake ratios (%).

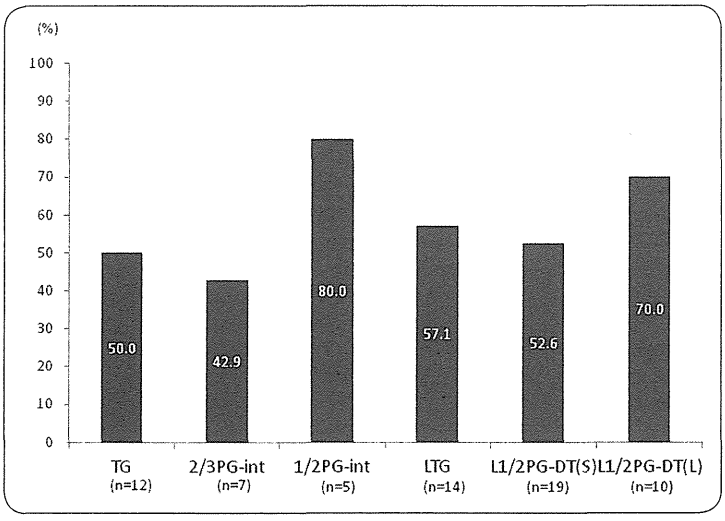


**FIGURE 4.** Percentages of patients who had none of the abdominal symptoms listed in the questionnaire.

It has been postulated that the pacemaker of gastric contraction exists in the large segment of the corpus of the stomach. Resection of the pacemaker along with a lower potential of a new pacemaker occurring in the remnant stomach leads to a decrease in movement of the remnant stomach with a delay in emptying after a solid meal (16). However, in our previous study using a liquid meal and acetaminophen, the pattern of emptying of acetaminophen in the 2/3PG-int group was similar to that in the TG group, suggesting that in subtotal proximal gastrectomy, the small remnant stomach may function only as a pipe (17). Hada *et al.* recommended a possible reduction in the extent of gastrectomy, because the postoperative movement of the remnant stomach was favorable in patients undergoing resection of two-thirds or less of the stomach (18).

In addition, following proximal gastrectomy, it is important to consider the occurrence of reflux esophagitis and ease of endoscopic examination of the remnant stomach. Shorter length of interposed jejunum between the esophagus and remnant stomach increases the chance of reflux esophagitis. Longer length of interposed jejunum makes endoscopic examination of the remnant stomach more difficult. From the viewpoint of endoscopic examination, shorter jejunal segment length is superior. It is difficult to state that shorter jejunal length is better for reconstruction if the problem of reflux cannot be solved. The larger the remnant stomach, the greater the chance of reflux. If the preservation of hepatic and pyloric branches of the vagus nerve restore the motion of pyloric ring faster, a short interposed jejunal segment may be used for reconstruction. Previous reports have addressed the ideal length of interposed jejunum between the esophagus and remnant stomach (5). Based on analysis of reported data, Okajima described the appropriate length of interposed jejunum to be between 10 and 15cm when the remnant stomach was more than one-half of the whole stomach (19). Our 15cm interposed jejunal segment was appropriate for prevention of reflux esophagitis and observation of the remnant stomach through endoscopy.

In our previous analysis of open surgery for early gastric cancer, reduction of the extent of gastrectomy and preservation of the vagal branches and of the pyloric ring were associated with better QOL (7). The data from this study showed that patients treated by the laparoscopic approach also benefited from a smaller resection. We hypothesized that the reservoir function of the remnant stomach was preserved in the one-half resection groups, leading to improved nutritional status and body composition. Proximal gastrectomy with double tract reconstruction is appropriate for patients with a large gastric remnant, and laparoscopically assisted gastrectomy and reconstruction is associated with no apparent disadvantages, while offering favorable cosmetic results.

Our study had limitations. Internationally validated questionnaires were not used to evaluate the patient-reported outcomes. We evaluated patients with the questionnaire shown in **Table 1** because established instruments are not focused on specific postgastrectomy symptoms such as dumping syndromes that we often encountered. These instruments may not be sufficiently sensitive to detect subtle differences caused by differences in the mode of reconstruction. Inconsistency in the intervals between surgery and the acquisition of functional data, ranging from 6 to 12 months, could affect patient outcomes. It has been reported, however, that functional scores, symptom scales, and body composition tend to

recover by 6 months after gastrectomy, with little difference thereafter, whereas these outcomes clearly revealed worse values when evaluated at 1 month postoperatively (20,21).

In conclusion, better functional outcomes were observed in patients with a large remnant stomach and with easy flow of food into the remnant stomach regardless of whether partial gastrectomy was performed as an open procedure or by laparoscopy. A 15cm interposed jejunal segment was appropriate for prevention of reflux esophagitis and for endoscopic observation of the remnant stomach.

## REFERENCES


1. **Maehara Y, Kakeji Y, Oda S, et al.:** Time trends of surgical treatment and the prognosis for Japanese patients with gastric cancer. Br J Cancer 2000; 83:986-991.
2. **Kitano S, Shiraishi N, Fujii K, et al.:** Y. A randomized controlled trial comparing open vs. laparoscopy-assisted distal gastrectomy for the treatment of early gastric cancer: an interim report. Surgery 2002; 131:306-311.
3. **Maki T, Shiratori T, Sugawa K:** Pylorus-preserving gastrectomy as an improved operation for gastric ulcer. Surgery 1967; 370(61):838-845.
4. **Kameyama J, Ishida H, Yasaku Y, et al.:** Proximal gastrectomy reconstructed by interposition of a jejunal pouch. Eur J Surg 1993; 159:491-493.
5. **Nomura E, Shinohara H, Mabuchi H, et al.:** Postoperative evaluation of the jejunal pouch reconstruction following proximal and distal gastrectomy for cancer. Hepato-gastroenterol 2004; 51:1561-1566.
6. **Japanese gastric cancer association:** Guidelines for the treatment of gastric cancer. Tokyo: Kanehara-Shuppan; 2001.
7. **Isozaki H, Okajima K, Yamada S, et al.:** Proximal subtotal gastrectomy for the treatment of carcinoma of the upper third of the stomach: its indications based on lymph node metastasis and paragastric lymphatic flow. Surg Today Jpn J Surg 1995; 25:21-26.
8. **Tanimura S, Higashino M, Fukunaga Y, et al.:** Laparoscopic gastrectomy with regional lymph node dissection for upper gastric cancer. Br J Surg 2007; 94:204-207.
9. **Uyama I, Sugioka A, Fujita J, et al.:** Completely laparoscopic proximal gastrectomy with jejunal interposition and lymphadenectomy. J Am Coll Surg 2000; 191:114-119.
10. **Dent J, Brun J, Fendrick AM, et al.:** An evidence-based appraisal of reflux disease management-the Genval Workshop Report. Gut 1999; 44:1-16.
11. **Takaori K, Nomura E, Mabuchi H, et al.:** A secure technique of intracorporeal Roux-Y reconstruction after laparoscopic distal gastrectomy. Am J Surg 2005; 189:178-183.
12. **Japanese gastric cancer association:** Japanese classification of gastric carcinoma. 2nd English ed. Gastric Cancer 1998; 1:10-24.
13. **Maruyama K, Kaminishi M, Hayashi K, et al.:** Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. Gastric Cancer 2006; 9:51-66.
14. **Moreaux J, Misika S:** Carcinoma of the gastric cardia: Surgical management and long-term survival. World J Surg 1988; 12:229-235.
15. **Hirahara N, Monnma H, Shimojyo Y, et al.:** Reconstruction of the esophagojejunostomy by double stapling method using EEA™ OrVil™ in laparoscopic total gastrectomy and proximal gastrectomy. World J Surg Oncol 2011; 9:55-59.
16. **Bruce GK, Keith AK, Charles FC:** Effect of gastric fundectomy on canine gastric electrical and motor activity. Am J Physiol 1974; 226:1445-1449.
17. **Nomura E, Isozaki H, Fujii K, et al.:** Postoperative evaluation of function-preserving gastrectomy for early gastric cancer. Hepato-gastroenterol 2003; 50:2246-2250.
18. **Hada R, Ono K:** Effect of gastric resection on gastrointestinal motility. Surgical Therapy 1986; 55:265-270.
19. **Okajima K:** Recent advances in surgical procedure for proximal gastrectomy. Surg Therapy 2007; 97:209-220.
20. **Kobayashi D, Kodera Y, Fujiwara M, et al.:** Assessment of quality of life after gastrectomy using EORTC QLQ-C30 and STO22. World J Surg 2011; 35:257-262.
21. **Abdiev S, Kodera Y, Fujiwara M, et al.:** Nutritional recovery after open and laparoscopic gastrectomies. Gastric Cancer 2011; 14:144-149.

Original Paper

# Prognoses of GEP-Nets with Undetermined Malignant Potentials of their Primary Sites

*Atsushi Kudo[1], Daisuke Ban[1], Takumi Akashi[2], Jiro Kumagai[2], Arihiro Aihara[1], Mikito Inokuchi[3], Kazuyuki Kojima[3], Tatsuyuki Kawano[3], Shinji Tanaka[1] and Shigeki Arii[1]*

[1]Department of Hepatobiliary Pancreatic Surgery, [2]Department of Pathology and [3]Department of Esophagogastric Surgery, Tokyo Medical and Dental University, Tokyo, Japan

Corresponding author: Atsushi Kudo, MD, PhD, Department of Hepatobiliary-Pancreatic Surgery, Graduate School of Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113-8519, Japan; Tel.: +81-3-5803-5928, Fax: +81-3-5803-2564; E-mail: kudomsrg@tmd.ac.jp

**Key Words:** Neuroendocrine tumor; Ki-67 index of primary tumors; Unknown primary tumors; Unresectable liver metastatic tumors; WHO 2010 grading; NET-G1; NET-G2; NEC.

## ABSTRACT

**Background/Aims:** In gastroenteropancreatic neuroendocrine tumors (GEP-NETs), primary lesions cannot be resected when the patients have highly advanced disease or when the primary sites are undefined. Such GEP-NETs cannot be evaluated with Ki-67 or the mitotic index. The aim of this study was to examine the prognosis of GEP-NETs that were ungraded by WHO G1-3 grading (U-NET group). **Methodology:** Between 2000 and 2011, 75 patients with sporadic GEP-NETs were treated at our institution. The prognosis of patients graded as new WHO grading (G-NET group) was compared with that of the U-NET group. Cox proportional hazard regression analyses were performed to estimate the risk factors for overall survival (OS). **Results:** Overall 1-, 3- and 5-year survival rates were 90.7%, 79.9% and 74.9%, respectively. The odds ratio (OR) of patients with synchronous liver metastasis and U-NET was 1.73 ($p$=0.01) and 5.84 ($p$=0.002), respectively. Multivariate analyses of OS according to baseline characteristics revealed the only independent risk factor to be U-NET (OR, 3.95; $p$=0.02). **Conclusions:** The malignant potential of U-NET may be no less than that of G-NET, while WHO-G3 patients have the worst prognoses in the G-NET group.

## INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rare tumors that arise from endocrine cells (1-3). The tumors have various biological behaviors because of their heterogeneous features (4). The World Health Organization (WHO) classification has been established in order to evaluate the malignant potential of GEP-NETs. In the WHO 2000 and 2004 classifications, clinicopathological factors such as metastasis and local invasion determined the diagnosis of well-differentiated neuroendocrine carcinoma (WEC) (5). Pancreatic NETs and gastrointestinal NETs were distinguished in the criteria, which emphasized the distinction of malignant potential by the localization of the primary tumors (6). The Ki-67 index and mitosis were not considered important for the diagnosis of WEC. However, the WHO 2010 classification implemented the determination of the Ki-67 grading of tumors without regard to any clinical information (2). The criteria do not require information on the localization or the resection of the primary tumor.

Removing primary and metastatic tumors improves patient prognosis remarkably (1,7). Histology of the resected specimens enables grading with the WHO 2010 classification, which may serve as a predictor of prognosis (2). Without primary tumor resection, it is difficult to estimate the whole-slide grade of malignancy. Biopsy specimens from metastatic foci may estimate some of the primary tumor, and its reliability in selecting the appropriate treatment has been discussed (4,8). There may not be enough small material in the metastatic focus in 40× high-power fields to allow an evaluation of mitotic counts, and intratumoral Ki-67 heterogeneity prevents predictions of primary tumor features (4). Almost all previous studies have failed to demonstrate whether biopsy specimens with heterogeneity from metastatic foci reflect the malignant potential of primary tumors. It has been recognized that the distribution of Ki-67 is not always uniform throughout a given NET. Thus, the Ki-67 labeling index of the metastasis may not always reflect the primary malignant potential.

Based on these findings, the present study aimed to clarify whether the 2010 WHO classification can determine the prognosis of patients and to analyze the prognosis of patients who are unclassified by the new classification (U-NET group). The patients with radically resected primary tumors with or without resecting of the metastasis could be classified with the 2010 WHO grading (G-NET group). The other patients were classified into the U-NET group, which included the patients with unknown primary tumors or unresectable metastases. The overall survival of the U-NET patients turned out to be significantly worse than that of the G-NET patients ($p$<0.001), while there was no difference between the Ki-67 values of the primary tumors of the G-NET group and the value from the metastatic tumor biopsy of the U-NET group ($p$=0.5). Our results suggest that virtual Ki-67 scores of heterogeneous metastases have little utility for the prediction of prognosis. Furthermore, U-NET predicts overall survival independently without the new WHO grading system.

Hepato-Gastroenterology 2012; 59:1682-1686 doi 10.5754/hge12275
© H.G.E. Update Medical Publishing S.A., Athens

WORLD JOURNAL OF SURGICAL ONCOLOGY

RESEARCH Open Access

# Benefits of intracorporeal gastrointestinal anastomosis following laparoscopic distal gastrectomy

Sang-Woong Lee[1*], Nobuhiko Tanigawa[1,2], Eiji Nomura[1], Takaya Tokuhara[1], Masaru Kawai[1], Kazutake Yokoyama[1], Masako Hiramatsu[1], Junji Okuda[1] and Kazuhisa Uchiyama[1]

## Abstract

**Background:** Laparoscopic gastrectomy has recently been gaining popularity as a treatment for cancer; however, little is known about the benefits of intracorporeal (IC) gastrointestinal anastomosis with pure laparoscopic distal gastrectomy (LDG) compared with extracorporeal (EC) anastomosis with laparoscopy-assisted distal gastrectomy (LADG).

**Methods:** Between June 2000 and December 2011, we assessed 449 consecutive patients with early-stage gastric cancer who underwent LDG. The patients were classified into three groups according to the method of reconstruction LADG followed by EC hand-sewn anastomosis (LADG + EC) (n = 73), using any of three anastomosis methods (Billroth-I (B-I), Billroth-II (B-II) or Roux-en-Y (R-Y); LDG followed by IC B-I anastomosis (LDG + B-I) (n = 248); or LDG followed by IC R-Y anastomosis (LDG + R-Y) (n = 128)). The analyzed parameters included patient and tumor characteristics, operation details, and post-operative outcomes.

**Results:** The tumor location was significantly more proximal in the LDG + R-Y group than in the LDG + B-I group ($P < 0.01$). Mean operation time, intra-operative blood loss, and the length of post-operative hospital stay were all shortest in the LDG + B-I group ($P < 0.05$). Regarding post-operative morbidities, anastomosis-related complications occurred significantly less frequently in with the LDG + B-I group than in the LADG + EC group ($P < 0.01$), whereas there were no differences in the other parameters of patients' characteristics.

**Conclusions:** Intracorporeal mechanical anastomosis by either the B-I or R-Y method following LDG has several advantages over at the LADG + EC, including small wound size, reduced invasiveness, and safe anastomosis. Although additional randomized control studies are warranted to confirm these findings, we consider that pure LDG is a useful technique for patients with early gastric cancer.

**Keywords:** Laparoscopic distal gastrectomy, Intracorporeal anastomosis, Extracorporeal anastomosis, Billroth I, Roux-en-Y

## Background

Since the technique of laparoscopy-assisted Billroth-I gastrectomy was first reported by Kitano and colleagues in 1994 [1], laparoscopic gastrectomy for cancer (LGC) has been gaining increasing popularity worldwide because it is associated with earlier patient recovery compared with open surgery [2-4]. A national survey conducted by the Japan Society of Endoscopic Surgery (JSES) every 2 years has shown increasing use of laparoscopic procedures for gastric cancer in Japan [5]. According to the 10th JSES survey, more than 7,300 patients underwent LGC in 2009, which equated to 25.9% of 28,600 patients with gastric cancer who underwent open gastrectomy, LGC or endoscopic treatment such as endoscopic mucosal resection or and endoscopic sub-mucosal resection in the same institutions. Laparoscopic distal gastrectomy (LDG) was the most commonly performed type of LGC (75.7% of operation). The survey also reported the

* Correspondence: sur079@poh.osaka-med.ac.jp
[1]Department of General and Gastroenterological Surgery, Osaka Medical College, 2-7, Daigaku-Machi, Takatsuki City Osaka 569-8686, Japan
Full list of author information is available at the end of the article

BioMed Central

© 2012 Lee et al.; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

incidence of post-operative complications in a total of 10,355 LDGs performed in 2008 and 2009 [6], with the most frequent being stomal stenosis (2.0%), followed by pancreatitis or pancreatic fistula formation (1.3%), anastomotic leakage (1.1%), wound infection, peritoneal abscess, bleeding, pneumonia, and ileus. This suggests that anastomosis-related complications are the most common complication subsequent to LDG. In the context of gastrointestinal reconstruction, the majority of anastomoses following LDG were performed by laparoscopy-assisted procedures through a mini-laparotomy incision of 60 to 70 mm in length made on the epigastrium. In such a laparoscopy-assisted distal gastrectomy (LADG) [1] procedure, gastrointestinal reconstructive anastomosis is extracorporeally conducted in a limited working space with restricted vision, and it is possible that this may lead to increased risk of anastomotic leakage.

Although we originally began performing LADG, in the hope of overcoming the drawbacks of cumbersome reconstruction, we introduced intracorporeal (IC) stapled gastroduodenostomy and gastrojejunostomy in association with LDG in 2004 [7,8]. We then developed two methods for IC reconstructive anastomosis following LDG: 1) IC Billroth I anastomosis (B-I) was used when there was no tension expected at the gastroduodenal anastomosis, and 2) IC Roux-en-Y anastomosis (R-Y) was used when there were some concerns about strain.

We report our experience and results of three kinds of gastrointestinal reconstructive anastomosis: LADG followed by extracorporeal hand-sewn anastomosis (LADG + EC), LDG + B-I , and LDG + R-Y.

## Methods

Patients who had undergone LDG for gastric cancer during the period June 2000 to December 2011 in the Department of General and Gastroenterological Surgery, Osaka Medical College, Japan, were assessed in terms of their clinical outcomes subsequent to gastrointestinal reconstructive anastomosis following surgery.

### Indications for laparoscopic gastrectomy in cancer

Indications for LGC at our institute include all tumors confined to the muscularis propria that are not amenable to endoscopic mucosal resection, with lymph-node involvement limited to N1. Patients requiring salvage surgery after incomplete endoscopic resection are also included. Operations were converted to open surgeries when serosal invasion or extensive lymphadenopathy was detected during laparoscopy. LDG is indicated for distal and middle third gastric cancers in which tumor margins of at least 20 mm for early and 30 to 50 mm for advanced lesions are possible. Some patients with very early disease may have a more limited resection such as pylorus-preserving or segmental gastrectomy [9,10].

### Surgical techniques

The LDG procedure was carried out in all cases as follows. A 12-mm trocar was inserted through an umbilical wound, and pneumoperitoneum was established. Another 12-mm trocar was inserted 10 mm above and to the left of the umbilicus, and a 5-mm trocar was inserted 20 to 30 mm above and to the right of the umbilicus under laparoscopic guidance. A 5-mm trocar was inserted into each of the right and left costal margins, respectively. The intra-abdominal pressure was maintained at a constant 8 to 12 mmHg. After inspection of the peritoneal cavity, mobilization of the stomach and dissection of the lymph nodes were carried out as described previously [8,11,12].

Surgical procedures for gastrointestinal reconstructive anastomosis after LDG were as follows. For patients operated on before May 2004, LDG + EC was generally used, and for subsequent operations, one of the two IC mechanical anastomosis techniques were performed after LDG. Of the two IC methods, B-I reconstruction was the choice of reconstruction for LDG where possible, however, R-Y reconstruction was used when tension was expected on the anastomosis, when the patient had reflux esophagitis or a hiatus hernia, or when the patient was elderly and/or high risk [11].

#### *Extracorporeal anastomosis in laparoscopy-assisted distal gastrectomy*

The mini-laparotomy wound 60 to 70 mm long was made in the upper midline and opened to allow insertion of a wound protector. An end-to-end gastroduodenostomy (B-I) or end-to-side gastrojejunostomy (Billroth II (B-II) or R-Y) was created to allow open surgery between the gastric stump and duodenal stump or the biliopancreatic jejunum, using a two-layer hand-sewn anastomosis technique.

#### *Intracorporeal anastomosis in pure laparoscopic distal gastrectomy*

**Billroth I gastroduodenostomy** The original method for this procedure was first described by Kanaya *et al.* [7]. We partly modified the technique for ease of use, as follows. A gastrotomy was performed on the greater curve corner of the staple line on the remnant stomach, then a small hole was made on the posterior tip of the duodenal stump. The cartridge fork of the 45-mm linear stapler was inserted into the gastric remnant, and another fork was inserted into the duodenal stump. This was followed by firing of the stapler to form the functional end-to-end gastroduodenal anastomosis. After the anastomosis was inspected from the lumen to check for bleeding, the common enterotomy was apposed vertically with three intracorporeally placed stay sutures, and

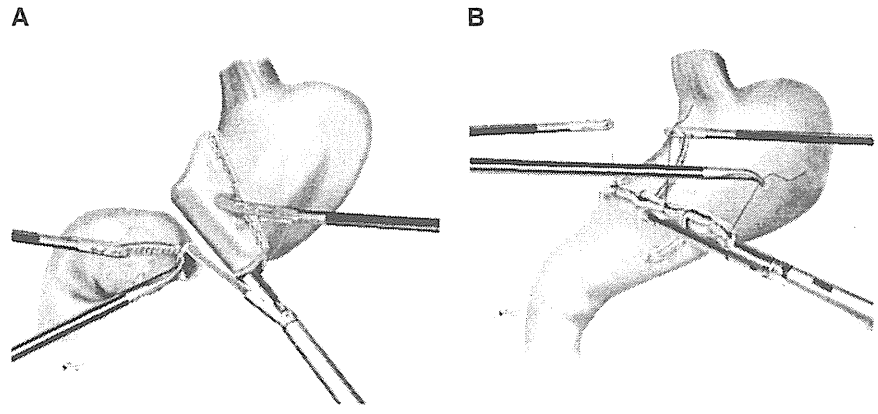


**Figure 1 Intracorporeal Billroth I anastomosis.** (**A**) A side-to-side gastroduodenostomy was formed by firing the 45-mm linear stapler; and (**B**) the common enterotomy was closed with two further firings of the stapler.

closed with two further firings of the stapler. This strategy resulted in a satisfactory V-shaped anastomosis, and security was confirmed with an air-leak test at the end of the anastomosis (Figure 1A, B).

**Roux-en-Y reconstruction** We have previously published descriptions of this method [8,12]. In brief, a distance of 200 mm was measured on the jejunum from the ligament of Treitz, and a sacrifice jejunum was created 70 mm distally by division of the corresponding jejunal mesentery. Following this maneuver, the sacrifice jejunum became discolored as a result of ischemia. A small enterotomy was made on the healthy part of the bowel just distal to the sacrifice jejunum. The cartridge fork of the 60-mm linear stapler was inserted into the enterotomy on the jejunum, and the other fork of the linear stapler was then inserted into the stomach through a gastrostomy made on the greater curve corner of the gastric stump. A side-to-side gastrojejunostomy was formed by firing the stapler. The anastomosis was checked from the lumen for any bleeding, which was controlled by bipolar coagulation. The remaining enterotomy was closed with a further firing of the linear stapler. The jejunum was divided simultaneously to complete the anti-peristaltic side-to-side gastrojejunostomy (Figure 2A). Finally, using a linear stapler and laparoscopic sutures, a side-to-side jejunojejunostomy was fashioned between the descending alimentary jejunum and the biliopancreatic jejunum (Figure 2B).

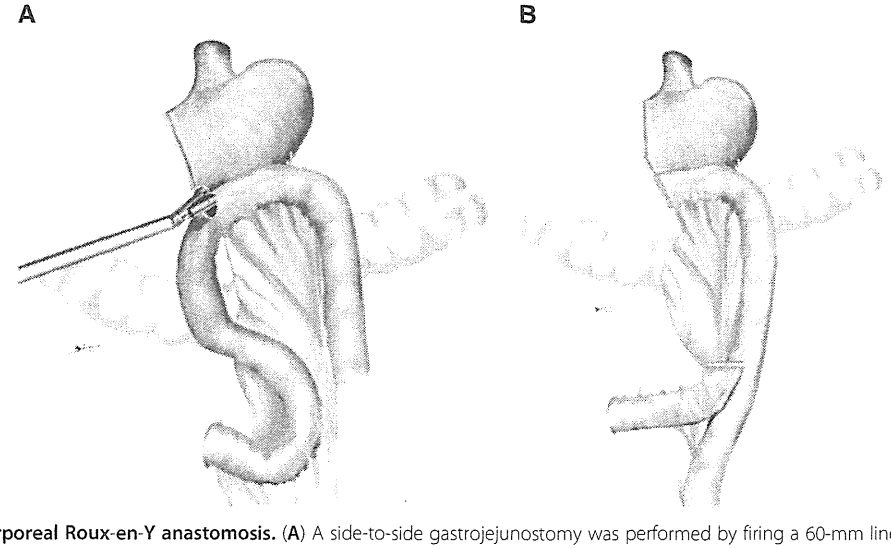


**Figure 2 Intracorporeal Roux-en-Y anastomosis.** (**A**) A side-to-side gastrojejunostomy was performed by firing a 60-mm linear stapler, then the remaining enterotomy was closed with a further firing of the linear stapler. (**B**) An end-to-side jejunojejunostomy was created between the descending alimentary jejunum and the biliopancreatic jejunum, using a linear stapler and sutures.

### *Definition of post-operative complications*

The diagnosis of a clinically relevant anastomotic leak was based on clinical signs, including an inflammatory reaction requiring treatment and confirmation of the insufficiency, either endoscopically or radiologically by computed tomography or using a contrast medium (diatrizoate meglumine and diatrizoate sodium; Gastrografin; Bracco Diagnostics Inc., Princeton, NJ, USA). Anastomotic stenosis was defined as any form of narrowing in the anastomosis region by contrast swallow studies or gastroscopy (≤10 mm in diameter) and any symptom of dysphagia when swallowing solid, semi-solid or liquid nourishment, which then required, endoscopic dilation. Gastric stasis was defined if the patients exhibited symptoms such as upper abdominal distension and remnant stomach fullness on X-ray, or if the patient required starvation for longer than 24 hours.

Pancreatic fistula (PF) was defined by the International Study Group Pancreatic Fistula (ISGPF) criteria [13], and divided into four categories: no PF, biochemical PF without clinical sequelae (grade A), PF requiring any therapeutic intervention (grade B), and PF with severe clinical sequelae (grade C). Clinically relevant PF was defined as grades B and C, in accordance with the ISGPF grading system.

### *Statistical analysis*

Statistical analysis of the data was performed using SSPS (12.0; SPSS, Chicago, IL, USA). All data are presented as the mean ± standard deviation (SD) or as the number and percentage of patients. Continual variables are expressed as mean ± SD, and comparisons between groups were performed using the *t*-test and the Mann–Whitney *U*-test. Comparisons of categorical variables were performed by means of the Fisher exact test. $P < 0.05$ was considered significant.

## Results

LGC was performed on 769 patients: 449 (58.4%) underwent LADG or pure LDG, while the remainder consisted of 160 (20.8%) laparoscopic pylorus-preserving gastrectomies, 48 (6.2%) laparoscopic proximal gastrectomies, 47 (6.1%) laparoscopic segmental gastrectomies, 39 (5.1%) laparoscopic total gastrectomies, and 26 (3.4%) laparoscopic wedge resections. In the group of 449 patients with LADG or pure LDG, 73 had LADG with EC anastomosis, and 376 had pure LDG with IC anastomosis (248 B-I and 128 R-Y). The methods of EC anastomosis for the 73 LADG operations were 56 B-I, 9 R-Y, and 8 B-II.

### Patients' characteristics of each reconstruction group

There were no significant differences in age, gender distribution, or body mass index (BMI) between the three reconstruction-method groups (Table 1). The mean age (mid-sixties), male:female ratio (around 15) and BMI (22 ± 3.1) were almost comparable for the three groups. The tumor locations were defined using the Japanese Classification of Gastric Carcinoma [14] as being in the upper (U), middle (M) or lower (L) third of the stomach. Regarding both IC techniques, there were 0 U, 121 M and 127 L in the LDG + B-I group, and 20 U, 89 M and 19 L in the LDG + R-Y group; that is, there were significantly more tumors located distally in the LDG + B-I than in the LDG + R-Y group ($P < 0.01$). However, for LADG, there was no significant difference in tumor location between the B-I (n = 56) and R-Y (n = 9) subgroups, probably because the number of operative cases of R-Y reconstruction in the LADG group was too small.

### Intraoperative variables

The mean operating time was 261 ± 63 minutes for the LDG + B-I group, 333 ± 79 minutes for the LDG + R-Y

**Table 1 Patient's characteristics for three kinds of reconstruction**

| | LADG + EC (n = 73)[a] | | | LDG + B-I (n = 248)[b] | LDG + R-Y (n = 128)[c] |
|---|---|---|---|---|---|
| Age, years | 64 ± 11 | | | 65 ± 11 | 66 ± 10 |
| Male : female | 48 : 25 | | | 147 : 101 | 90 : 38 |
| BMI, kg/m$^2$ | 22.3 ± 3.2 | | | 22.0 ± 3.1 | 22.6 ± 3.0 |
| | Type of anastomosis | | | | |
| | B-I | R-Y | B-II | | |
| Tumor location | | | | | |
| Upper | 0 | 1 | 2 | 0 | 20 |
| Middle | 24 | 4 | 6 | 121 | 89 |
| Lower | 32 | 4 | 0 | 127 | 19 |

Abbreviations: *BMI* body mass index; *B-I* Billroth I, *B-II* Billroth-II; *EC* extracorporeal, *IC* intracorporeal; *LADG* laparoscopy-assisted distal gastrectomy; *LDG* laparoscopic distal gastrectomy.
[a]LADG with any of the three types of EC anastomosis.
[b]Pure LDG with IC B-I.
[c]Pure LDG with IC R-Y.

group, and 339 ± 83 minutes for the LADG + EC group, respectively (Table 2). Operating time was significantly shorter for the LDG + B-I group than for the LDG + RY and LADG + EC groups ($P < 0.01$), whereas there was no significant difference in operating time between these latter two groups.

The intraoperative blood loss was 47 ± 48 ml for the LDG + B-I group, 76 ± 80 ml for the LDG + R-Y group, and 119 ± 108 ml for the LADG + EC group. Blood loss was significantly less for the LDG + B-I group than for the other two groups ($P < 0.01$), and it was also significantly less for the LDG + R-Y group than for the LADG + EC group ($P < 0.05$).

### Post-operative morbidity

Anastomotic leakage rates were 1.2% (3/248) for the LAD + B-I group, 1.6% (2/128) for the LAD + R-Y group, and 6.8% (5/73) for the LADG + EC group (7.1% (4/56) for B-I, 11.1% (1/9) for R-Y group with LADG and none (0/8) for B-II) (Table 3). Three of these patients required reoperation, and seven patients had collections that were treated by percutaneous drainage.

Anastomotic stenosis was encountered in 0.4% (1/248) of the LDG + B-I group, none (0/128) of the LDG + R-Y group and 2.7% (2/73) of the LADG group (3.6% (2/56) for B-I, and 0% (0/17) for the other reconstruction types). All of the anastomotic strictures were successfully treated by endoscopic balloon dilatation.

Gastric stasis occurred in 1.2% (3/248) of the LDG + B-I group and in 2.3% (3/128) of the LDG + R-Y group, but was much higher at 6.8% (5/73) in the LADG + EC group (7.1% (4/56) for the B-I subgroup, 11.1% (1/9) for the R-Y subgroup and none for the B-II subgroup). Each case with gastric stasis improved spontaneously in 1 to 2 weeks.

Formation of PF (grades B and C of the ISGPF grading system) was found in 4.8% (12/248) of the LDG + B-I group, 1.6% (2/128) of the LDG + R-Y group and 2.7% (2/73) of the LADG + EC group. Although two of these patients had post-operative hemorrhage associated with pancreatic inflammation and secondary pseudoaneurysm of the gastroduodenal artery, both cases were successfully treated by endovascular coiling.

**Table 2 Intraoperative variables for three groups**

| | LADG + EC (n = 73)[a] | LDG + B-I (n = 248)[b] | LDG + R-Y (n = 128)[c] |
|---|---|---|---|
| Operation time, min | 339 ± 83[d] | 261 ± 63[e] | 333 ± 79[d] |
| Blood loss, ml | 119 ± 108 | 47 ± 48[e] | 76 ± 80[f] |

Abbreviations: *B-I* Billroth I anastomosis; *B-II* Billroth II anastomosis; *EC* extracorporeal; *IC* intracorporeal; *LADG* laparoscopy-assisted distal gastrectomy; *LDG* laparoscopic distal gastrectomy; *R-Y* Roux-en Y anastomosis.
[a]LADG with any of the three types of anastomosis.
[b]Pure LDG with IC B-I.
[c]Pure LDG with IC R-Y.
[d]Groups were not significantly different from each other.
[e]$P < 0.01$ compared with the other two groups.
[f]$P < 0.05$ compared with the LADG group.

**Table 3 Post-operative complications for three groups**

| | LADG + EC (n = 73)[a] | LDG + B-I (n = 248)[b] | LDG + R-Y (n = 128)[c] | *p* Value |
|---|---|---|---|---|
| Anastomotic leakage,%[d] | 5 (6.8) | 3 (1.2) | 2 (1.6) | 0.04 |
| Anastomotic stenosis,% | 2 (2.7) | 1 (0.4) | 0 | 0.32 |
| Gastric stasis,% | 5(6.8) | 3 (1.2) | 3 (2.3) | 0.06 |
| Pancreatic fistula,% | 2 (2.7) | 12 (4.8) | 2 (1.6) | 0.40 |

Abbreviations: *B-I* Billroth I; *B-II* Billroth II; *LADG* laparoscopy-assisted distal gastrectomy; *LDG* laparoscopic distal gastrectomy; *R-Y* Roux-en Y anastomosis.
[a]LADG with any of the three types of anastomosis.
[b]Pure LDG with IC B-I.
[c]Pure LDG with IC R-Y.
[d]Bleeding from the anastomosis was not encountered in any of the patients.

The length of post-operative hospital stay was significantly shorter for the LDG + B-I group (11.2 ± 0.7 days) than for the LDG + R-Y (17 ± 1.3 days) or LADG + EC (21.6 ± 11.2 days) groups ($P < 0.05$), whereas there was no significant difference between the latter two groups. This trend was similar to those for the operating time and intra-operative blood loss, suggesting that the surgical stresses represented by those parameters may be closely associated with the length of post-operative hospital stay.

## Discussion

Laparoscopic surgery is being been increasingly used for the treatment of gastric cancer over the past two decades, especially in East Asian countries such as Japan, Korea, China ,and Taiwan. In general, LGC can be divided into laparoscopy-assisted and pure laparoscopic techniques. With laparoscopy-assisted gastrectomy, lymph-node dissection is performed laparoscopically, but the transection of the stomach and the anastomosis are performed thorough an epigastric mini-laparotomy. Performing the anastomosis in this narrow and restricted space is often difficult, especially on obese patients with thick abdominal walls or on patients with a small remnant stomach.

Although we initially began performing LADG in the hope of overcoming the drawbacks of cumbersome reconstruction, we introduced the use of LDG followed by IC stapled gastroduodenostomy and gastrojejunostomy in 2004 [11]. To investigate the feasibility and benefits of IC anastomosis, we compared our experience of using LADG and pure LDG in the current study, using a consecutive series of patients in our institution. We found that the rates for anastomotic complications, including leakage, stenosis, and gastric stasis, were significantly lower for either method of IC mechanical anastomosis (B-I or R-Y) after LDG than for LADG follwed by hand-sewn anastomosis (using any of the three methods). The rate of anastomotic leakage in the IC groups (1.3%)

seems to be within the permissible level compared with other accounts using these techniques [15,16]. Similarly, the rate of of 6.8% for anastomotic leakage after LADG (7.1% for B-I, 11.1% for R-Y and 0% for B-II ) in the current study was comparable with other reports using LADG, with a rate of 7.8% (8.1% (7/87) for B-I and 0% (0/3) for R-Y) reported by Fujiwara *et al.* [17] and 5.3% (4/76 for B-I with no case for R-Y reconstruction) by Shimizu *et al.* [18]. The relatively high incidences of anastomotic leakage were possibly associated with the results obtained from initial experience of LADG in each institution.

In the current study, the LADG + EC group had the largest blood loss and longest operating time of the three groups tested. Because patients underwent LADG until May 2004, when we changed our strategy to pure LDG plus IC anastomosis [8,11], our LADG results might have been subject to some degree of learning-curve effect while we gained experience of laparoscopy-assisted surgical techniques. However, although this dataset does therefore have the drawback of different time periods when each surgical procedure was performed, the reduced blood loss seen with pure LDG may be also reflective of the small wound length required and avoidance of cumbersome anastomosis through a minilaparotomy.

The current study also indicates that pure LDG + B-I resulted in a significantly smaller volume of blood loss and shorter operating time than did pure LDG + R-Y. The consequent reduction in surgical stresses, including operating time and blood loss, and the lower incidence of post-operative complications seemed to be associated with the fact that the LDG + B-I group also had the shortest length of post-operative hospital stay. It should be noted that the mean length of hospital stay in the current study was rather longer than reported elsewhere [19]; however, because the Japanese medical insurance system is structured differently from those in other countries, it is difficult to estimate the correct length of hospital stay based solely on surgical aspects.

In our institution, B-I reconstruction using the delta-shape method with linear staplers [7] was our first choice of reconstruction after LDG, with R-Y reconstruction (also with linear staplers) [8,12] reserved for selected cases, including those for which tension would be expected on the reconstruction, those with reflux esophagitis or a hiatus hernia, and those with elderly or high-risk patients. As indicated by the numbers of each reconstruction method used (248 B-I reconstructions and 128 R-Y reconstructions in the current consecutive series), B-I was used for the majority of patients who underwent distal gastrectomy.

With regard to post-operative nutritional status, we already confirmed that decreases in body weight and food intake at 12 months post-operatively compared with pre-operative values were significantly less for the LDG + B-I group than for the LDG + R-Y group. In addition, there were fewer subjective reports from patients about their small stomach in the LDG + B-I group than in the LDG + R-Y group [20]. Certainly, bile reflux into the remnant stomach and lower esophagus is one of the drawbacks for B-I reconstruction compared with R-Y reconstruction. It may be closely associated with the development of remnant gastritis, mainly caused by bile reflux [21]. However, as we recently suggested, based on another nationwide survey, the risk of the development of remnant gastric cancer does not appear to be directly associated with the reconstruction method [22].

The development of our strategy for digestive reconstruction after LDG is indicative of the trend toward IC mechanical reconstruction, which offers advantages in wound length and avoidance of tension through a mini-laparotomy during cumbersome anastomosis. For LDG + R-Y reconstruction, we were able to successfully use IC jejunojejunostomy, which saved a further 20 mm length for the umbilical wound [12]. This also allowed for reduced manipulation of the bowel, and was particularly useful for obese patients, for whom access through a mini-laparotomy can be limited. Reconstruction was performed under continuous laparoscopic guidance, and the disorientating and time-consuming switch to open surgery was thus avoided. In addition, totally IC laparoscopic gastrectomy has been shown to lead to earlier bowel function recovery compared with laparoscopy-assisted and open resections [23]. As indicated by others [15,23], IC anastomosis is more costly than EC anastomosis, because it requires three to four applications of endoscopic linear stapler cartridges for the anastomosis. We are currently trying to lower the cost by closing the entry hole using an IC hand-sewn technique instead of stapling [24].

## Conclusions

In conclusion, we found in this study that LDG followed by IC mechanical anastomosis using either the B-I or R-Y method has several advantages over LADG followed by EC hand-sewn anastomosis, including small wound size, reduced invasiveness, and more effective anastomosis. Although additional randomized control studies are warranted to confirm these findings, we consider that pure LDG is a useful technique for patients with early gastric cancer.

### Competing interests

None of the authors have any conflicts of interest or financial ties to disclose.

### Authors' contributions

SL designed and conducted the study, analyzed the data, and helped to write the manuscript. NT helped to design the study, conducted surgical operations, and helped to write the manuscript. EN conducted surgical operations and helped to write the manuscript. TT, MK, KY, MH, and JO

helped to design the study and helped to write the manuscript. KU is the principal investigator, and designed the study, assisted in writing, revising and editing the manuscript. All authors approved the final manuscript.

**Author details**
[1]Department of General and Gastroenterological Surgery, Osaka Medical College, 2-7, Daigaku-Machi, Takatsuki City Osaka 569-8686, Japan. [2]Tanigawa Memorial Hospital, Kasuga 1-Chome, Ibaraki City, Osaka 567-0031, Japan.

Received: 28 August 2012 Accepted: 24 November 2012
Published: 12 December 2012

**References**

1. Kitano S, Iso Y, Moriyama M, Sugimachi K: **Laparoscopy-assisted Billroth I gastrectomy.** *Surg Laparosc Endosc* 1994, 4(2):146–148.
2. Noh SH, Hyung WJ, Cheong JH: **Minimally invasive treatment for gastric cancer: approaches and selection process.** *J Surg Oncol* 2005, 90(3):188–193. discussion 193–184.
3. Shiraishi N, Yasuda K, Kitano S: **Laparoscopic gastrectomy with lymph node dissection for gastric cancer.** *Gastric Cancer* 2006, 9(3):167–176.
4. Varela JE, Hiyashi M, Nguyen T, Sabio A, Wilson SE, Nguyen NT: **Comparison of laparoscopic and open gastrectomy for gastric cancer.** *Am J Surg* 2006, 192(6):837–842.
5. Etoh T, Shiraishi N, Kitano S: **Current trends of laparoscopic gastrectomy for gastric cancer in Japan.** *Asian J Endosc Surg* 2009, 2(1):18–23.
6. Etoh T, Inomata M, Shiraishi N, Kitano S: **Minimally invasive approaches for gastric cancer-Japanese experiences.** *J Surg Oncol* 2012. doi:10.1002/jso.23128.
7. Kanaya S, Gomi T, Momoi H, Tamaki N, Isobe H, Katayama T, Wada Y, Ohtoshi M: **Delta-shaped anastomosis in totally laparoscopic Billroth I gastrectomy: new technique of intraabdominal gastroduodenostomy.** *J Am Coll Surg* 2002, 195(2):284–287.
8. Takaori K, Nomura E, Mabuchi H, Lee SW, Agui T, Miyamoto Y, Iwamoto M, Watanabe H, Tanigawa N: **A secure technique of intracorporeal Roux-Y reconstruction after laparoscopic distal gastrectomy.** *Am J Surg* 2005, 189(2):178–183.
9. Lee SW, Bouras G, Nomura E, Yoshinaka R, Tokuhara T, Nitta T, Tsunemi S, Tanigawa N: **Intracorporeal stapled anastomosis following laparoscopic segmental gastrectomy for gastric cancer: technical report and surgical outcomes.** *Surg Endosc* 2010, 24(7):1774–1780.
10. Shinohara H, Sonoda T, Niki M, Nomura E, Nishiguchi K, Tanigawa N: **Laparoscopically-assisted pylorus-preserving gastrectomy with preservation of the vagus nerve.** *Eur J Surg* 2002, 168(1):55–58.
11. Lee SW, Nomura E, Bouras G, Tokuhara T, Tsunemi S, Tanigawa N: **Long-term oncologic outcomes from laparoscopic gastrectomy for gastric cancer: a single-center experience of 601 consecutive resections.** *J Am Coll Surg* 2010, 211(1):33–40.
12. Bouras G, Lee SW, Nomura E, Tokuhara T, Nitta T, Yoshinaka R, Tsunemi S, Tanigawa N: **Surgical outcomes from laparoscopic distal gastrectomy and Roux-en-Y reconstruction: evolution in a totally intracorporeal technique.** *Surg Laparosc Endosc Percutan Tech* 2011, 21(1):37.
13. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W: **Special article Postoperative pancreatic fistula: An international study group (ISGPF) definition.** *Surgery* 2005, 138(1):8–13.
14. Japanese Gastric Cancer Association: **Japanese classification of gastric carcinoma: 3rd English edition.** *Gastric Cancer* 2011, 14(2):101–112.
15. Kim JJ, Song KY, Chin HM, Kim W, Jeon HM, Park CH, Park SM: **Totally laparoscopic gastrectomy with various types of intracorporeal anastomosis using laparoscopic linear staplers: preliminary experience.** *Surg Endosc* 2008, 22(2):436–442.
16. Tanimura S, Higashino M, Fukunaga Y, Takemura M, Nishikawa T, Tanaka Y, Fujiwara Y, Osugi H: **Intracorporeal Billroth 1 reconstruction by triangulating stapling technique after laparoscopic distal gastrectomy for gastric cancer.** *Surg Laparosc Endosc Percutan Tech* 2008, 18(1):54–58.
17. Fujiwara M, Kodera Y, Miura S, Kanyama Y, Yokoyama H, Ohashi N, Hibi K, Ito K, Akiyama S, Nakao A: **Laparoscopy-assisted distal gastrectomy with systemic lymph node dissection: a phase II study following the learning curve.** *J Surg Oncol* 2005, 91(1):26–32.
18. Shimizu S, Noshiro H, Nagai E, Uchiyama A, Tanaka M: **Laparoscopic gastric surgery in a Japanese institution: analysis of the initial 100 procedures.** *J Am Coll Surg* 2003, 197(3):372–378.
19. Wong SK, Tsui DK, Li MK: **Laparoscopic distal gastrectomy for gastric cancer: initial experience on hand-assisted technique and totally laparoscopic technique.** *Surg Laparosc Endosc Percutan Tech* 2009, 19(4):298–304.
20. Nomura E, Lee SW, Bouras G, Tokuhara T, Hayashi M, Hiramatsu M, Okuda J, Tanigawa N: **Functional outcomes according to the size of the gastric remnant and type of reconstruction following laparoscopic distal gastrectomy for gastric cancer.** *Gastric Cancer* 2011, 14(3):279–284.
21. Kojima K, Yamada H, Inokuchi M, Kawano T, Sugihara K: **A comparison of Roux-en-Y and Billroth-I reconstruction after laparoscopy-assisted distal gastrectomy.** *Ann Surg* 2008, 247(6):962–967.
22. Tanigawa N, Nomura E, Lee SW, Kaminishi M, Sugiyama M, Aikou T, Kitajima M: **Current state of gastric stump carcinoma in Japan: based on the results of a nationwide survey.** *World J Surg* 2010, 34(7):1540–1547.
23. Song KY, Park CH, Kang HC, Kim JJ, Park SM, Jun KH, Chin HM, Hur H: **Is totally laparoscopic gastrectomy less invasive than laparoscopy-assisted gastrectomy?: prospective, multicenter study.** *J Gastrointest Surg* 2008, 12(6):1015–1021.
24. Lee SW, Nomura E, Tokuhara T, Kawai M, Matsuhashi N, Yokoyama K, Fujioka H, Hiramatsu M, Okuda J, Uchiyama K: **Laparoscopic technique and initial experience with knotless, unidirectional barbed suture closure for staple-conserving, delta-shaped gastroduodenostomy after distal gastrectomy.** *J Am Coll Surg* 2011, 213(6):e39–45.

doi:10.1186/1477-7819-10-267
**Cite this article as:** Lee *et al.*: Benefits of intracorporeal gastrointestinal anastomosis following laparoscopic distal gastrectomy. *World Journal of Surgical Oncology* 2012 10:267.

**Submit your next manuscript to BioMed Central and take full advantage of:**

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

BioMed Central

Gastric Cancer
DOI 10.1007/s10120-012-0220-z

ORIGINAL ARTICLE

# Risk of lymph node metastases from intramucosal gastric cancer in relation to histological types: how to manage the mixed histological type for endoscopic submucosal dissection

**Kohei Takizawa · Hiroyuki Ono · Naomi Kakushima · Masaki Tanaka · Noriaki Hasuike · Hiroyuki Matsubayashi · Yuichiro Yamagichi · Etsuro Bando · Masanori Terashima · Kimihide Kusafuka · Takashi Nakajima**

Received: 7 August 2012 / Accepted: 10 November 2012
© The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2012

**Abstract**
*Background* The behavior of early gastric cancer (EGC) with mixed-type histology (differentiated and undifferentiated) is incompletely understood. This study aimed to clarify the clinicopathological features of EGC with mixed-type histology in relation to lymph node (LN) metastasis.
*Methods* Clinicopathological data from 410 patients who underwent surgical resection for intramucosal EGC were reviewed. Lesions were classified into four types according to the proportion of differentiated and undifferentiated components at histopathology: pure differentiated (PD) type, mixed predominantly differentiated (MD) type, mixed predominantly undifferentiated (MU) type, and pure undifferentiated (PU) type. We examined the clinicopathological differences between PD and MD, and between PU and MU, and the rate of LN metastasis according to tumor size and ulceration.
*Results* Moderately differentiated adenocarcinoma was the primary component in MD relative to PD (90.7 vs. 46.1 %). Signet ring cell carcinoma was the main component in PU relative to MU (81.5 vs. 33.3 %). LN metastasis was more common in MU than PU (19.0 vs. 6.0 %). For intramucosal tumors larger than 20 mm without lymphovascular invasion and without ulceration, the rate of LN metastasis was 0 % for MD and 24 % for MU. For intramucosal lesions less than 30 mm with ulceration but without lymphovascular invasion, the rate of LN metastasis was 0 % for MD and 20 % for MU.
*Conclusions* Histologically mixed-type EGC with a predominantly undifferentiated component should be managed as an undifferentiated-type tumor. Further investigation is required to determine whether mixed-type EGC with a predominantly differentiated component could be managed the same way as a differentiated-type EGC.

**Keywords** Gastric neoplasms · Differentiated type · Undifferentiated type · Mixed type

Meeting presentations: 8th International Gastric Cancer Congress 2009.

K. Takizawa (✉) · H. Ono · N. Kakushima · M. Tanaka · H. Matsubayashi · Y. Yamagichi
Endoscopy Division, Shizuoka Cancer Center,
1007 Shimonagakubo Nagaizumi-cho, Sunto-gun,
Shizuoka 411-8777, Japan
e-mail: k.takizawa@scchr.jp

N. Hasuike
Gastroenterology Division, Sano Hospital, Hyogo, Japan

E. Bando · M. Terashima
Gastric Surgery Division, Shizuoka Cancer Center,
Nagaizumi-cho, Shizuoka, Japan

K. Kusafuka · T. Nakajima
Pathology Division, Shizuoka Cancer Center,
Nagaizumi-cho, Shizuoka, Japan

## Introduction

Endoscopic submucosal dissection (ESD) allows en-bloc resection of large superficial lesions and is a widely applied treatment for early gastric cancer (EGC) with little risk of lymph node (LN) metastasis [1–3]. Pathologically, gastric cancer can be broadly divided into two types according to the presence or absence of tubular structures: differentiated and undifferentiated types [4]. Characteristically, undifferentiated gastric cancer carries a higher risk of LN metastasis than differentiated gastric cancer [5–9]. However, some tumors contain a mixture of differentiated and undifferentiated components.

Published online: 29 November 2012

Precise histopathological evaluation of EGC is now possible because of en-bloc resection using ESD; this has introduced dilemmas when a mixture of histological types is identified in the same lesion. According to the Japanese Classification of Gastric Carcinoma [4], gastric cancers showing a mixture of differentiated and undifferentiated components are classified according to the predominant histological type. To determine indications for ESD, many studies have examined surgically resected LN metastasis in EGC [5]. However, most of these tumors were predominately of mixed histological type.

To our knowledge, the behavior of histologically mixed-type EGC is incompletely understood, and there is no consensus regarding its clinical management [10, 11]. This study aimed to clarify the clinicopathological features of histologically mixed-type EGC in relation to LN metastasis and to determine indications for endoscopic treatment of mixed-histologic-type EGC.

## Patients and methods

A total of 410 intramucosal gastric cancers in 410 consecutive patients treated surgically between September 2002 and January 2010 in a prefectural cancer center (Shizuoka Cancer Center, Japan) were retrospectively analyzed. Exclusion criteria were: (1) multiple synchronous gastric cancers, (2) local recurrences, (3) unavailable precise pathological records (due to ESD performed at outside hospital, etc.), (4) cancers from remnant stomach, and (5) Barrett cancers. Clinical records and endoscopic and pathological reports of each patient were examined. To assess the histological type, all specimens were reviewed to determine the percentages of differentiated components (well and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma) and undifferentiated components (poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma). Lesions were classified into the following four types according to the proportions of intramucosal differentiated and undifferentiated components at histopathology: pure differentiated (PD) type (composed of differentiated type only), mixed predominantly differentiated (MD) type (major component of differentiated type), mixed predominantly undifferentiated (MU) type (major component of undifferentiated type), and pure undifferentiated (PU) type (undifferentiated type only).

We examined the following parameters: (1) clinicopathological differences between PD- and MD-type tumors, (2) clinicopathological differences between PU type and MU type, and (3) the rate of LN metastasis by tumor size and presence or absence of ulceration. Clinicopathological findings analyzed were: gender, age, predominant histological type, tumor location, macroscopic type, tumor size, presence of lymphatic and venous invasion, presence of ulceration, and LN metastasis. Tumor location was determined based on the Japanese Classification of Gastric Carcinoma [4] as the upper third (U), middle third (M), or lower third (L) of the stomach. Macroscopic type was divided into three groups: elevated type (elevated lesions such as 0-I, and 0-IIa), depressed type (depressed lesions such as 0-IIc), and combined type (such as 0-IIa + IIc and 0-IIc + III). Predominant histological type, tumor size, lymphatic/venous invasion, presence or absence of ulceration, and LN metastasis were determined histopathologically after surgery.

All lesions were thinly sliced at intervals of 3–5 mm. One section each of all dissected LNs (at least 15 nodes per case) was stained with hematoxylin and eosin. Sections were examined histologically to assess the presence or absence of metastasis. Lymphatic invasion was identified immunohistochemically using the D2–40 antibody (Dako-Cytomation, Glostrup, Denmark). The local ethics committee approved the use of pathological samples, with patients' informed consent, at Shizuoka Cancer Center.

Data were analyzed using the chi-squared test and Student's $t$ test. $P < 0.05$ was considered statistically significant.

## Results

### Patient characteristics

Table 1 reports patients' characteristics. The study group consisted of 240 male and 170 female patients with a median age of 61 years (range 29–87 years). Forty-seven lesions were in the upper third of the stomach, 244 in the middle third, and 119 in the lower third. Histopathologically, tumors were divided into four groups as follows: 130 (31.7 %) PD, 54 (13.2 %) MD, 42 (10.2 %) MU, and 184 (44.9 %) MU. The overall rate of lymphatic invasion was 3.7 %, venous invasion was 0 %, and LN metastasis was 7.1 %, respectively.

### Clinicopathological differences between PD type and MD type

Table 2 shows relationships between clinicopathological findings and histological type (PD and MD). Moderately differentiated type was observed significantly more often as the main component in MD than in PD lesions (90.7 vs. 46.1 %, $P < 0.0001$). Rates of lymphatic invasion (9.3 vs. 3.1 %) and LN metastasis (11.1 vs. 3.1 %) were higher in the MD type than in the PD type, but these differences were not statistically significant. Table 3 shows the

**Table 1** Patients' characteristics

| All | 410 (%) |
|---|---|
| Age (years) | |
| Median (range) | 61 (29–87) |
| Gender | |
| Male | 240 (58.5) |
| Female | 170 |
| Location | |
| Upper third | 47 (11.5) |
| Middle third | 244 (59.5) |
| Lower third | 119 (29.0) |
| Macroscopic type | |
| Elevated (I, IIa) | 17 (4.1) |
| Depressed (IIc) | 346 (84.4) |
| Complex (IIa + IIc) | 119 (11.5) |
| Tumor size (mm) | |
| Median (range) | 33 (1–130) |
| Histological type | |
| PD (pure differentiated) | 130 (31.7) |
| MD (mixed predominantly differentiated) | 54 (13.2) |
| MU (mixed predominantly undifferentiated) | 42 (10.2) |
| PU (pure differentiated) | 164 (44.9) |
| Lymphatic invasion | |
| Present | 15 (3.7) |
| Absent | 395 |
| Vascular invasion | |
| Present | 0 (0) |
| Absent | 410 |
| Pathological ulceration | |
| Present | 194 (47.3) |
| Absent | 216 |
| LN metastasis | |
| Present | 29 (7.1) |
| Absent | 381 |

relationship between lymph node metastases and the pattern of combination of the major differentiated component and the minor undifferentiated component in the MD type. Regarding the minor component, 32 cases were poorly differentiated adenocarcinoma, and 21 cases were signet ring cell carcinoma. There was no significant difference between these minor components and lymph node metastasis.

### Clinicopathological differences between PU type and MU type

Table 4 reports relationships between clinicopathological findings and histological type (PU and MU). Signet ring cell type was observed significantly more often as the main component in the PU versus MU type (81.5 vs. 33.3 %, $P < 0.01$). LN metastasis was significantly more common in the MU type than in the PU type (19.0 vs. 6.0 %, $P < 0.01$). Table 5 shows the relationship between lymph node metastases and the pattern of combination of the major undifferentiated component and the minor differentiated component in the MU type. Most of the minor component was moderately differentiated adenocarcinoma (40/42).

### Rate of LN metastasis by tumor size and ulceration

Table 6 shows relationships between LN metastasis and tumor size, presence or absence of ulceration, and histological type. For intramucosal tumors larger than 20 mm in size without lymphovascular invasion and without ulceration, the rate of LN metastasis was 0 % (0/17) for the MD type and 24 % (4/17) for the MU type. For intramucosal tumors less than 30 mm with ulceration and without lymphovascular invasion, the rate of LN metastasis was 0 % (0/8) for the MD type and 20 % (2/10) for the MU type.

## Discussion

New difficulties in determining the appropriate management of mixed histological type gastric cancer arose as a result of improvements in ESD, which allow en-bloc resection of large superficial gastric lesions and precise histopathological evaluation [10, 11].

In general, there are two distinct groups of differentiated and undifferentiated mixed-type gastric tumors. The first group has both differentiated- and undifferentiated-type histology in the mucosa. The second group shows differentiated type in the mucosa and undifferentiated type only in the submucosa, which may show features of invasion. We hypothesized that these two groups had different prognoses and should be evaluated and managed independently. For this reason, we investigated only intramucosal gastric cancer in this study.

We histologically classified early gastric cancers into four groups according to the proportion of differentiated and undifferentiated components. We found that mixed tumors with predominantly differentiated type were larger than purely differentiated-type tumors. This is in agreement with studies that reported 86 % of early gastric cancer less than 10 mm in size were pure differentiated type, and the ratio of mixed type increased with tumor size over 10 mm [12]. Furthermore, the current study revealed that mixed-type tumors were more often composed of moderately and poorly differentiated histological types than well-differentiated and signet ring cell types. These results suggest that as the tumor grows, moderately differentiated-type lesions might

**Table 2** PD (pure differentiated) type versus MD (mixed predominantly differentiated) type

| *n* | PD 130 (%) | MD 54 (%) | *P* value |
|---|---|---|---|
| Age (years) | | | |
| Mean ± SD (range) | 64.2 ± 9.9 (41–83) | 61.2 ± 11.9 (29–78) | 0.086† |
| Main component | | | |
| Well differentiated | 69 (53.1) | 4 (7.4) | <0.0001* |
| Moderately differentiated | 60 (46.1) | 49 (90.7) | |
| Papillary | 1 (0.6) | 1 (1.9) | |
| Macroscopic type | | | |
| Elevated (I, IIa) | 14 (10.8) | 6 (1.9) | 0.059* |
| Depressed (IIc) | 94 (72.3) | 31 (87.0) | |
| Complex (IIa + IIc) | 22 (16.9) | 17 (11.1) | |
| Tumor size (mm) | | | |
| Mean ± SD (range) | 37.2 ± 20.2 (8–130) | 44.4 ± 30.5 (5–127) | 0.063† |
| Lymphatic invasion | | | |
| Present | 4 (3.1) | 5 (9.3) | 0.125§ |
| Absent | 126 | 49 | |
| Vascular invasion | | | |
| Present | 0 (0) | 0 (0) | >0.999§ |
| Absent | 130 | 54 | |
| Pathological ulceration | | | |
| Present | 63 (48.5) | 29 (53.7) | 0.517* |
| Absent | 67 | 25 | |
| LN metastasis | | | |
| Present | 4 (3.1) | 6 (11.1) | 0.066* |
| Absent | 126 | 48 | |

*SD* standard deviation

* Chi-squared test, † Student's *t* test, § Fisher's exact test

**Table 3** The relationship between lymph node metastases and the pattern of combination of the major differentiated component and the minor undifferentiated component in MD type

| MD | Minor component | | |
|---|---|---|---|
| | Poorly differentiated | Signet ring cell | Mucinous |
| Major component | | | |
| Well differentiated | 0/2 | 0/2 | 0 |
| Moderately differentiated | 4/30 | 2/18 | 0 |
| Papillary | 0 | 0/1 | 0 |

progress to poorly differentiated type, and PD type might change into MD type.

Regarding indications for ESD of EGC, MD and PD types are currently managed in the same way as differentiated type tumors according to the Japanese Classification of Gastric Carcinoma [4]. However, our data show that the rate of lymphatic invasion and LN metastasis was higher in the MD type than in the PD type lesions, although the difference was not statistically significant. Hanaoka et al. [10] also reported that the prevalence of LN metastasis was higher with differentiated-type-dominant mixed type (MD type in the current study) than with differentiated type (PD type in the current study). We are apprehensive that MD-type tumors might warrant different treatment protocols from PD-type lesions. The Guidelines for Diagnosis and Treatment of Carcinoma of the Stomach, 3rd edition, were edited by the Japanese Gastric Cancer Society and released in October 2010. In these guidelines there are some modifications concerning the management of mixed histological types. For example, an intramucosal tumor measuring 30 mm or less, with ulceration, of differentiated-type-dominant mixed type, and without lymphovascular invasion, used to be treated with ESD for curative resection. The new guidelines consider ESD as non-curative resection, because there are no convincing data that these tumor types can be curatively resected. In our study (Table 4), we fortunately found no cases of this tumor type with LN metastasis [MD type, intramucosal, ≤30 mm, ulceration (+), lymphovascular invasion (−)], but the number of cases was very small. These findings should be confirmed by additional clinical research.

Hanaoka et al. [10] also reported that the prevalence of lymphatic invasion and LN metastasis was higher with undifferentiated-type-dominant mixed-type tumors (MU in

**Table 4** PU (pure undifferentiated) type versus MU (mixed predominantly undifferentiated) type

| *n* | PU 184 (%) | MU 42 (%) | *P* value |
|---|---|---|---|
| Age (years) | | | |
| Mean ± SD (range) | 59.6 ± 11.0 (30–87) | 56.7 ± 11.5 (29–81) | 0.126† |
| Main component | | | |
| Poorly differentiated | 34 (18.5) | 14 (33.3) | 0.009* |
| Signet ring cell | 150 (81.5) | 27 (64.3) | |
| Mucinous | 0 (0) | 1 (2.4) | |
| Macroscopic type | | | |
| Elevated (I, IIa) | 1 (0.5) | 1 (2.4) | 0.161* |
| Depressed (IIc) | 165 (89.7) | 40 (95.2) | |
| Complex (IIa + IIc) | 18 (9.8) | 1 (2.4) | |
| Tumor size (mm) | | | |
| Mean ± SD (range) | 36.3 ± 23.3 (1–110) | 36.9 ± 19.6 (8–95) | 0.883† |
| Lymphatic invasion | | | |
| Present | 4 (2.2) | 2 (4.8) | 0.310§ |
| Absent | 180 | 40 | |
| Vascular invasion | | | |
| Present | 0 (0) | 0 (0) | >0.999§ |
| Absent | 184 | 42 | |
| Pathological ulceration | | | |
| Present | 81 (44.0) | 21 (50.0) | 0.482* |
| Absent | 103 | 21 | |
| LN metastasis | | | |
| Present | 11 (6.0) | 8 (19.0) | 0.006* |
| Absent | 173 | 34 | |

*SD* standard deviation

* Chi-squared test, † Student's *t* test, § Fisher's exact test

**Table 5** The relationship between lymph node metastases and the pattern of combination of the major undifferentiated component and the minor differentiated component in MU type

| MU | Minor component | | |
|---|---|---|---|
| | Well differentiated | Moderately differentiated | Papillary |
| Major component | | | |
| Poorly differentiated | 0/0 | 1/13 | 0/1 |
| Signet ring cell | 1/1 | 6/26 | 0 |
| Mucinous | 0 | 0/1 | 0 |

the current study) than with undifferentiated type (PU type in the current study). Our results showed that LN metastases were significantly more common in MU type than in PU type lesions. Although there is a difference between Hanaoka's study, which examined submucosal invasive cancer, and our study examining intramucosal cancer, results should be comparable. That is, MU type tumors might have greater malignant potential than PU tumors.

Limitations of the present study include the retrospective design and inclusion of only surgically resected cases

**Table 6** Rate of lymph node metastasis by tumor size and ulcer findings

| Intramucosal cancer without lymphovascular invasion (pM, ly0, v0) | PD | MD | MU | PU |
|---|---|---|---|---|
| UL− | | | | |
| ≤20 mm | 0/16 (0 %) | 0/6 (0 %) | 0/3 (0 %) | 0/39 (0 %) |
| >20 mm | 0/49 (0 %) | 0/17 (0 %) | 4/17 (24 %) | 1/62 (2 %) |
| UL+ | | | | |
| ≤30 mm | 0/21 (0 %) | 0/8 (0 %) | 2/10 (20 %) | 2/28 (7 %) |
| >30 mm | 2/40 (5 %) | 4/18 (22 %) | 2/10 (20 %) | 6/51 (12 %) |

*M* intramucosal, *ly* lymphatic invasion, *v* vascular invasion, *UL* ulcer findings